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Age and Sex Differences in Duration of Pre-Hospital Delay, Hospital Treatment Practices, and Short-Term Outcomes in Patients Hospitalized with an Acute Coronary Syndrome/Acute Myocardial Infarction: A Dissertation

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AGE AND SEX DIFFERENCES IN DURATION OF PRE-HOSPITAL DELAY, HOSPITAL TREATMENT PRACTICES, AND SHORT-TERM OUTCOMES IN PATIENTS HOSPITALIZED WITH AN ACUTE CORONARY SYNDROME/ACUTE MYOCARDIAL INFARCTION

A Dissertation Presented

By

HOA L. NGUYEN, M.D., M.S.

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Anthony Carruthers, Ph.D.,
Dean of the Graduate School of Biomedical Sciences
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May 7th, 2010

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Abstract

Background

The prompt seeking of medical care after the onset of symptoms suggestive of acute coronary syndromes (ACS)/acute myocardial infarction (AMI) is associated with the receipt of coronary reperfusion therapy, and effective cardiac medications in patients with an ACS/AMI and is crucial to reducing mortality and the risk of serious clinical complications in these patients. Despite declines in important hospital complications and short-term death rates in patients hospitalized with an ACS/AMI, several patient groups remain at increased risk for these adverse outcomes, including women and the elderly. However, recent trends in age and sex differences in extent of pre-hospital delay, hospital management practices, and short-term outcomes associated with ACS/AMI remain unexplored.

The objectives of this study were to examine the overall magnitude, and changing trends therein, of age and sex differences in duration of pre-hospital delay (1986-2005), hospital management practices (1999-2007), and short-terms outcomes (1975-2005) in patients hospitalized with ACS/AMI.

Methods

Data from 13,663 residents of the Worcester, MA, metropolitan area hospitalized at all greater Worcester medical centers for AMI 15 biennial periods between 1975 and 2005 (Worcester Heart Attack Study), and from 50,096 patients hospitalized with an ACS in 106 medical centers in 14 countries participating in the Global Registry of Acute Coronary Events (GRACE) between 2000 and 2007 were used for this investigation.

Results

In comparison with men <65 years, patients in other age-sex strata exhibited significantly longer pre-hospital delay, with the exception of women < 65 years; had a significantly lower odds of receiving aspirin, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), beta blockers, statins, and undergoing coronary artery bypass graft surgery (CABG) surgery or percutaneous coronary intervention (PCI), and were significantly more likely to develop atrial fibrillation, cardiogenic shock, heart failure, and to die during hospitalization and in the first 30 days after admission. There was a significant interaction between age and sex in relation to the use of several medications and the development of several of these outcomes; in patients <65 years, women were less likely to have received these treatments and were more likely to develop these complications and die compared with men; in patients ≥ 65 years, however, there were no significant sex differences in these outcomes. Age and sex differences in duration of pre-hospital delay have narrowed over time; however, age and sex differences in hospital management practices and short-term outcomes have not changed significantly over time.

Conclusions

Our results suggest that the elderly were more likely to experience longer pre-hospital delay, were less likely to be treated with evidence-based treatments during hospitalization for acute coronary syndrome, and were more likely to develop adverse outcomes compared to younger persons. Younger women were less likely to be treated with effective treatments and were more likely to develop adverse outcomes compared with younger men while there was no sex difference in these outcomes. Interventions targeted at older patients, in particular, are needed to encourage these high-risk patients to seek medical care promptly to maximize the benefits of currently available treatment modalities. More targeted treatment approaches during hospitalization for ACS/AMI for younger women and older patients are needed to improve their hospital prognosis.

Word count: 522

Key words: Acute myocardial infarction, pre-hospital delay, evidence-based treatment, hospital complications, hospital mortality, 30-day mortality, age and sex differences.

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List of Acronyms

Acronym	**Definition**
CHD	Coronary heart disease
ACS	Acute coronary syndrome
AMI	Acute myocardial Infarction
STEMI	ST segment elevation acute myocardial infarction
NSTEMI	Non-ST segment elevation acute myocardial infarction
UA	Unstable angina
WHAS	Worcester heart attack study
GRACE	Global registry of acute coronary events
ACE inhibitors	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft surgery
LDL	Low-density lipoprotein
GFR	Glomerular filtration rate
OR	Odds ratio
HR	Hazard ratio
CI	Confidence interval
IQR	Inter quartile range

CHAPTER I

Introduction

1.1 Specific Aims

The acute coronary syndromes (ACS), an acute manifestation of underlying coronary heart disease (CHD), are a major cause of morbidity and mortality throughout the world.[1] Thrombolytic agents and other coronary reperfusion therapies are more effective in patients with evolving acute coronary disease if patients are treated promptly.[2-4] Older individuals and women have been shown to be at greater risk for dying after acute myocardial infarction than respective comparison groups, suggesting that there are differences in disease characteristics, health care seeking behaviors, receipt of different treatment strategies, and other factors between men and women of different ages. Although several studies have suggested that older patients and women with an acute coronary syndrome/ acute myocardial infarction (ACS/AMI) are more likely to present to the hospital after prolonged delay, to be less aggressively treated, and to suffer poorer outcomes compared to younger patients and men, a limited number of studies have examined differences in these outcomes from a long-term, population-based, and/or multinational perspective. Moreover, little contemporary research has been conducted examining potentially changing differences in these outcomes between men and women of varying ages during recent as compared to earlier periods.

The objectives of my proposed research were to examine age and sex differences in extent of pre-hospital delay, receipt of evidence-based medications and cardiac procedures, and short-term outcomes in patients with an ACS/AMI; a secondary study goal was to investigate whether differences in these outcomes have changed over time between men and women and in patients of various age strata. This was accomplished through the secondary analysis of data from two large registries for patients hospitalized with ACS/AMI: the Worcester Heart Attack Study (WHAS) and the Global Registry of Acute Coronary Events (GRACE). The WHAS is an ongoing population-based surveillance study which is examining long-term trends in the clinical epidemiology of AMI in patients hospitalized at all greater Worcester, MA, medical centers in 15 study periods between 1975 and 2005[2,5,6]. The GRACE project is a large multinational observational study of patients hospitalized with ACS at 106 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand over the period 1999-2007.[7,8]

The specific aims and accompanying hypotheses of this proposal were as follows:

Aim 1: To examine age and sex differences in duration of pre-hospital delay, defined as the time interval from the onset of acute symptoms suggestive of an AMI to arrival at the hospital's emergency department, and changing trends, among residents of the Worcester metropolitan area with AMI in the WHAS over the period 1986-2005.

Hypothesis: Older patients and women will exhibit longer pre-hospital delays than younger patients and men both crudely and after adjusting for factors that could potentially confound these associations; however, these age and sex differences will have narrowed over time.

Aim 2: To examine age and sex differences in the receipt of evidence-based cardiac medications and procedures, and changing trends, during hospitalization in patients with an ACS enrolled in the GRACE registry over the period 1999 -2007.

Hypothesis: Older patients and women will be less likely to be prescribed evidence-based cardiac medications and procedures than younger patients and men both crudely and after adjusting for factors that could potentially confound these associations; however, these age and sex differences will have narrowed over time.

Aim 3: To examine age and sex differences in important hospital clinical complications, hospital case fatality rates (CFRs), 30-day mortality, and changing trends, in patients with an AMI included in the WHAS over the period 1975-2005.

Hypothesis: Older patients and women will experience higher complication and death rates than younger patients and men both crudely and after adjusting for factors that might potentially confound these associations; however, these age and sex differences in these endpoints will have narrowed over time.

1.2 Background and Significance

1.2.1 Scope of the Problem of ACS/AMI

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in men and women throughout the world.[1] In 2004, 3.8 million men and 3.4 million women worldwide died from CHD.[1] Beginning in the early part of the 20th century, death rates from CHD in the U.S. increased dramatically reaching epidemic proportions by the mid to late 1960's.[9-11] Since that time, there have been continuing declines in these death rates , with an approximate 5% average annual decline in the age-adjusted mortality from CHD in the U.S. between 1999 and 2004.[12,13] However, CHD continues to be the leading cause of mortality in American men and women, claiming almost 450,000 lives in 2005.[13] In 2009, an estimated 1 million Americans will have an AMI and more than one-quarter of these persons will die as a result of this disease.[13] Persons with an AMI have a sudden death rate 4 to 6 times higher than that of the general population and upwards of one half of patients with AMI will die before reaching the hospital with men were more likely to die out of hospital than women.[13]

Internationally, inconsistent trends in CHD mortality have occurred since the late 1960's and into the mid-2000's.[12,13] The death rates from CHD in some countries have declined, whereas mortality from CHD has either remained stable or increased in others during this period. In 2004, the U.S. ranked 7th highest for CHD mortality in men and 5th highest in women in published data from 18 industrialized countries.[1,12,13]

1.2.2 Pre-hospital Delay in Patients with an ACS/AMI

For persons with an evolving AMI, the prompt administration of coronary reperfusion therapy has been shown to reduce mortality and important clinical complications in these high risk patients. Thrombolytics and other coronary reperfusion therapies are more effective if patients are treated earlier in their disease course than later.[2-4] The National Heart Attack Alert Program (NHAAP)[14] recommends that thrombolytic treatment should be administered within 30 minutes of hospital arrival, and percutaneous coronary intervention (PCI) procedures within two hours of hospital arrival, for maximum benefits. Previous studies have shown that the duration of pre-hospital delay is inversely associated with the receipt of hospital reperfusion treatments, including thrombolytic agents and primary PCI; patients with longer pre-hospital delay are less likely to receive reperfusion treatments compared to those with shorter delay times.[15,16] However, more than one-half of patients with AMI delay seeking medical care by more than 2 hours,[17-19] and more than one-quarter of patients with AMI delay seeking care by more than 6 hours.[17-20]

Pre-hospital delay is defined as the time interval from the development of acute symptoms suggestive of AMI to arrival at the hospital's emergency department and consists of the following two components:

1. Decision time or patient delay: The period between the awareness of symptoms and the decision to seek treatment;
2. Transportation time or transportation delay: The period between initiation of travel to the emergency room and emergency department arrival.

While delay can occur at any of these stages, the majority of pre-hospital delay in patients with AMI has been attributed to patient indecision in acting on and failure to recognize the seriousness of their acute and evolving symptoms suggestive of AMI.[21]

Factor Associated with Duration of Pre-hospital delay

To effectively reduce pre-hospital delay, the factors that contribute to it must be identified. A summary from the National Heart, Lung, and Blood Institute Educational Strategies Working Group suggested that clinical presentation (hemodynamic instability, large infarction, and sudden onset of severe chest pain), knowledge of the disease (recognition by patients that symptoms are heart related), and health care seeking behaviors (e.g., consulting friend, co-workers or strangers) were associated with reduced pre-hospital delay. On the other hand, socio-demographic characteristics (e.g., older age, female, African American, low SES), medical history of angina or diabetes, psychological factors (low emotional/somatic awareness), and other health seeking behaviors (consulting spouse and other relative, consulting physicians and self treatment) were associated with longer pre-hospital delay.[14,22]

Although considerable public health efforts have been made to educate patients about the symptoms of AMI, and the importance of seeking health care immediately in the setting of possible acute coronary disease, little change in extent of pre-hospital delay has been achieved through current or past efforts.[18,23,24] For example, the Rapid Early Action for Coronary Treatment (REACT) study, a randomized, controlled community trial of 20 U.S. communities pair matched on several demographic characteristics, was conducted from 1995-1997 to examine the effects of an extensive community –wide intervention on patient delay and emergency medical service (EMS) use in patients with acute CHD.[25,26] The intervention targeted mass media, community organizations, and professional, public, and patient education. Despite the intensive 18-month intervention, time from symptom onset to hospital arrival for patients with chest pain did not change significantly between intervention and control communities, although increased appropriate EMS use was observed in the intervention communities. In addition, a recent trial (2000-2006) using a nurse-counseling intervention for patients with documented CHD that focused on information, emotional issues, and social factors also failed to reduce pre-hospital delay in 3,500 patients with documented CHD.[27] The results of these relatively recent trials suggest that our understanding of the reasons for delay in seeking care in patients with symptoms suggestive of ACS may be inadequate, as may be our educational approaches and intervention efforts, or health care providers are not effectively educating the public about the importance of seeking care quickly after the onset of acute coronary symptoms. On the other hand, the negative results of several published trials may be partially due to inaccurate information on duration of pre-hospital delay since data on pre-hospital delay is subject to information bias; patients may fail to recognize signs and symptoms suggestive of AMI, accurately recall the time of acute symptoms onset, or medical staff may fail to collect accurate and reliable information.

Age and Sex Differences in Duration of Pre-hospital Delay

The limited number of studies examining potential age and sex differences in the distribution and extent of pre-hospital delay in patients hospitalized with AMI has found inconsistent results.[8,18,19,23,28-40] Several studies have found that women are more likely to experience longer delay compared to men,[23,24,29,41-44] while other studies have suggested that there are no differences in duration of pre-hospital delay between men and women.[17,18,45] In terms of age, most previous studies have suggested that older individuals are more likely to report prolonged pre-hospital delay for AMI than younger persons.[18,23,24,42] However, several studies have failed to find any association between age and extent of pre-hospital delay.[28,29,44,46] These discrepant results may due to differences in study populations (eg. STEMI vs. NSTEMI; incident AMI vs. prior AMI), sample sizes, level of adjustment for potential confounders, and other related factors.

Several factors may account for possible age and sex differences in extent of pre-hospital delay in the setting of evolving acute coronary disease. Compared to younger patients and men, older patients and women are more likely to report atypical symptoms of AMI [47-50] and to have additional co-morbidities present,[49-51] including diabetes, hypertension, and heart failure, which may make them misinterpret the symptoms of AMI.[18-20,35,52] Furthermore, women may lack adequate knowledge of the symptoms of AMI or consider heart attack as a "male disease"; therefore, they did not recognize the importance of their symptoms in seeking medical care in a more timely fashion. Women have also been shown to be more likely to contact their physician, or self treat their symptoms of AMI than men, which likely have contributed to prolonged delay patterns.[53] Women are also more likely to be widowed and living alone at the time of symptom onset,[39] which has previously been shown to be an independent predictor of prolonged delay.[29,35] Women have also been reported to be more likely to cope with their illness by themselves and did not want to trouble anyone, which has been found to be associated with longer delay times.[29,44]

Few contemporary population-based data have examined these associations or whether these associations have changed over time. In addition, limited studies have examined factors associated with pre-hospital delay according to age and sex; several of these studies have had a number of methodological limitations including lack of population-based designs and having small sample sizes that likely limited the generalizability of their findings. A systematic review including 44 articles (from 42 studies) which were published between 1960 and 2008 showed that in the majority of studies examined, women and older persons (≥65 years) were more likely to arrive at the hospital later, compared to men and younger persons, among patients hospitalized with AMI. Several factors associated with pre-hospital delay, including socio-demographic, medical history, clinical presentation, psychological and contextual characteristics, also differed according to sex.[54]

In the proposed study, contemporary trends in age and sex differences in duration of pre-hospital delay among persons experiencing an AMI were examined using data from the WHAS, a long-term, population-based observational study of patients with AMI.

1.2.3 Evidence-based Treatments for ACS/AMI

The decline in mortality attributed to CHD in the U.S. during the past 4 decades has been due in large part to the increasing adoption of new preventive and therapeutic strategies, with changes in medical treatment having contributed substantially to these declining death rates.

Particularly striking changes have taken place in the medical management of patients experiencing an AMI during the past 20 years. The effectiveness of aspirin, β-blockers, and early administration of coronary reperfusion therapy in patients with AMI has been well established.[55,56] National expert panels have advocated for the routine use of aspirin and β-blockers in patients with a recent AMI and for the long-term use of angiotensin converting enzyme (ACE) inhibitors and lipid-lowering therapy.[57-63] The introduction of ACE inhibitors to clinical practice in the early 1990's has been shown to improve left ventricular function and early survival after AMI.[64,65] More recently, primary PCI has been increasingly adopted as the main modality for the timely reperfusion of the infarct related coronary artery, in conjunction with the use of several adjunctive therapies. Data from the National Registry of Myocardial Infarction, study (1995-1999), which included more than 1.5 million patients hospitalized with AMI, showed increasing utilization of aspirin, β-blockers, ACE inhibitors and cardiac procedures during the first 24 hours of hospitalization over the decade long period under study.[47,66-68] A review paper of changing trends in patient management practices in patients hospitalized with AMI between 1975-1995 showed encouraging increases in the utilization of aspirin (5% vs. 75%) and beta blockers (21% vs. 50%) over this period.[69]

The American College of Cardiology, the American Heart Association (ACC/AHA) and European guidelines for the hospital management for patients with ST segment elevation MI (STEMI) and patients with non- ST segment elevation MI (NSTEMI) /Unstable angina (UA) were published in the 1990s and 2000s. These guidelines recommend that evidence –based treatments, including aspirin, β-blockers, ACE inhibitors, and lipid lowering agents, should be used for all eligible patients with ACS during hospitalization, irrespective of age and sex.[62,63] The updated guidelines in 2007 have reinforced the use of these treatments[70,71] and further emphasize that older patients and women have the same benefits from these effective treatments as do younger patients and men. Even though published clinical evidence does not support withholding the most effective cardiac therapies on the basis of age,[72,73] elderly patients with an ACS are typically treated less aggressively than younger patients.[19,45,74-76] Moreover, despite the greater prevalence of CHD in men,[5,77] women with an ACS are more likely than men to experience adverse in-hospital and post-discharge outcomes.[78,79]

Factors Associated with the Use of Evidence-based Treatments in Patients with ACS/AMI

Several studies examining factors associated with the receipt of evidence-based medications and procedures among persons with ACS/AMI have found that admission to teaching/academic hospitals and treatment by cardiologists are associated with higher utilization rates of evidence-based medications and procedures.[75] On the other hand, being from a lower SES, not having medical insurance, history of heart failure, diabetes, hypertension, kidney disease, PCI, or CABG, prolonged pre-hospital delay, and development of hospital complications were associated with lower rates of utilization of evidence-based cardiac medications and interventional procedures.[75,80,81]

Age and Sex Differences in the Use of Evidence-based Treatments in Patients with ACS/AMI

Several prior studies have examined possible age and sex differences in cardiac medication and procedure use during hospitalization in patients with ACS[17,48,51,76,82-86] with discrepant results. Some studies found that older individuals and women were less likely to be treated with evidence–based cardiac medications and procedures, while other studies suggested that there were no differences between men and women and among patients of different age groups in the utilization of these effective treatments. These conflicting results may be due to differences in study populations (eg., STEMI vs. NSTEMI/UA), study period, timing of treatment administration (treatments received in the first 24 hours of hospitalization vs. treatments prescribed at any time during hospitalization), sample sizes and level of adjustment for potential confounders. Age and sex differences in the hospital management of patients with ACS may be partially explained by differences in the extent of pre-hospital delay between younger and older patients and between men and women.[18,52] Older patients and women are also more likely to have multiple complex co-morbidities present, including heart failure, hypertension, and diabetes,[17,39,86-88] and tend to present with more atypical signs and symptoms of acute coronary disease than younger patients and men,[50,89] which can make their diagnosis and management all the more difficult. Furthermore, physicians may not believe that the effectiveness of these treatments is as great in the elderly and women or they are more likely to have adverse events or complications. Differences in these treatment practices may also be due to patients' preferences or to their health insurance status.

While a number of studies have examined associations between age and sex and the use of evidence-based treatments for ACS in the US[26,90] and in Europe,[81,86] few studies have examined these associations from the broader perspective of a multinational investigation. Moreover, little contemporary multinational research has investigated changes in age and sex differences in the prescribing of evidence-based therapies in patients hospitalized with an ACS and whether previously noted differences in the receipt of effective cardiac medications have narrowed over time between men and women and among patients of different ages.

In the proposed study, contemporary trends in the utilization of evidence-based cardiac medications and interventional procedures according to age and sex were examined using data from 14 countries participating in the GRACE study.

1.2.4 Hospital Complications and Mortality in Patients with an ACS/AMI

Over the past several decades, substantial improvements in pharmacological and interventional therapies for ACS/AMI have been accompanied by reductions in in-hospital complications and in hospital death rates. According to data from the National Registry of Myocardial Infarction (NRMI) , adjusted hospital mortality declined among all patients by approximately one quarter between 1994 (10.4%) and 2006 (6.3%).[91]

In terms of clinical complications after an AMI, including atrial fibrillation (AF), heart failure, cardiogenic shock, ventricular fibrillation (VF), stroke, and complete heart block, few long-term assessments of contemporary, population-based estimates of the magnitude and trends in these important clinical complications according to age and sex after an ACS/AMI are available.

Factors Associated with Declines in Hospital Mortality

The factors contributing to the encouraging decline in mortality attributed to CHD seen nationally over the past nearly 40 years have not been fully elucidated, and the relative contributions of changing trends in the incidence and case-fatality rates of acute CHD overall, as well as in men and women of different age strata, remain incompletely understood.

Several studies have shown that the use of evidence-based treatments accounted for a significant reduction in mortality in patients with CHD. For example, a report from the CDC suggested that approximately 47% of this decrease was attributed to the increased utilization of effective cardiac treatments, including secondary preventive therapies after myocardial infarction or revascularization (11%), initial treatments for AMI or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other therapies (12%). Approximately 44% of the decline in the CHD death rate over the period 1980-2000 was attributed to changes in important coronary risk factors including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%), although these reductions were partially offset by increases in body-mass index and the prevalence of diabetes, which accounted for an increased number of deaths (8% and 10%, respectively).[92]

A review paper examining trends in outcomes associated with hospitalization for AMI estimated that the increase in use of aspirin, beta blockers, ACE inhibitors and coronary reperfusion therapy explained approximately three quarters of the decrease in the 30-day age and sex adjusted mortality rate from 1975-1995.[69] This study suggested that if other treatments (such as heparin or non-primary angioplasty) are included, up to 90% of the decrease in 30-day mortality can be explained by changes in treatment practices over the past several decades.

Age and Sex Differences in Hospital Complications and Mortality

Previous studies examining age and sex differences in hospital complications and deaths in the setting of AMI have demonstrated inconsistent results. Some studies found that older persons had higher rates of hospital complications and deaths compared to younger patients[51,93] and that women had higher rates of hospital complications and mortality compared with men.[94,95] On the other hand, several studies failed to find any association between age/sex and hospital complications/deaths.[81,85,86] For example, data from the NRMI-2 showed that, among patients less than 50 years of age, the mortality rate for women was more than twice that for men; however, these differences decreased with advancing age.[94] On the other hand, a recent report from the large AMIS Plus registry in Switzerland showed that women were, in general, no more likely to die during hospitalization for AMI than men, within various age categories and overall.[81] There are several possible explanations for these discrepant study results including differences in patient populations, study period, sample sizes, and the level of adjustment for major confounders. Age and sex differences in hospital outcomes including complications and deaths may be partially explained by differences in the extent of pre-hospital delay between men and women, and between younger and older patients.[18,52,86] Older patients and women are also more likely to have multiple complex co-morbidities present, including heart failure, hypertension, and diabetes[17,39,86-88] that may contribute to their higher risk of adverse outcomes compared to younger patients and men. Lastly, older patients and women have been shown to be less likely to be treated with effective cardiac medications and procedures compared to younger patients and men.[80,90,96]

Few contemporary population-based studies have examined whether differences in hospital outcomes observed in prior studies according to age and sex have changed over time or whether these gaps have narrowed between men and women and among patients of different age strata.

In the proposed study, contemporary trends in the occurrence of various hospital complications and short-term (in hospital and 30-day) mortality according to age and sex were examined using data from the WHAS, a long term, contemporary, population-based observational study of greater Worcester (MA) residents hospitalized with AMI at all area medical centers

1.3 Significance of Proposed Study

In summary, ACS/AMI is a significant and growing public health and clinical concern. Despite improving trends in short-term outcomes after an ACS/AMI, important gaps between men and women and among individuals of different ages may persist. Therefore, there is a need for contemporary epidemiologic research that systematically describes differences in extent of patients' pre-hospital delay, receipt of hospital treatments and outcomes, including mortality and complications, according to age and sex and to determine whether differences in these endpoints have changed over time. The findings of this proposed research will provide useful current information regarding age and sex differences in patients hospitalized with an ACS/AMI with regards to duration of pre-hospital delay, hospital management practices, and hospital outcomes that can inform the design of appropriate public health interventions and clinical guidelines to improve the prognosis of men and women of different ages with ACS/AMI.

1.4 Research Design and Methods

This dissertation consists of secondary data analyses of patients enrolled in the WHAS and the GRACE project. The purpose of the proposed study was to examine differences in the duration of pre-hospital delay, the receipt of evidence-based treatments, and in hospital complications and CFRs according to age and sex. A secondary study goal is to determine whether differences in these outcomes between men and women and among patients of different age strata have changed over time. A particular strength of this study is the use of long-term, contemporary data from two large registries of ACS/AMI from population-based and multinational perspectives. The WHAS is an ongoing population-based surveillance study which is examining long-term trends in the clinical epidemiology of AMI among residents of the Worcester metropolitan area hospitalized at all greater Worcester, MA, medical centers.[2,5] The GRACE project is a large multinational observational study of patients hospitalized with ACS at 106 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand.[7]

1.4.1 Study Designs, Participating Hospitals, and Patient Populations

1.4.1.1 The Worcester Heart Attack Study (WHAS)

The WHAS is an ongoing population-based investigation that is describing long-term trends in the clinical epidemiology of AMI among residents of the Worcester, MA, metropolitan area hospitalized at all 16 greater Worcester (MA) medical centers[2,5].

Fewer hospitals (n=11) have been included during recent study years due to hospital closures, mergers, or conversion to chronic care facilities. Data have been collected in this observational study on an approximate biennial basis since the initial study year of 1975, and continuing to the most recent year of investigation in 2005, which presently includes a total of 15 cohorts. The study years were originally selected due to funding availability and for purposes of examining changing trends in the principal study outcomes on an approximate alternating yearly basis. The city of Worcester is the second largest city in MA and is centrally located in New England. The Worcester SMSA is characterized by a diverse urban/suburban population whose demographic and socioeconomic characteristics are similar to national estimates. These socio-demographic characteristics, with the exception of race, reinforce the potential generalizability of findings from this stable population base, where outmigration rates remain extremely low.

Methods of Ascertainment for Newly Diagnosed Cases of AMI

Computerized printouts of primary as well as secondary discharge diagnoses of AMI and related acute and chronic coronary disease rubrics were obtained from all participating greater Worcester hospitals for the purpose of identifying newly diagnosed cases of AMI occurring during the study periods. The acute care general hospitals included 2 in the city of Worcester (UMass Memorial Health Care and St. Vincent/Worcester Medical Center), and 9 hospitals in the Worcester metropolitan area (Clinton, Harrington Memorial, Health Alliance, Henry Heywood, Hubbard, Marlboro, Metrowest, Milford-Regional and Wing). Once the computerized discharge diagnosis printouts were obtained from all greater Worcester hospitals, the appropriate (9th and/or

10th) International Classification of Disease (ICD) codes for CHD were reviewed by the PI and the project director for purposes of sample selection. The 9th revision ICD codes included codes 410-414 and 786.5 and the corresponding 10th revision codes of I20-I25 and R07. The vast majority of validated cases of AMI came from ICD-9 diagnostic rubric 410 (AMI), followed by a small number of cases from ICD rubric 411 (other acute and subacute forms of CHD). An extremely low yield of cases of definite AMI have come from ICD rubrics 412 (old MI), 413 (angina pectoris), 414 (other forms of chronic CHD), and 786.5 (chest pain); these latter disease categories primarily included patients with chronic manifestations of CHD or nonspecific chest pain.

Diagnostic Criteria for AMI and Study Inclusion/Exclusion criteria:

Cases of possible AMI treated at all greater Worcester medical centers selected were validated according to predefined criteria of AMI. The diagnosis of AMI was made on the basis of the well accepted criteria developed by the World Health Organization which includes clinical history, serum enzyme, and serial electrocardiographic findings, which has been utilized in a number of clinical and epidemiological investigations including the MONICA study.[97] These diagnostic criteria consist of:

- A typical history of prolonged chest pain suggestive of AMI that is not relieved by rest and/or use of nitrates

- Enzyme level elevations of CK and/or its isoenzyme subfraction (CK - MB)

- Serial ECG changes consistent with the presence of an evolving MI.

Patients who satisfied at least 2 of these 3 criteria, and were residents of the Worcester metropolitan area, since the study is population-based, were included in this study. Patients who developed AMI secondary to an interventional procedure or surgery were excluded from the study sample.

Data Collected from the Review of Hospital Medical Records

For each patient satisfying the diagnostic and geographic eligibility criteria, socio-demographic, medical history, and clinical data were abstracted from the medical records by trained study physicians and nurses. Information was collected about patient's age, sex, race, body mass index (height and weight), pre-hospital delay, comorbidities (e.g., angina, diabetes, hypertension, heart failure, stroke), AMI order (initial vs. prior), type (Q wave vs. non–Q wave), and location (anterior vs. inferior/posterior), receipt of hospital medications and coronary interventional procedures, the occurrence of clinically significant in-hospital complications including stroke, heart failure, atrial fibrillation, and cardiogenic shock, and hospital discharge status.

Characteristics of the WHAS Population over Time

Table 1.1 describes changes in the WHAS population over time. There have been relatively dramatic increases in the age profile of greater Worcester residents hospitalized with AMI as well as in the proportion of women. There has been a smaller proportion of patients presenting to WHAS with a history of angina, but a greater proportion of patients presenting with previously diagnosed diabetes, heart failure, MI and stroke. The increasing age and prevalence of serious comorbidities in patients currently hospitalized with AMI present significant challenges for the management of these complex high risk patients. In term of clinical complications, the proportion of patients developing AF has increased, but the proportions of patients developing heart failure, shock and stroke have remained relatively unchanged. In-hospital mortality rates have declined appreciably over time, despite the presence of an increasingly older patient population with a greater prevalence of comorbidities. The duration of pre-hospital delay has remained unchanged over time but length of stay has declined significantly over time.

Table 1.1 Characteristics of the Worcester Heart Attack Study (WHAS) Population Over Time

Characteristics	1975/1978 (n=1,626)	1990/1991 (n=1,614)	2003/2005 (n=2,060)
Age (median, yrs)	66.0	70.0	74.0
Male (%)	62.1	57.6	54.3
Medical history (%)			
Angina	24.5	27.3	18.7
Diabetes	22.1	26.6	34.4
Heart failure	13.8	16.8	25.9
MI	32.6	31.8	34.8
Stroke	5.4	9.2	12.0
Clinical complications (%)			
Atrial fibrillation	14.1	17.9	22.5
Heart failure	40.5	40.7	39.6
Stroke	NA	0.5	0.7
Shock	7.2	6.1	4.7
Hospital mortality (CFRs) (%)	20.8	14.8	9.1
Median (mean) of pre-hospital delay, hours	NA	2 (3)	2(4)
Mean of length of stay, days	18.4	15.6	5.2

1.4.1.2 Global Registry of Acute Coronary Events Project (GRACE)

The GRACE study is a large, multinational, observational study of patients hospitalized with ACS in 14 countries in North and South America, Europe, Australia, and New Zealand between 1999 and 2008. The objectives of GRACE are to improve the hospital and long-term outcomes of patients with ACS[7].

Participating Centers and Sampling Methods

Study hospitals were located in 18 cluster sites of 14 countries. Data collection activities began in April 1999 with the goal of collecting data on approximately 10,000 patients hospitalized with ACS on an annual basis. A total of four sites were included in the United States (Massachusetts, Michigan, North Carolina, and California), whereas an additional 16 sites were included from Canada, Europe, Australia, and New Zealand. The two geographic clusters in South America have recruited relatively more study hospitals than other clusters to provide a more descriptive overview of national practices in the management and outcomes of patients with ACS.

These geographic clusters were chosen to represent populations with varying demographic, clinical, and treatment characteristics as well as hospital systems of different sizes and treatment and diagnostic capabilities. A total of 46 hospitals were included at these population sites, representing hospitals of varying size, characteristics, and diagnostic and treatment capabilities. At the study clusters in which a population-based site (where ACS patients from geographically defined catchment areas) was considered either not feasible or not cost effective, a sample of hospitals representative of those from that region or country was selected and cases of ACS were included irrespective of the patient's geographic origin. A total of 47 hospitals were included at these study clusters. Where required, hospitals received approval from their local hospital's ethics or institutional review board, and signed, informed consent for follow-up contact was obtained from the patients at enrollment. For those sites using active surveillance for case identification, verbal or written consent was obtained from patients to review information contained in their medical charts.

Patients who died early during their index hospitalization were thereby excluded from study consideration at the sites where active case ascertainment was carried out. The impact of this and other exclusionary factors needed to be considered in interpreting hospital outcomes and the descriptive characteristics and treatment practices used in the respective study samples.

Patient Identification Approaches

To facilitate the review of medical records in a systematic manner, and accommodate the varying ways in which the data were collected, prospective ("warm" or active pursuit) and retrospective ("cold" or passive pursuit) surveillance approaches for identifying cases of ACS, similar to the MONICA Project[97] were adopted. In hospitals that used warm pursuit, eligible patients were identified during the index admission and medical records were reviewed on an ongoing basis after appropriate consent has been obtained, if necessary. In study sites that used the cold pursuit method of approach to case identification, hospital listings of persons discharged from participating hospitals were reviewed to identify potentially eligible cases with use of the International Classification of Diseases, Ninth Revision (ICD-9), codes 410 or 411 or corresponding codes in ICD-10. These charts were subsequently reviewed after the patient has been discharged from the hospital. The majority of study centers adopted warm pursuit whereas a limited number of centers used cold pursuit to identify cases of ACS.

Patients hospitalized with a discharge diagnosis of ACS constitute the primary sample of interest at the clusters where passive or cold pursuit surveillance was adopted. At the centers where warm pursuit surveillance approaches were used, patients with an admission diagnosis of ACS were studied irrespective of whether their final discharge diagnosis is ACS, another cardiac diagnosis, or non-cardiac disease. The medical records of patients with a primary or secondary discharge diagnosis of AMI (ICD-9 code 410) or unstable angina (ICD-9 code 411) were reviewed in their entirety at the study sites using passive surveillance. Previous surveillance studies have shown a relatively low yield of confirmed cases of ACS, particularly AMI, from other possible coronary disease diagnostic categories (eg, ICD-9 codes 412-414, 786.5). Thus, the medical records of patients with a discharge diagnosis of these latter diagnostic codes were not reviewed. As previously mentioned, at the study sites where active or warm pursuit surveillance was used, hospitalized patients with a suspected diagnosis of ACS were identified on a regular basis and charts were concurrently reviewed. Given the varying sizes of the populations under study and the number of patients hospitalized with a suspected or a discharge diagnosis of ACS, a sampling scheme was used to select possible cases of ACS for subsequent review. Each study site selected a final annual sample of approximately 600 cases of ACS from each study cluster spread out over the entire year.

GRACE inclusion/Exclusion criteria

- Must have one of the ACS as a presumptive diagnosis.
- Must be ≥18 years old.
- Must be alive at the time of hospital presentation.
- The qualifying ACS must not have been precipitated or accompanied by a significant comorbidity such as a motor vehicle crash, trauma, severe gastrointestinal bleeding, operation, or procedure. In-patients who were already hospitalized, for any reason, when ACS symptoms develop were not eligible for enrollment.
- Patients transferred into or out of a registry hospital could be enrolled regardless of the time spent at the transferring hospital.
- For patients transferred out of a registry hospital, data collection for the initial case report form ended with the transfer and indication of purpose of transfer.
- Patients could be re-enrolled in GRACE provided that 6 months or more passed since the prior enrollment. When a patient was re-enrolled, a new patient number must be assigned.
- The criteria for ACS must be met, with one exception: patients hospitalized for <1 day who died and did not meet the criteria could be enrolled provided that the cause of death was confirmed to be due to ACS.

Data Abstraction

A standardized data abstraction form was developed for study-wide use. The team of investigators developed the initial case report form, which was subsequently finalized for field use after pilot testing at each of the participating hospitals. Information was collected on patient demographic characteristics, medical history, duration of pre-hospital delay from the time of onset of acute symptoms to seeking medical care, presenting symptoms, electrocardiographic findings, clinical characteristics, use of cardiac medications and interventional procedures, and hospital-associated outcomes. Standardized definitions for patient-related variables and clinical diagnoses were used. All cases of confirmed ACS were assigned to 1 of the following categories: ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). Patients were diagnosed with STEMI when they had new or presumed new ST-segment elevation ≥1 mm seen in any location, or new left bundle branch block on the index or subsequent electrocardiogram with at least one positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent electrocardiogram had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in each hospital's laboratory were within the normal range. Full definitions can be found on the GRACE web site at www.outcomes.org/grace

Characteristics of the GRACE Population Over Time

Table 1.2 presents changing characteristics of the GRACE population over time. The mean age and sex distribution of study sample have been unchanged over time. There has been a lower proportion of patients presenting to GRACE hospitals with a history of angina, heart failure and renal disease, but a greater proportion of patients presenting with a history of diabetes. The proportion of patients presenting with a history of MI and stroke have unchanged. In term of clinical complications and death, the proportions of patients developing clinical complications and dying during hospitalization have declined over time. Pre-hospital delay (median) has remained unchanged whereas the length of hospital stay has declined in the most recent study years.

Table 1.2 Characteristics of the Global Registry of Acute Coronary Events (GRACE) Population Over Time

Characteristic	1999/2001 (n=16,951)	2002/03 (n=13,417)	2004/2005 (n=11,726)	2006/2007 (n=8,002)
Age (median, yrs)	67.0	66.9	67.4	66.7
Male (%)	66.0	66.4	66.7	67.4
Medical history (%)				
Angina	63.6	51.6	46.7	45.4
Diabetes	24.3	24.9	25.5	25.7
Heart failure	11.6	10.9	10.5	9.5
MI	31.0	30.1	30.7	31.7
Renal disease	8.1	7.1	8.1	7.8
Stroke	8.7	8.5	8.5	8.4
Clinical complications (%)				
Atrial fibrillation	9.1	8.4	7.2	6.4
Heart failure	17.2	13.7	10.7	9.3
Stroke	0.9	0.7	0.7	0.5
Shock	4.6	3.9	3.9	3.7
Hospital mortality (CFRs) (%)	6.0	5.7	5.0	4.6
Median (mean) of pre-hospital delay, hours	3 (76)	3 (94)	3 (24)	3 (31)
Mean of Length of stay, days	8.2	7.4	6.9	6.8

1.4.2 Measures

1.4.2.1 Aim 1: Association between age/sex and duration of pre-hospital delay: WHAS 1986-2005

Age was categorized into 3 strata: <65 years, 65-74 years, and ≥75 years. Age (categorized as 3 groups) and sex were the main independent variables. Duration of pre-hospital delay, which was defined as the time interval from the onset of symptoms suggestive of AMI to hospital arrival, was the main outcome. First, pre-hospital delay was modeled as a continuous variable. Second, duration of pre-hospital delay was categorized into 3 categories: 0-1.9; 2-5.9, and ≥6 hours to distinguish early from late responders to their symptoms of AMI based on the distribution of delay times in the present study sample and on findings from the previously published literature.

Candidate variables considered as potential confounders were chosen based on findings from prior studies. These potential confounding variables included study year, race (white vs. non-white), marital status (single, married, divorced, widowed),medical insurance (private vs. others), comorbidities (e.g., angina, diabetes, hypertension, stroke, PCI, CABG), AMI order (initial vs. prior), type (Q wave vs. non–Q wave) and location (anterior vs. other), type of AMI (NSTEMI or STEMI), and acute symptoms (chest pain, sweating, shortness of breath, nausea, left hand pain and others), time of acute symptoms onset (time of day and day of week), and do not resuscitate order (DNR) status.

1.4.2.2 Aim 2: Association between age/sex and hospital treatment practices: GRACE 1999-2008

Age was categorized into four strata: <65 years, 65-74 years, 75-84 years, and ≥85 years. Age (categorized as 4 groups) and sex were the main independent variables. The uses of single cardiac medications including aspirin, beta blockers, ACE inhibitors/ARBs, statins and the receipt of either PCI or CABG during hospitalization of patients with an ACS were the main outcomes for this analysis. Receipt of these treatments was assessed individually (yes/no). In addition, the use of multiple medications (3 or more and all 4 medications) (yes/no) was also assessed.

Candidate variables considered as potential confounders were chosen based on findings from prior studies. Potential confounding variables included study year, geographic region(Australia/NewZealand/Canada, Europe, South America and US), type of hospital (teaching vs. other), admission diagnoses (STEMI vs. NSTEMI/UA), medical history (eg, heart failure, hypertension, diabetes), DNR status and factors in the GRACE in-hospital risk model (systolic blood pressure, initial serum creatinine findings, heart rate, cardiac enzyme, Killip class, ST-segment deviation, and cardiac arrest at the time of hospital arrival for an ACS).[98]

1.4.2.3 Aim 3: Association between age/sex and hospital clinical complications, hospital mortality (CFRs), and 30-day mortality: WHAS 1975-2005

The key independent variables of age (3 groups: <65 years, 65-74 years, ≥ 75 years) and sex have been previously defined. The hospital CFRs of patients with AMI was the main outcome for this analysis. Information on hospital CFRs was collected through the review of hospital charts. The development of important clinical complications during hospitalization of patients with AMI was the secondary outcome including stroke, atrial fibrillation (AF), heart failure and cardiogenic shock. The occurrence of acute stroke is defined as the development of neurologic changes consistent with the presence of a stroke based on information contained in medical records and reviewed by a team of nurse and physician abstractors.[99] The criteria for AF include the documentation of AF in the physicians' progress notes, based on the review of hospital medical records, or occurrence of typical electrocardiographic changes consistent with a diagnosis of AF.[100] Heart failure is defined when there is clinical or radiographic evidence of pulmonary edema or bilateral basilar rales with an S3 gallop.[101] Cardiogenic shock is defined as a systolic blood pressure of less than 80 mm Hg in the absence of hypovolemia and associated with cyanosis, cold extremities, changes in mental status, persistent oliguria, or congestive heart failure.[102]

Additional secondary outcome was 30-day mortality. Patients with a validated diagnosis of AMI discharged from all Worcester SMSA hospitals have been followed on an annual basis through the review of records for additional hospitalizations, search of death certificates at state and local Divisions of Vital Statistics, and through use of the National Death Index. At the time of the present proposal, some form of additional follow-up has been obtained for more than 99% of discharged hospital survivors from the cohorts included to date with follow-up completed through 2007.

Candidate variables considered to be potential confounders were chosen based on findings from prior studies. Potential confounding variables included study year, demographic characteristics, medical history, clinical presentation, characteristics of AMI and hospital treatments. Demographic variables include race (white vs. non-white), marital status (single, married, divorced, widowed), insurance (private vs. others). Co-morbidities include history of angina, diabetes, hypertension, stroke, heart failure, and MI. Information on clinical presentation included pre-hospital delay, acute symptoms, and information on DNR status. Characteristics of AMI included AMI order (initial vs. prior), type (Q wave vs. non–Q wave) and location (anterior vs. other), type of AMI (NSTEMI or STEMI). Information on hospital treatment approaches (aspirin, ACE inhibitors, beta blockers, lipid agents, PCI, CABG, pacing and others) and length of stay were also collected.

1.4.3 Statistical Analysis

1.4.3.1 Descriptive Analysis and Graphical Analysis of Associations

The distribution of all independent and dependent variables was examined. This was primarily done to determine the appropriateness of model distributional assumptions for dependent variables (outcomes) and variability of independent variables (exposures/predictors) to assess the informational content as well as the choice to categorize a value or not. If the assumptions of normality were not met, transformation of the data was considered before categorizing outcomes or using non-parametric methods. Transformation was also guided by interpretability issues. In all model building described below, a careful examination was made of the functional association of variables. Lowess curves guided our examination and testing of linear vs. non-linear associations. The preference was to find simple polynomial curves if a linear association was not appropriate. Most models described below were used notation of simple linear association but more complex functional associations were possible if not likely.

1.4.3.2 Analysis for Study Aims 1-3:

In general, similar analytic approaches (univariate followed by multivariable modeling) were carried out to examine the three aims of the proposed study.

Aim 1: Association between age/sex and duration of pre-hospital delay

The possible association between age/sex and extent of pre-hospital delay was examined using two approaches. In the first approach, a median regression model was used to examine the association between age/sex with duration of pre-hospital delay (hours), taking into account the skewed distribution of pre-hospital delay. In addition, both multinomial logistic and ordered logistic regression models were created to determine the association of age/sex with our principal study outcome expressed as an ordinal variable (e.g., pre-hospital delay 0-1.9, 2-5.9, and ≥ 6 hours).

In each analysis, a series of regression models were used to examine the impact of demographic characteristics, comorbidities, and clinical presentation on the association between age/sex and pre-hospital delay. The first model included only age, sex, and study year. Model 2 further adjusted for other demographic factors and medical history of various cardiovascular diseases and comorbidities. Model 3 was further adjusted for AMI associated characteristics and acute presenting symptoms (see footnotes to each table for the list of controlling variables). To assess whether any age or sex differences in extent of pre-hospital delay have changed over time, 2-way and 3-way interaction terms between age, sex, and study year were created and included in each regression model. The evidence supporting an association between decreased pre-hospital delay and improved short-term outcomes is strongest in patients with STEMI; therefore we repeated all analyses in this patient subgroup.

Since 42% of the study sample had information missing from hospital records on extent of pre-hospital delay, we conducted a sensitivity analysis using a propensity-weighted method to assess whether the missing data influenced our primary study results.

Other modeling approaches included forward selection and backward elimination were considered and compared. Furthermore, since there may be clustered data (patients grouped by participating hospitals or regions), random effect models (random intercept and random slopes) were considered and compared.

Model equation:

$$\text{Log\_delay}=\beta_0+\beta_{1\text{-}3}\text{age group}_{1\text{-}3}+\beta_4\text{sex}+\beta5_{\text{-}n}(\text{confounders})+\beta_{n\text{-}m}\text{ interaction terms}+\varepsilon i$$

$$\varepsilon i \sim N(0,\delta)$$

Aim 2: Association between age/sex and the use of cardiac medications and interventional procedures

Logistic regression models were used to determine the overall associations between age/sex and the use of single evidence-based cardiac medications (eg, aspirin, beta blockers, ACE inhibitors/ARBs, and statins), the utilization of either PCI or CABG procedures, and the receipt of multiple medications (≥ 3 medications) during the patient's index hospitalization as well as in examining changing trends over time. Similar univariate analyses followed by multivariable regression modeling as described previously in aim 1 were performed. The analyses were performed among all eligible patients as well as in subgroups according to type of ACS (STEMI and NSTEMI/UA).

Model equation:

$$\text{logit}(p)= \beta_0+\beta_{1\text{-}4}\text{age group}_{1\text{-}4}+\beta_5\text{sex} + \beta_{6\text{-}n}(\text{confounders})+ \beta_{n\text{-}m}\text{interaction terms}$$

Aim 3: Association between age/sex and short-term outcomes

Logistic regression models were used to determine the association between age/sex and hospital complications and mortality outcomes (CFRs) and changing trends over time. Similar univariate analyses followed by multivariable regression modeling as described previously in aim 1 were applied. For 30-day mortality outcome, the Cox Proportional Hazards (PH) models were used to examine unadjusted and adjusted associations between age/sex and this outcome. Proportional Hazards assumption was checked graphically. A similar multiple regression approach described previously in aim 1 was applied.

Model equation:

$$\log[h(t)/h_0(t)] = \beta_{1\text{-}3}\text{age group}_{1\text{-}3}+\beta_4\text{sex}+ \beta_{5\text{-}n}(\text{confounders})+ \beta_{n\text{-}m}\text{interaction terms.}$$

1.4.4 Power Calculation

Aim1: The analysis in aim 1 included approximately 6,000 patients with AMI from 1986-2005. We used estimations for means of duration of pre-hospital delay and theirs standard deviations (SDs) for men and women and patients in different age groups from the NRMI study.[52] With an available sample size of approximately 6000 patients with AMI, we had power of greater than 90% to detect estimated differences in means of duration of pre-hospital delay between men and women and in patients of different age groups at α level of 0.05 (Table 1.3).

Table 1.3 Power Calculation for Hypothesis in Aim 1

Patient groups	n	Estimated mean of pre-hospital delay (mins)	SD (mins)	Power
age <65 yrs (reference)	2,160	107	0.3	
65-74 yrs	1,560	117	0.4	>90%
≥75 yrs	2,280	126	0.5	>90%
Men (reference)	3,600	114	0.2	
Women	2,400	125	0.4	>90%

Aim2: The analysis in aim 2 included approximately 50,000 patients with ACS from 1999 to 2007. We used estimations of proportions of the use of single cardiac treatments for men and women and patients in different age groups from the NRMI study.[83] With this sample, we had power of more than 80% to detect estimated differences of 2-4% in proportions of the uses of single treatment approaches (range: 60%-90% in this population) during hospitalization between men and women and in patients of different age groups at α level of 0.05 (Table 1.4).

Table 1.4 Power Calculation for Hypothesis in Aim 2

Patient groups	n	Difference in hospital treatment	Power
Age <65 yrs (reference)	22,500	0%	
65-74 yrs	13,000	2%	>80%
≥75-84 yrs	10,500	3%	>80%
85 yrs	4,000	4%	>80%
Men (reference)	33,000	0%	
Women	17,000	3%	>80%

Aim3: The analysis in aim 3 included 13,000 AMI patients from 1975 to 2005. We used estimations of in-hospital CFRs for men and women and patients in different age groups from the NRMI.[103] With this sample, we had power of greater than 80% to detect differences of 2 % in proportions of in hospital CFRs between men and women, and 4-12% differences in hospital mortality in patients of different age groups at α level of 0.05 (Table 1.5).

Table 1.5. Power Calculation for Hypothesis in Aim 3

Patient groups	n	Difference in hospital CFRs	Power
Age <65 yrs (reference)	4,680	0	
65-74 yrs	3,380	4% (8% vs. 4%)	>90%
≥75yrs	4,940	8% (12% vs. 4%)	>90%
Men (reference)	7,800	0	
Women	5,200	2% (18% vs. 16%)	>80%

This study has been reviewed and approved by University of Massachusetts Medical School IRB.

CHAPTER II

Age and Sex Differences in Duration of Pre-hospital Delay, and Changing Trends, in Patients Hospitalized with Acute Myocardial Infarction

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Abstract

Background

The prompt administration of coronary reperfusion therapy for patients with an evolving acute myocardial infarction (AMI) is crucial in reducing mortality and the risk of serious clinical complications in these patients. However, long-term trends in extent of pre-hospital delay, and factors affecting patient's care seeking behavior, remain relatively unexplored, especially in men and women of different ages. The objectives of this study were to examine the overall magnitude, and 20 year trends (1986-2005), in duration of pre-hospital delay in middle-aged and elderly men and women hospitalized with AMI.

Methods

The study sample consisted of 5, 967 residents of the Worcester, MA, metropolitan area hospitalized at all greater Worcester medical centers for AMI between 1986 and 2005, who had information available about duration of pre-hospital delay.

Results

Compared with men <65 years, patients in other age-sex strata exhibited longer pre-hospital delays over the 20-year period under study. The multivariable adjusted medians of pre-hospital delay were 1.96, 2.07, and 2.57 hours for men <65 years, men 65 -74 years, and men ≥75 years, and 2.08, 2.33, and 2.27 hours for women <65 years, women 65-74 years, and women ≥75 years, respectively. These age and sex differences have narrowed over time which has been largely explained by changes in patient's comorbidity profile and AMI associated characteristics.

Conclusions

Our results suggest that community-based educational interventions remain needed to encourage patients to seek medical care promptly after the development of symptoms suggestive of AMI to maximize the benefits of currently available treatment modalities.

Word count: 249

Key words: Pre-hospital Delay, Acute Myocardial Infarction, Age and Sex differences.

2.1 Introduction

The prompt administration of reperfusion therapy to patients with an evolving acute myocardial infarction (AMI) can be crucial to reducing mortality and serious complications in these patients. Results from prior studies have shown that reperfusion treatment is most effective if patients with ST-segment elevation myocardial infarction are treated promptly, particularly within one hour of acute symptom onset.[3,4] Although an association between extent of pre-hospital delay and outcomes after non-ST-segment elevation myocardial infarction has not been firmly established, it is assumed that earlier evaluation and management of these patients would be preferable.

Despite the importance of seeking medical care as soon as possible after the onset of acute coronary symptoms, upwards of one half of patients with AMI delay seeking medical care by more than 2 hours, [17,19] and upwards of one quarter of patients with AMI delay seeking care by more than 6 hours. [17,19,20] Several previous studies have also suggested that extent of pre-hospital delay is associated with delays in the receipt of effective hospital therapies,[19,104] primarily coronary reperfusion therapy.

Although considerable efforts have been expended to educate patients about the symptoms of AMI, and the importance of seeking medical care promptly, the care seeking behavior of patients hospitalized with AMI has not changed appreciably.[18,23,24] The Rapid Early Action for Coronary Treatment (REACT) trial, a randomized, controlled trial of 20 pair-matched U.S. communities, was designed to examine the effects of a community–wide intervention on patient delay and emergency medical service use in patients with acute coronary disease.[25,26] The intervention targeted the mass media, community organizations, and professional, public, and patient education. Despite the intensive 18-month long intervention, time from symptom onset to hospital arrival for patients with acute chest pain did not change significantly between intervention and control communities over the course of this trial. A recent trial (2000-2006) using a nurse-counseling intervention for patients with documented coronary heart disease (CHD) that focused on information, emotional issues, and social factors also failed to reduce extent of pre-hospital delay in approximately 3,500 patients with documented CHD.[27]

A limited number of previous studies have examined age and sex differences in duration of pre-hospital delay in patients hospitalized with AMI. Several studies have found that women are more likely to delay seeking timely medical care compared with men [23,24,29,41,44] whereas other studies have suggested that there are no sex differences in patterns of delay.[17,18] The majority of prior studies have demonstrated that older individuals are more likely to delay seeking medical care after developing symptoms of AMI,[18,23,24] though several studies have failed to find differences in medical care seeking behavior according to age.[28,29,44] More importantly, few studies have examined whether age and sex differences in extent of delay in patients hospitalized with AMI have changed over time, particularly from the more generalizable perspective of a population-based investigation.[18,23,24]

Due to national interest in age and sex differences in disease outcomes, the increasing number of women and older individuals hospitalized with acute coronary disease, and because a number of prior studies have not controlled for the effects of various potentially confounding variables in examining age and sex differences in extent of pre-hospital delay, it is important to assess long-term trends in delay patterns among different age-sex groups to see if improvement, or lack thereof, is occurring in some groups but not others. Targeting of educational efforts to high-risk groups to decrease extent of pre-hospital delay may also have an important impact on patient related outcomes. Therefore, we examined age and sex differences, as well as 20 year trends (1986-2005), in duration of pre-hospital delay in residents of a large central New England metropolitan area hospitalized with validated AMI at all central Massachusetts medical centers.[6,105]

2.2 Methods

The Worcester Heart Attack Study is an ongoing population-based investigation that is examining long-term trends in the incidence and case-fatality rates of AMI among residents of the Worcester metropolitan area hospitalized at all 16 greater Worcester medical centers in 15 biennial periods between 1975 and 2005.[6,105] Fewer hospitals (n=11) have been included during recent study years due to hospital closures, mergers, and conversion to chronic care facilities.

The details of this study have been described previously.[6,105] In brief, computerized printouts of patients discharged from all greater Worcester hospitals with possible AMI were obtained, and International Classification of Disease (ICD) codes for possible AMI (ICD-9 codes 410-414, 786.5) were reviewed for purposes of sample selection. The vast majority of validated cases of AMI came from ICD-9 diagnostic rubric 410 (AMI), followed by a small number of cases from ICD rubric 411 (other acute and subacute forms of CHD). Cases of possible AMI treated at all greater Worcester medical centers were independently validated according to predefined criteria for AMI. The diagnosis of AMI was made on the basis of the well accepted criteria developed by the World Health Organization which includes a suggestive clinical history, serum enzyme elevations, and serial electrocardiographic findings during hospitalization; these criteria have been previously utilized in other population-based investigations of AMI including the MONICA study.[97]

Patients who satisfied at least 2 of these 3 criteria, and were residents of the Worcester metropolitan area, were included in this population-based investigation. Patients, who developed symptoms of AMI after hospital admission, or after an interventional procedure or surgery, were excluded as were patients with an unknown time of acute symptom onset.

Data Collection

Information about patient's demographic characteristics, medical history, clinical presentation, hospital treatment approaches, and hospital discharge status was abstracted from the hospital medical records of patients with confirmed AMI. Pre-hospital delay was defined as the time interval between the onset of symptoms suggestive of AMI and arrival time in the emergency department.[18,104] This information was collected by our trained nurse and physician reviewers who reviewed any information they could find in hospital medical records which described extent of pre-hospital delay from emergency personnel, nurses, and physicians notes. Information on pre-hospital delay was collected in minutes (as a continuous variable). This variable was further categorized according to cut-points that had been commonly utilized in the published literature, based on the distribution of our data, and according to what we considered to be clinically meaningful cut-points of pre-hospital delay.

While information about age was collected from hospital medical records as a continuous variable, we described age- specific differences in extent of pre-hospital delay using categories (<65 years, 65-74 years, and ≥ 75 years) that have been previously used in this and in other investigations for ease of reporting and for consistency with the literature. Candidate variables considered as potential confounders of the association between age/sex and pre-hospital delay were chosen based on findings from prior studies including study year, race (white vs. non-white), marital status (single, married, divorced, widowed), comorbidities (e.g., heart failure, diabetes), time of hospital admission (weekday vs. weekend), time of day (12 am-5:59 am; 6 am-11:59 am; 12 pm-5:59 pm and 6 pm-11:59 pm), and AMI order (initial vs. prior), type (Q wave vs. non–Q wave) and location (anterior vs. other). Information about whether the AMI was a non–ST-segment elevation myocardial infarction (NSTEMI) or an ST-segment elevation myocardial infarction (STEMI) was recorded beginning in 1997.

Data Analysis

Categorical data were compared between patients who delayed ≥2 hours or ≥6 hours, and those who delayed for shorter intervals, using the chi-square test. Distributions of continuous variables were checked and some variables were not normally distributed (e.g., serum triglycerides); therefore, Wilcoxon sum rank tests were used to compare the values of all variables between various patient groups according to extent of delay (e.g., <2 hours vs. ≥2 hours) for consistency. Patient characteristics were also analyzed according to age and sex (data not shown).

We examined the possible association between age/sex and extent of pre-hospital delay using two approaches. In the first approach, we used a median regression model to examine the association between age/sex with duration of pre-hospital delay (hours), taking into account the skewed distribution of pre-hospital delay. In addition, we created both multinomial logistic and ordered logistic regression models to determine the association of age/sex with our principal study outcome expressed as an ordinal variable (e.g., pre-hospital delay 0-1.9, 2-5.9, and ≥ 6 hours). Results were similar, and the assumptions of ordered logit were met, so we reported the results from our ordered logistic regression model.

In each analysis, a series of regression models were used to examine the impact of demographic characteristics, comorbidities, and clinical presentation on the association between age/sex and pre-hospital delay. The first model included only age, sex, and study year. Model 2 further adjusted for other demographic factors and medical history of various cardiovascular diseases and comorbidities. Model 3 was further adjusted for AMI associated characteristics and acute presenting symptoms (see footnotes to each table for the list of controlling variables). To assess whether any age or sex differences in extent of pre-hospital delay have changed over time, 2-way and 3-way interaction terms between age, sex, and study year were created and included in each regression model. Since the evidence supporting an association between decreased pre-hospital delay and improved short-term outcomes is strongest in patients with STEMI, we repeated all analyses in this patient subgroup.

Since 42% of the study sample had information missing from hospital records on extent of pre-hospital delay, we conducted a sensitivity analysis using a propensity-weighted method to assess whether the missing data influenced our primary study results. We constructed logistic regression models predicting missing vs. non-missing data on extent of pre-hospital delay using baseline characteristics which yielded a c statistic of 0.70. Propensity scores for non-missing data were calculated for each patient. We estimated the median regression models weighted for 1/propensity score for missing data and compared the results with analyses among patients with information available on pre-hospital delay. All covariates included in our analyses had missing information in less than 5% of cases; inasmuch, missing data were not imputed.

We also used random effect models (random intercept) to assess whether the different patient clusters within participating hospitals might have affected our observed results. To examine the impact of hospital level effects, we estimated linear random effect models with log of pre-hospital delay as the outcome.

2.3 Results

A total of 10,310 patients were hospitalized with validated AMI at all greater Worcester medical centers during the 11 study years between 1986 and 2005. Patients who had information missing on pre-hospital delay (42%; n=4,334) were more likely to be older and women, to have a history of diabetes, hypertension or heart failure, to have developed important clinical complications or to have died during hospitalization, and were less likely to have reported chest pain, and to have an initial, Q-wave, or anterior MI compared with patients who had information available on delay time (Appendix 2.1).

The final study sample consisted of 5,976 patients in whom information on duration of pre-hospital delay was available. The average age of this sample, which was comprised of approximately three-fifths men, was 67.5 years; of these, 40% were <65 years, 26% were between the ages of 65-74 years, and 34% were ≥75 years. Women were considerably older than men at the time of hospital admission (means: 73 years vs. 64 years, $p<0.001$). Among 2,771 patients who were hospitalized for AMI between 1997 and 2005, approximately 47% were diagnosed as having STEMI at the time of hospital admission.

Patient Characteristics According to Duration of Pre-Hospital Delay

Patients who delayed ≥2 hours in seeking medical care after the onset of symptoms suggestive of AMI were more likely to be older (≥65 years), female, and widowed compared to those who delayed <2 hours (Table 2.1). Patients who delayed seeking medical care were more likely to have a history of diabetes, hypertension and heart failure, and present at greater Worcester hospitals from 6 am to 6 pm; on the other hand, these patients were less likely to have developed a Q-wave and STEMI and to report chest pain, shortness of breath, or diaphoresis than patients who sought medical care at an earlier time. Patients who delayed seeking medical care were more likely to present with higher heart rates and systolic blood pressure on admission compared to patients who exhibited shorter delay (Table 2.1). Demographic and clinical differences between patients who delayed ≥6 hours in seeking medical care and those who delayed < 6 hours are also displayed in Table 2.1.

Pre-hospital Delay in Patients Hospitalized with AMI and Trends over Time

The overall median duration of pre-hospital delay in our total study population was 2 hours (mean: 3.6 hours). The proportions of patients who delayed <1 hour , 1-1.9 hours, 2-3.9 hours, 4-5.9 hours, 6-11.9 hours, and ≥12 hours were 18%, 28%, 25%, 9%, 11%, and 9%, respectively (Figure 2.1). Women delayed seeking medical care significantly longer than men (Medians: 2.2 hours vs. 2.0 hours, $p<0.001$). The median durations of pre-hospital delay were 2.0, 2.1, and 2.4 hours in patients <65 years, 65 -74 years, and in those ≥75 years, respectively ($p<0.001$).

Duration and distribution of pre-hospital delay for patients further stratified according to age and sex are presented in Table 2.2. Over the 2 decade long period under study, duration of pre-hospital delay in patients hospitalized with AMI was relatively unchanged (Figure 2.2). Similar patterns in the delay time distributions were observed between 1986 and 2005. For example, the proportion of patients who delayed ≥2 hours and ≥6 hours were 53.6% and 18.4%, respectively, in 1986/1988 (initial 2 study years), and were 52.2% and 17.4%, respectively, in 2003/2005 (2 most recent study years).

Pre-hospital Delay in Patients Hospitalized with AMI According to Age and Sex

Delay Time Modeled as a Continuous Outcome

A significant interaction between age and sex in relation to duration of pre-hospital delay was found when pre-hospital delay was examined as a continuous outcome (Table 2.3). Among patients <65 years, there were no differences in pre-hospital delay between men and women. Among patients 65 -74 years, women were more likely to delay seeking medical care compared with men; however, among patients ≥75 years, men were more likely to have delayed seeking medical care compared with women.

Overall, compared with men <65 years, other groups, with the exception of women <65 years, delayed seeking medical care significantly longer in all 3 regression models (Table 2.2, model 3). Compared with men <65 years, duration of pre-hospital delay increased by 0.11 and by 0.61 hours for men 65 -74 years and men ≥75 years, and by 0.12, 0.37, and 0.31 hours for women <65 years, women 65-74 years, and women ≥75 years, respectively (Table 2.3 model 3). In absolute terms , the adjusted medians of pre-hospital delay were 1.96, 2.07, and 2.57 hours for men <65 years, men 65 -74 years, and men ≥75 years, and 2.08, 2.33, and 2.27 hours for women <65 years, women 65-74 years, and women ≥75 years, respectively (Table 2.3, model 3).

The significant 3- way interactions among age, sex, and study period in model 1 (p=0.004) indicated that the overall age and sex differences in extent of pre-hospital delay have changed over time (Table 2.3, figure 2.3A). Adjustment for other variables and comorbidities (particularly a history of diabetes) made the interaction between age, sex, and study period no longer statistically significant (p=0.18), suggesting that more recent trends in the increasing frequency of important comorbidities partially explained the narrowing in age and sex differences over time in extent of pre-hospital delay (Table 2.3, Figure 2.3B). Additional adjustment for clinical presentation and AMI associated characteristics further contributed to these narrowing trends (Table 2.3, Figure 2.3C).

Results from a propensity-weighted adjustment, which took into account missing data on delay time, yielded similar results (Appendix 2.2). In random intercept models (outcome was log of pre-hospital delay) assessing the effect of different patient clusters within hospitals, we obtained a within hospital correlation of 0.04; the estimated coefficients and standard errors were similar to models without the random effect, suggesting that the effects of cluster data by hospitals were small.

Delay Time Modeled as an Ordinal Outcome

Overall odd ratios for delaying seeking medical care after the onset of symptoms suggestive of AMI, stratified according to age and sex, showed that, compared with men <65 years, men ≥75 years and women ≥65 years were significantly more likely to delay seeking medical care in all 3 regression models (Table 2.4). The interaction between age and sex was significant in models further adjusted for clinical presentation only (Table 2.4, model 3); among patients <65 years, there were no differences in pre-hospital delay between men and women. Among patients 65 -74 years, women were more likely to delay seeking medical care compared with men; however, among patients ≥75 years, men were more likely to delay seeking acute medical care compared with women.

Subgroup analyses in patients with STEMI (n=1,299)

In the subgroup of patients with STEMI (n=1,299), there was a non- significant 3 way interaction among age, sex, study year, and extent of pre-hospital delay (p=0.88). Furthermore, there was no evidence of any interaction between age and sex in relation to extent of pre-hospital delay (p=0.24)

In absolute terms, the adjusted medians of pre-hospital delay were 1.73, 1.76, and 1.89 hours for men <65 years, 65-74 years, and ≥75 years, and 1.66, 2.20, and 2.07 hours for women <65 years, 65-74 years, and for those ≥75 years, respectively.

2.4 Discussion

The results of this study in nearly 6,000 residents of a large central New England metropolitan area hospitalized with AMI found that patient's care seeking behavior after the onset of acute coronary symptoms has been relatively unchanged between 1986 and 2005. In addition, and compared with younger men, other age/sex groups were significantly more likely to have delayed seeking medical care after the onset of symptoms suggestive of AMI, with the exception of women <65 years. Differences in duration of pre-hospital delay (continuous outcome) according to age and sex have narrowed over time and were largely explained by changes in patient's comorbidities and AMI associated characteristics during the years under study.

Our results are consistent with the findings from previous studies[18,23,24] which have shown that older persons were significantly more likely to delay seeking medical care than younger individuals. Older patients are more likely to have atypical symptoms of AMI compared with younger patients.[36,47,50] Older patients are also more likely to have additional comorbidities present, including diabetes, hypertension, and heart failure,[20,39,52] which may make patients misinterpret the symptoms of AMI and delay seeking medical care. Other factors such as limited health care access, denial and embarrassment, and living alone may also have contributed to the longer delays noted in older persons.

Sex differences in extent of delay were found in patients ≥65 years, but not in patients <65 years, which is consistent with the findings from previous studies.[36,44] For example, findings from the Northern Sweden MONICA myocardial infarction registry, which included approximately 6,500 patients with a confirmed AMI over the period 1989-2003, demonstrated that among patients <65 years there were no sex differences in duration of pre-hospital delay; on the other hand, among patients 65-74 years, women were more likely to delay seeking medical care than men.[36] Since there was no upper age cap in our study, we were able to further stratify older patients into two subgroups, finding that women were more likely to delay seeking medical attention than men among patients 65-74 years old, whereas men 75 years and older were more likely to delay seeking hospital care compared with older women. This may be partially explained by the fact that women <75 years old in the present study had more comorbidities present, and were less likely to have developed a Q wave and/or STEMI, compared with men; on the other hand, in patients 75 years and older this sex profile was reversed. Previous studies have shown that these comorbidities are associated with patient's care seeking behavior.[20,52,106]

We also found that age and sex differences in duration of pre-hospital delay have narrowed over time, and were largely explained by changes in patient's comorbidity profile and AMI associated characteristics. These findings are consistent with the results from a limited number of other studies.[24,52] Data from the National Registry of Myocardial Infarction, which included nearly 480,000 patients hospitalized with STEMI, suggested that age and sex differences in pre-hospital delay slightly narrowed between 1995 and 2004.[52]

Although we found that age and sex differences in pre-hospital delay have narrowed over time, our findings suggest that overall duration of pre-hospital delay has remained relatively constant over time and that approximately one half of patients who presented with AMI to metropolitan Worcester hospitals did so after delaying for at least 2 hours following the onset of symptoms suggestive of AMI; these results are consistent with the findings from prior studies.[17,19,20] In the present study, all age-sex subgroups experienced a relatively long duration of pre-hospital delay (medians > 1.9 hours). These results reinforce the need for the development of intervention programs to educate patients about the importance of seeking medical care promptly after the onset of symptoms suggestive of AMI. This is because excessive delay may increase an individual's risk of sudden cardiac death and may also be associated with delays in the receipt of effective hospital therapies, primarily coronary reperfusion therapy.

Several community intervention trials have been undertaken with the expressed purpose of reducing extent of pre-hospital delay in patients with signs and symptoms of AMI; however, 2 recent trials which employed both broad population approaches and more personalized interventions[107,1087] failed to reduce extent of pre-hospital delay. These and earlier findings suggest that our understanding of the reasons for care seeking behavior in patients with symptoms suggestive of AMI is inadequate as may be our educational approaches and intervention efforts. The findings from the present study demonstrated that both older men and women were at greatest risk for prolonged delay.

Inasmuch, interventions designed to reduce pre-hospital delay might be primarily focused on these high risk groups and address specific issues that may contribute to delay in these individuals.

Further in depth qualitative studies should be carried out in older men and women to identify the reasons why these high risk groups fail to react promptly to their symptoms of acute coronary disease focusing on their levels of cognition, knowledge, and attitudes toward health care. Further studies remain needed to explore the effects of educational attainment, extent of insurance coverage, neighborhood level characteristics, psychosocial variables, and other factors that may serve as either facilitators or obstacles by patients to the more timely seeking of medical care, particularly of those factors that may be amenable to change.

Study Strengths and Limitations

This study has several strengths including its population-based design that captured all validated cases of AMI occurring among residents of the Central Massachusetts area hospitalized at all greater Worcester medical centers over a 20 year period. However, several limitations need to be kept in mind in interpreting the present findings. First, a considerable proportion of patients had data missing on pre-hospital delay and missing data differed by age and sex; therefore, our findings should be interpreted with appropriate caution. However, we used propensity-weight adjusted analysis to take into account missing data and we also examined some simple estimates of median delay times assuming missing patients had 50% higher or lower delay times. The combined estimated delay time (actual + imputed missing) resulted in similar patterns of differences by age and sex. Second, information about pre-hospital delay was abstracted from hospital medical records whose documentation may have varied over time and according to patient's demographic and/or clinical characteristics. In addition, the majority of the study population was White; therefore, the generalizability of our findings may be limited. We did not have information available on several patient associated characteristics (e.g., socioeconomic status) which may have confounded some of the observed associations, nor did we have information on the reasons why patients delayed seeking medical care and how these contributory factors may have differed according to age and sex. Finally, since patients who died out of the hospital from AMI were not included, the findings may only apply to patients hospitalized with AMI; the direction and magnitude of the associations between age/sex and pre-hospital delay in patients who died before reaching the hospital may be different from those who are hospitalized.

2.5 Conclusions

The results of our study suggest that duration of pre-hospital delay has remained relatively unchanged over time, and the elderly are more likely to delay seeking medical attention after the development of symptoms suggestive of AMI compared to younger persons. While public educational campaigns and interventions targeted at older individuals are needed to encourage patients to seek medical care promptly to maximize the benefits of currently available therapies, further research remains needed to identify why all patients, including men and women of different ages, delay seeking medical care in the setting of AMI and the best means to encourage patients to seek medical care in a timely fashion.

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Table 2.1 Characteristics of Patients with Acute Myocardial Infarction (AMI) according to Extent of Delay in Seeking Medical Care

Characteristic	< 2 hours (n=2,762)	≥ 2 hours (n=3,267)	P-value	< 6 hours (n=4791)	≥ 6 hours (n=1,238)	P-value
Age (years, mean)	66.2	68.7	0.004	67.4	68.2	0.15
Age (years, %)						
<65	43.5	36.2	<0.001	40.3	36.4	0.002
65-74	25.7	26.2		25.7	26.9	
≥75	30.8	37.6		23.0	36.6	
Female (%)	36.2	40.8	<0.001	38.4	39.7	0.43
White (%)	94.6	94.8	0.82	94.5	95.4	0.26
Marital Status (%)						
Single	10.9	9.7	0.001	10.1	10.7	0.71
Married	63.3	61.1		62.5	60.3	
Divorced	7.1	6.4		6.6	6.9	
Widowed	18.7	22.7		20.6	21.9	
Medical history (%)						
Atrial fibrillation	9.4	9.3	0.85	9.3	9.6	0.76
Diabetes mellitus	24.9	30.1	<0.001	27.2	29.8	0.07
Hypertension	58.4	61.6	0.012	60.6	58.4	0.17
Heart failure	15.0	16.9	0.047	16.0	16.2	0.90
Stroke	8.7	9.2	0.55	8.9	9.1	0.84
PCI*	34.9	34.7	0.94	36.6	25.5	0.06
CABG	6.4	5.4	0.12	6.0	5.2	0.25
AMI characteristics (%)						
Initial	66.4	67.1	0.52	65.9	70.1	0.005
Q-wave	42.8	39.2	0.006	40.3	42.8	0.13
Anterior	30.3	31.8	0.23	30.7	32.9	0.15
STEMI†	52.6	41.7	<0.001	48.4	40.5	0.001
Acute symptoms (%)						

Chest pain	39.5	35.0	<0.001	38.1	33.2	0.002
Shortness of breath	28.5	24.6	0.001	27.3	22.9	0.002
Nausea	18.4	16.9	0.13	17.9	16.6	0.27
Diaphoresis	25.5	19.3	<0.001	23.6	15.9	<0.001
Fatigue	5.3	5.5	0.80	5.2	6.1	0.21
Weekday hospitalization (%)	70.6	71.5	0.19	71.2	72.4	0.40
Time of day hospitalization (%)						
12am-5:59 am	21.6	18.6	<0.001	22.1	12.0	<0.001
6-11:59 am	30.6	32.2		29.8	37.9	
12 pm-5:59 pm	25.2	28.7		25.8	31.9	
6 pm-11:59 pm	22.7	20.4		22.3	18.2	
DNR order‡ (%)	14.4	15.8	0.20	15.1	15.1	0.97
Clinical presentations, median						
Heart rate, beats/min	80	82	<0.001	80	83	0.001
Systolic BP, mmHg	142	145	0.018	144	145	0.36
Diastolic BP, mmHg	80	80	0.89	80	80	0.55
BMI (kg/m2)¶	27.1	27.0	0.31	27.1	26.8	0.59
Laboratory findings, median						
Cholesterol (mg/dl)	198	201	0.14	199	203	0.08
LDL (mg/dl)	109	112	0.18	109	116	0.034
Triglyceride (mg/dl)	121	123	0.97	120	130	0.34
Glucose (mg/dl)	145	147	0.27	147	142	0.019
Creatinine (mg/dl)	1.1	1.1	0.56	1.1	1.1	0.99

*Data on history of PCI were recorded beginning in 2003 and available for 546 patients.

†Data were recorded beginning in 1997 and available for 2,771 patients.

‡Data were recorded beginning in 1991 and available for 4,384 patients.

¶Data were recorded beginning in 1995 and available for 2,931 patients.

Table 2.2 Unadjusted Pre-hospital Delay Duration and Distribution according to Age and Sex

	Men			Women		
	<65y	65-74y	≥ 75y	<65y	65-74y	≥ 75y
Mean (SD), hour	4.00 (5.8)	4.65 (8.0)	5.21 (9.3)	4.50 (7.6)	5.00 (7.0)	4.63(6.4)
Median (IQR), hour	1.92 (1.00-4.17)	2.00 (1.00-4.65)	2.25 (1.25-5.18)	2.00 (1.03-4.67)	2.43 (1.30-5.50)	2.28 (1.22-5.10)
Distribution (%)						
0-1.9 h	51	47	39	47	41	41
2-5.9 h	30	32	38	34	36	38
≥ 6 h	19	21	23	19	23	21

SD: Standard deviation; IQR: inter-quartile range

Table 2.3 Overall Association between Age/Sex and Duration of Pre-hospital Delay

	Men			Women			P value†	P value‡
	< 65 y	65-75 y	≥ 75 y	< 65 y	65-75 y	≥ 75 y		
Difference in Median of Pre-hospital Delay (95% CIs), hours								
Model 1	0	0.12	0.62	0.13	0.48	0.4	0.001	0.004
	reference	(-0.07; 0.30)	(0.43; 0.81)	(-0.09; 0.36)	(0.27; 0.70)	(0.23;0.57)		
Model 2	0	0.12	0.55	0.14	0.37	0.37	0.10	0.18
	reference	(-0.13; 0.36)	(0.29; 0.82)	(-0.16; 0.44)	(0.07; 0.66)	(0.10;0.65)		
Model 3	0	0.11	0.61	0.12	0.37	0.31	0.001	0.69
	reference	(-0.10; 0.32)	(0.39; 0.84)	(-0.14; 0.37)	(0.21; 0.72)	(0.08;0.55)		
Absolute Medians of Pre-hospital Delay (95% CIs), hours								
Model 1	1.89	2.01	2.51	2.02	2.37	2.29	0.001	0.004
	(1.78-1.99)	(1.85-2.15)	(2.35-2.66)	(1.82-2.22)	(2.18-2.56)	(2.15-2.42)		
Model 2	1.94	2.06	2.49	2.08	2.31	2.31	0.10	0.18
	(1.79-2.09)	(1.86-2.26)	(2.29-2.70)	(1.82-2.34)	(2.06-2.56)	(2.11-2.52)		
Model 3	1.96	2.07	2.57	2.08	2.33	2.27	0.001	0.69
	(1.83-2.09)	(1.90-2.24)	(2.40-2.75)	(1.85-2.30)	(2.22-2.63)	(2.10-2.45)		

Model 1: Included age, sex, and study year.

Model 2: Further adjusted for race, marital status, and history of angina, diabetes, heart failure, hypertension, stroke, and CABG.

Model 3: Further adjusted for clinical presentation including day of week admission, time of day, chest pain, AMI order (initial vs. prior), AMI type (Q wave vs. non-Q wave), and AMI location (anterior vs. inferior/posterior).

Notes: Information on DNR and STEMI was recorded beginning in 1991 and 1997, respectively; therefore, they were not included as controlling variables in regression model #3.

† p values for interaction between age and sex

‡ p values for interaction among age, sex, and study year

Table 2.4 Overall Odds Ratios (95% CIs) From Ordered Logistic Model for Extent of Delay in Seeking Medical Care According to Age and Sex

	Men			Women			P	P
	< 65 y	65-75 y	≥ 75 y	< 65 y	65-75 y	≥ 75 y	value†	value‡
Model 1	1.00	1.14 (0.98-1.32)	1.51 (1.31-1.75)	1.15 (0.96-1.37)	1.43 (1.21-1.70)	1.43 (1.25-1.64)	0.06	0.12
Model 2	1.00	1.13 (0.97-1.31)	1.50 (1.28-1.75)	1.12 (0.93-1.34)	1.34 (1.11-1.61)	1.34 (1.14-1.58)	0.10	0.19
Model 3	1.00	1.12 (0.96-1.32)	1.55 (1.31-1.84)	1.11 (0.91-1.35)	1.34 (1.11-1.62)	1.28 (1.07-1.53)	0.013	0.56

Model 1: Included age, sex, and study year.

Model 2: Further adjusted for race, marital status, and history of angina, diabetes, heart failure, hypertension, stroke, and CABG.

Model 3: Further adjusted for clinical presentation including day of week admission, time of day, chest pain, AMI order (initial vs. prior), AMI type (Q wave vs. non-Q wave), and AMI location (anterior vs. inferior/posterior).

Notes: Information on DNR and STEMI was recorded beginning in 1991 and 1997, respectively; therefore, these variables were not included in regression model #3

† p values for interaction between age and sex

‡ p values for interaction among age, sex, and study year

Figure 2.1 Distribution of Pre-Hospital Delay in Patients Hospitalized with Acute Myocardial Infarction

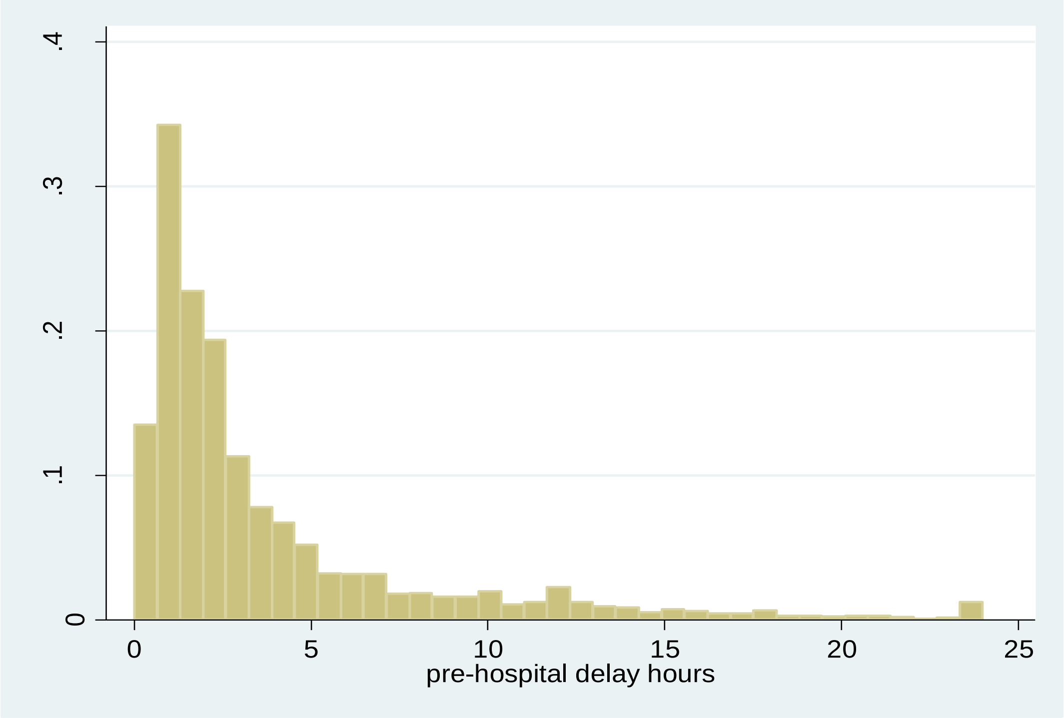


Figure 2.2 Duration of Pre-Hospital Delay According to Study Year

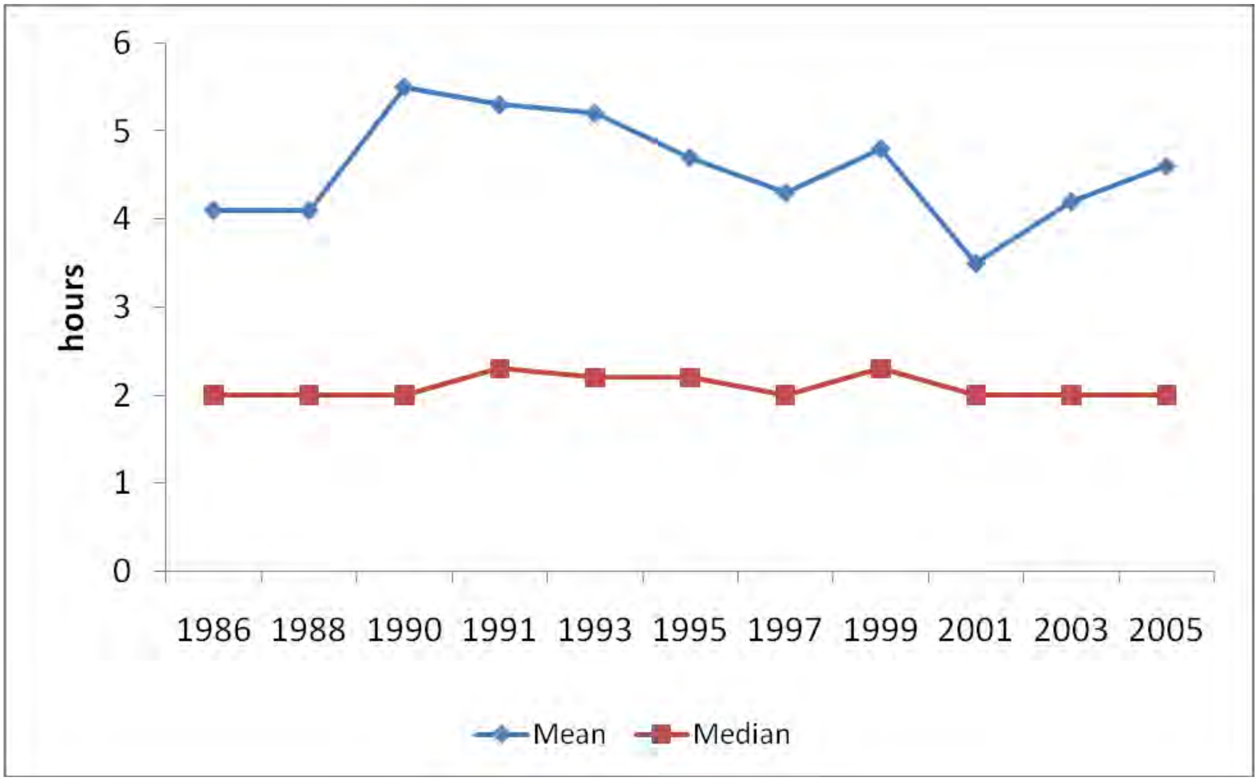
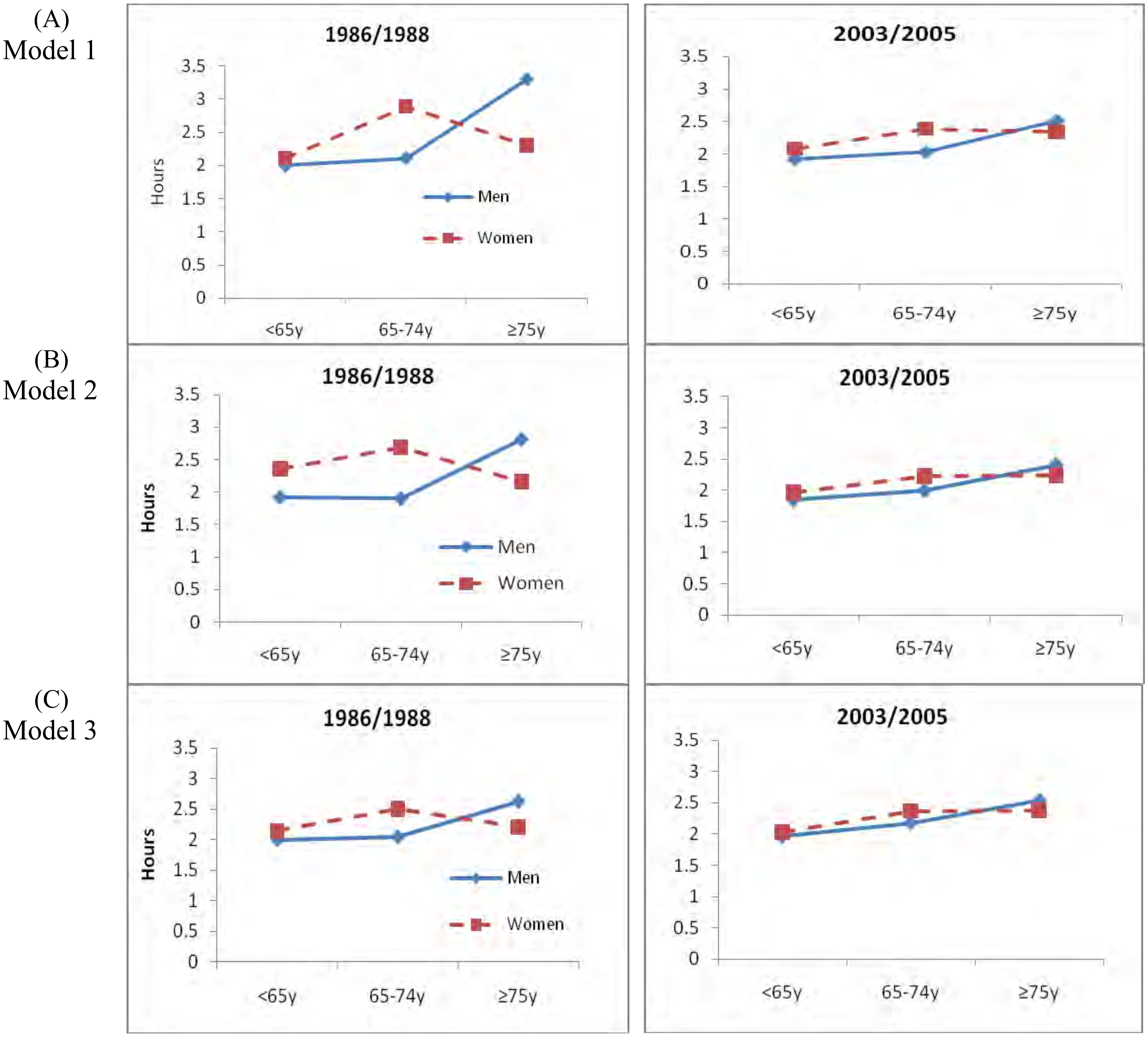


Figure 2.3 Age and Sex Differences in Duration of Pre-hospital Delay according Study Period



Appendix 2.1: Characteristics of Patients with and without Information on Pre-hospital Delay

	Data on Pre-hospital Delay		
Characteristics (n, %)	Available (n=5,967)	Not available (n=4,358)	P value
Age, mean (years)	68±14	73±3	<0.001
Female	2,308(38.7)	2,101(48.2)	<0.001
Age/Sex group			
Men			
<65 y	1825(50)	730(32)	<0.001
65-74 y	936(26)	609(27)	
≥ 75y	893(24)	914(41)	
Female			
<65 y	541(24)	314(15)	<0.001
65-74 y	609(26)	483(23)	
≥ 75y	1153(50)	1303(62)	
White	5,463(94.7)	3,970(94.0)	0.13
Medical history			
Diabetes	1,655(27.7)	1,436(33.0)	<0.001
Hypertension	3,587(60.1)	2,755(63.3)	<0.001
Heart Failure	957(16.0)	1,148(26.4)	<0.001
AMI characteristics			
Initial	3974(67)	2749(63)	<0.001

Q-wave	2221(41)	1142(30)	<0.001
Anterior	1695(31)	1060(28)	<0.001
STEMI*	1299(47)	772(30)	<0.001
Shock	318(5)	347(8)	<0.001
Hospital mortality	553(9)	759(17)	<0.001

*Information on STEMI was recorded beginning in 1997.

Appendix 2.2: Overall Association between Age/Sex and Duration of Pre-hospital Delay: Results from Propensity- weight Adjusted Method

	Men			Women			P	P
	< 65 y	65-75 y	≥ 75 y	< 65 y	65-75 y	≥ 75 y	value†	value‡
	Difference in Median of Pre-hospital Delay (95% CIs), hours							
Model 1	0 (reference)	0.12 (-0.09; 0.33)	0.59 (0.36; 0.80)	0.20 (-0.06; 0.46)	0.66 (0.41; 0.90)	0.3 (0.10;0.50)	<0.001	0.074
Model 2	0 (reference)	0.14 (-0.11; 0.39)	0.62 (0.35; 0.90)	0.22 (-0.09; 0.53)	0.53 (0.23; 0.84)	0.29 (0.001;058)	0.002	0.85
Model 3	0 (reference)	0.15 (-0.60; 0.35)	0.56 (0.34; 0.78)	0.16 (-0.09; 0.41)	0.52 (0.27; 0.76)	0.30 (0.07;0.55)	0.001	0.50
	Absolute Medians of Pre-hospital Delay (95% CIs), hours							
Model 1	1.92 (1.80-2.04)	2.04 (1.86-2.21)	2.50 (2.35-2.68)	2.12 (1.89-2.35)	2.57 (2.36-2.79)	2.22 (2.06-2.38)	<0.001	0.074
Model 2	1.96 (1.79-2.12)	2.09 (1.88-2.31)	2.58 (2.36-2.80)	2.18 (1.90-2.46)	2.49 (2.23-2.76)	2.24 (2.03-2.46)	0.002	0.85
Model 3	1.98 (1.85-2.11)	2.13 (1.96-2.29)	2.54 (2.37-2.72)	2.14 (1.92-2.36)	2.50 (2.29-2.70)	2.29 (2.12-2.45)	0.001	0.50

CHAPTER III

Age and Sex Differences in Hospital Management Practices, and Changing Trends, in Patients Hospitalized with Acute Coronary Syndrome

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Abstract

Background

A limited number of studies have examined age and sex differences, and potentially changing trends, in cardiac medication and procedure use in patients hospitalized with an acute coronary syndrome (ACS).

Methods

Using data from a large multinational study, we examined age and sex differences, and changing trends (1999-2007) therein, in the hospital use of evidence-based therapies in patients hospitalized with an ACS using data from the Global Registry of Acute Coronary Events (n=50,096).

Results

After adjustment for several variables, in comparison with men <65 years, patients in other age-sex strata had a significantly lower odds of receiving aspirin (Odds ratios for men 65-74 years, 75-84 years, and ≥85 years, women <65 years, 65-74 years, 75-84 years, and ≥85 years were 0.86, 0.84, 0.72, 0.80, 0.86, 0.68 and 0.46, respectively), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (Odds ratios, 1.08, 1.01, 0,71, 0.83, 0.90, 0.89, and 0.63), beta blockers (Odds ratios, 0.66, 0.52, 0.53, 0.67, 0.54, 0.53, and 0.52), statins (Odds ratios, 0.72, 0.49, 0.29, 0.82, 0.68, 0.44, and 0.22), and undergoing coronary artery bypass graft surgery or a percutaneous coronary intervention (Odds ratios, 0.79, 0.53, 0.21, 0.64, 0.57, 0.38 and 0.13) during their acute hospitalization. Age and sex differences in the receipt of these therapies remained relatively unchanged during the period under study

Conclusions

While there were increasing trends in the use of evidence-based medications and cardiac procedures over time, important gaps in the utilization of effective cardiac treatment modalities persist in elderly patients and younger women.

Word count: 250

Keywords: aging, sex, acute coronary syndromes, effective cardiac therapies

3.1 Introduction

Over the past several decades, a variety of clinical trials have evaluated the use of different treatment strategies in patients hospitalized with an acute coronary syndrome (ACS), finding that various treatment regimens can reduce the risk of hospital complications and improve short-term prognosis.[109-111] However, patients enrolled in clinical trials often need to satisfy stringent inclusion and exclusion criteria, leading to the omission of several at-risk patient groups, such as the elderly, as well as potentially limited generalizability to patients treated in the broader community setting.

Even though published clinical evidence does not support withholding effective cardiac therapies on the basis of age,[72,73] elderly patients hospitalized with an ACS are often treated less aggressively than younger patients.[75,76] Moreover, despite the greater prevalence of coronary heart disease in men as compared with women, [5,77] women are more likely to experience adverse in-hospital and post-discharge outcomes [78,79] in the setting of an ACS. Women's poorer prognosis may be due to differences in demographic and clinical characteristics, pathophysiology of acute coronary disease, or to the lower use of effective management strategies as compared with men.[17,78]

Several prior studies have examined possible age and sex differences in cardiac medication and procedure use in patients hospitalized with an ACS.[17,48,76,83,85,86] However, a limited number of studies have examined these associations from the perspective of a multinational investigation. Moreover, little contemporary research has been conducted examining potentially changing age and sex differences in the utilization of evidence-based therapies in patients hospitalized with an ACS, and whether differences in the receipt of effective cardiac therapies have narrowed over time between men and women of different ages.

The objectives of this large multi-site observational study were to describe age and sex differences in the hospital use of several evidence-based cardiac therapies, namely aspirin, angiotensin -converting (ACE) inhibitors/ angiotensin II receptor blockers (ARBs), beta blockers, and statins, as well as receipt of invasive cardiac procedures, in patients hospitalized with an ACS. A secondary study objective was to examine changing trends (1999-2007) in the hospital use of these treatment strategies according to patient's age and sex. Data from the GRACE (Global Registry of Acute Coronary Events) study were used for purposes of this investigation.[7,8]

3.2 Methods

Details on the GRACE registry and methods of patient identification and data collection have been previously published.[7,8] Study data were contributed by 106 hospitals located in 14 countries in North and South America, Europe, Australia and New Zealand.

Patients entered in the registry had to be at least 18 years old and alive at the time of hospital presentation, be admitted for an ACS as a presumptive diagnosis, and have at least 1 of the following present: electrocardiographic changes consistent with an ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease.

To ensure the enrollment of an unbiased population, the first 10 consecutive, eligible patients were recruited from each site on a monthly basis. Data were collected by trained abstractors using standardized case report forms. Demographic characteristics, medical history, presenting symptoms, duration of pre-hospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected.[7,8] The medical therapies prescribed for patients enrolled in the GRACE registry were at the discretion of the treating physicians at participating study hospitals. . Standardized definitions of all patient-related variables, clinical diagnoses, and hospital complications and outcomes were utilized.[8] All cases of confirmed ACS were assigned to 1 of the following categories: ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA) using standardized case definitions.[7,8] Patients who were transferred from another hospital or to another health care facility were excluded from the present study.

The present analyses were carried out only in patients who did not have exclusions to the receipt of the evidence-based cardiac therapies examined.[7,8] The exclusion criteria for receipt of each of the cardiac medications under study included the following:

- Aspirin: history of bleeding or hemorrhagic stroke, in-hospital bleeding, or hemorrhagic stroke; on warfarin therapy; and other contraindications to aspirin.
- Angiotensin-converting enzyme inhibitors: hospital development of cardiogenic shock; serum creatinine >2.5 mg/dL; and a previous adverse reaction to ACE inhibitors.

- Beta blockers: pulse <60 beats per minute while not on beta blockers; atrioventricular block; systolic blood pressure <90 mm Hg; development of cardiogenic shock during hospitalization; and other contraindications to beta blockers.
- Statins: no additional exclusion criteria.

These criteria were based on contemporary published guidelines, were designed to be permissive, and could be noted by the GRACE investigators without the specific contraindication being indicated. The receipt of effective cardiac medications and coronary interventional procedures were the primary study outcomes.

Data Analysis

Categorical data were summarized as percentages and were compared between patients of various age strata (<65, 65-74, 75-84, ≥85 years) in both sexes using the chi-square test. Continuous variables were presented as medians (inter-quartile range, IQR) and were tested for possible differences according age and sex using the Kruskal-Wallis test.

We examined the possible association between age/sex and the receipt of each of these treatments, as well as receipt of 3 or more of these medications in combination, in all eligible patients and in subgroups further defined according to type of ACS (STEMI and NSTEMI/UA), using a series of multivariable logistic regression models to control for the potentially confounding effects of demographic characteristics (other than age and sex), comorbidities, and clinical characteristics. Model 1 included age, sex, and study year. Model 2 further adjusted for geographic region, type of hospital (teaching vs. other), and medical history of cardiovascular disease. Model 3 further adjusted for the 8 factors included in the GRACE hospital risk model.[98] To test whether any age or sex differences in the utilization of these therapeutic approaches have changed over time, 2-way and 3-way interaction terms among age, sex, and study year were created and included in each regression model. Likelihood ratio tests were used to test nested models with and without interaction terms. Random effect models were used to assess whether the different patient clusters within geographic regions affected our observed results. All analyses were performed using STATA 10.0.

3.3 Results

The study population consisted of 50,096 patients hospitalized with an ACS, who were enrolled in the GRACE registry between April, 1999 and December, 2007. The average age of study patients, which was comprised of approximately two-thirds men, was 66.3 years; 45.2% of patients were <65 years, 25.9% were 65-74 years, 21.6% were 75-84 years, and 7.3% of patients were ≥ 85 years. Women were considerably older than men at the time of hospital admission (mean: 70.7 years vs. 64.0 years). In this patient population, 35.2%, 32.3%, and 32.5% were diagnosed as having STEMI, NSTEMI, and UA, respectively, at the time of hospital admission for an ACS.

Baseline Characteristics

The proportion of patients with a history of MI, atrial fibrillation, heart failure, hypertension, kidney disease, and stroke increased with advancing age in both sexes (Table 3.1). Within the same age strata, women were more likely to report a history of hypertension or heart failure, but were less likely to have a history of MI, than men.

Older patients were more likely to have multiple co-morbidities present than younger patients in both sexes. In 3 of the 4 age strata, women were more likely to have multiple co-morbidities previously diagnosed than men (Table 3.1).

In general, heart rate, serum creatinine, and serum glucose levels increased with advancing age in both sexes; on the other hand, serum levels of cholesterol and triglycerides, and patient's body mass index, decreased with advancing age in both women and men (Table 3.2). Within the same age strata, women were more likely to present at participating GRACE hospitals after more prolonged delay following the onset of acute coronary symptoms, have higher systolic blood pressure, heart rate, and serum cholesterol findings, but lower serum creatinine levels, compared with men. Older patients and women were more likely to be classified as presenting in a higher Killip class at the time of hospital admission than younger patients and men. The proportion of patients with STEMI increased with advancing age in women but declined with advancing age in men (Table 3.2).

Trends in the use of Evidence-Based Medications and Cardiac Procedures

The use of aspirin during hospitalization for an ACS remained relatively stable over time (94% utilization in 1999; 95% in 2007). Moderate increases were observed in the prescribing of ACE inhibitors/ARBs (57% in 1999 vs. 79% in 2007) and beta blockers (81% in 1999 vs. 92% in 2007) ($p<0.001$). The hospital use of statins increased significantly from 39% in 1999 to 83% in 2007 ($p<0.001$). The use of 3 or more effective cardiac medications increased from 57% in 1999 to 87% in 2007 ($p<0.001$). The use of combination evidence-based medications increased in both women and men and in patients of all age strata during the period under study (Figure 3.1). The use of coronary reperfusion and revascularization strategies (either CABG surgery or PCI) during hospitalization also increased significantly over time from 28% in 1999 to 51% in 2007 ($p<0.001$).

Use of Evidence-Based Medications and Cardiac Procedures According to Age and Sex

The use of aspirin and beta blockers during hospitalization for an ACS declined with advancing age (Table 3.3). Similarly, older patients were less likely to have undergone various cardiac procedures than younger patients. Within the same age groups, women were consistently less likely to be treated with aspirin and statins compared with men. Women in all age groups were much less likely to have undergone CABG surgery or PCI than men of similar ages.

Multivariable Analyses

The non significant 2-way and 3-way interactions among age, sex, and study period indicated that age and sex differences in the use of these medications (single or multiple) and cardiac procedures have remained relatively unchanged over time (Table 3.4 and Figure 3.2). Since the results of regression models 2 and 3 were similar, overall adjusted odds ratios for the utilization of single cardiac medications and procedures according to age and sex from model 3 are presented (Table 3.4).

Aspirin

In comparison with men <65 years, women had a significantly lower odds of receiving aspirin with the exception of women 65-74 years (Table 3.4). In examining the association between age/sex and the use of aspirin stratified according to type of ACS, in patients with NSTEMI/UA, compared with men <65 years, women ≥75 years had a significantly lower odds of receiving aspirin; a similar pattern was observed in patients with STEMI. There was no evidence of an interaction between age and sex with regards to aspirin use in all patients as well as in patients classified according to type of ACS (Table 3.4).

ACE inhibitors and/or ARBs

In comparison to men <65 years, men ≥85 years, and women had a significantly lower odds of receiving ACE inhibitors or ARBs during their acute hospitalization. In patients with NSTEMI/UA, compared with men <65 years, women <65 years and men and women ≥ 85 years had a significantly lower odds of receiving these medications. In patients with STEMI, compared with men <65 years, men and women ≥85 years had a significantly lower odds of receiving these medications. There was no evidence of an interaction between age and sex with the use of these medications in all patients as well as in patients with different ACS types (Table 3.4).

Beta blockers

In all patients, after adjustment for several potential confounders, in comparison with men <65 years, other age and sex groups had a significantly lower odds of receiving beta blockers during hospitalization (Table 3.4). Interactions between age and sex were statistically significant; in patients <75 years, women were less likely to be treated with beta blockers while there were no sex differences in the use of beta blockers in older patients (Table 3.4).

In patients with NSTEMI/UA, similar results were observed (Table 3.4). In patients with STEMI, while relatively similar patterns were observed, there was no evidence of an interaction between age and sex in relation to beta blocker utilization (Table 3.4).

Statins

In comparison with men <65 years, other age-sex strata had a significantly lower odds of receiving statins (Table 3.4). In examining the association between age/sex and the use of statins stratified according to type of ACS, similar patterns were observed in both NSTEMI/UA and STEMI patients. There was no evidence of an interaction between age and sex in relation to the use of statins in all patients as well as in subgroups of patients further classified according to type of ACS (Table 3.4).

CABG or PCI

After adjustment for several potential confounders, in comparison to men <65 years, other age-sex strata had a significantly lower odds of undergoing these cardiac procedures during their acute hospitalization. In examining these associations stratified according to type of ACS, similar patterns were observed. There was no evidence of an interaction between age and sex in relation to the use of these procedures in all patients as well as in subgroups of patients with an ACS (Table 3.4).

Multiple Cardiac Medications

In comparison with men <65 years, other age and sex groups had a significantly lower odds of receiving ≥3 effective cardiac medications during their index hospitalization (Table 3.4). Interactions between age and sex were statistically significant; in patients <65 years, women were less likely to be treated with ≥3 medications (Adjusted OR: 0.76; 95% CIs: 0.67-0.86), while there were no sex differences in the use of ≥3 medications in older patients. In examining these associations stratified according to type of ACS, similar patterns were observed though there was no evidence of an interaction between age and sex with regards to the use of ≥3 effective medications (Table 3.4).

Results from random effect models assessing the effects of the different patient clusters within geographic regions provided similar conclusions (data not shown).

3.4 Discussion

The results of this large contemporary multinational study demonstrate a marked increase in the hospital use of several key evidence-based cardiac medications, CABG surgery, and PCI in men and women of various age strata who were hospitalized with an ACS between 1999 and 2007. Despite encouraging increases in prescribing practices over time, age and sex differences with regards to the prescribing of most effective cardiac therapies have not changed significantly during the period under study. In comparison with men <65 years, patients in other age-sex strata were less likely to be treated with these medications and cardiac procedures. There was some evidence, however, which suggested that there were interactions between age and sex with the use of beta blockers and multiple medications; younger women were less likely to be treated with these medications during hospitalization compared with younger men, while there were no sex differences in these outcomes in older patients.

Improving Trends in the Use of Evidence-Based Medications and Cardiac Procedures

Increasing use of evidence-based medications and cardiac procedures in patients hospitalized with an ACS were observed in the present study, irrespective of changes in patient's demographic and clinical characteristics. Our findings are consistent with the results of several previous studies which have examined the use of various treatment practices in patients hospitalized with acute coronary disease between the mid-1970s and early 2000s.[47,77]

Increases in the administration of effective cardiac treatment practices over time is likely due to the accumulating evidence from published clinical trials and American College of Cardiology/ American Heart Association and European guidelines that have demonstrated the benefits associated with the use of these medications and procedures in reducing the risk of complications and death in patients with an ACS.[62,63,112] In addition, other factors such as increases in patient's and physician's awareness about different treatment options through educational campaigns, and hospital quality improvement programs, are likely to have contributed to the increased use of these evidence-based therapies as well.

Age and Sex Differences in the Receipt of Effective Cardiac Treatment Regimens

In the present study, we found that the differences between patients of different ages within the same sex were larger than the differences noted between men and women within the same age strata, suggesting that age, rather than sex, differences in the receipt of different cardiac therapies are more important. Similar patterns were observed in subgroups defined according to type of ACS.

Our findings are consistent with the results of previous studies.[48,51,76,113,114] For example, a retrospective cohort study of more than 17,000 patients enrolled between 1995-2001 in the ARIAM study (Analysis of Delay in AMI), a multi-center registry of patients with AMI admitted to 119 Spanish hospitals, found that older patients were less likely to be prescribed beta blockers, but were more likely to be prescribed ACE inhibitors, than younger patients.[51] Data from the Second National Registry of Myocardial Infarction suggested that younger patients were more than twice as likely to undergo cardiac catheterization in comparison to patients ≥70 years.[113]

Age differences in the hospital treatment of patients with an ACS may be partially explained by the fact that older patients are more likely to have multiple co-morbidities present,[17,86,87] and present with more contraindications to treatment practices, which may limit their receipt of more effective treatment regimens; however, in the present study, we restricted our analyses to eligible patients only, and age differences in various treatment practices still existed. Older patients tend to present with more atypical signs and symptoms of acute coronary disease than younger patients and men,[115] which can make their diagnosis and management all the more difficult. Furthermore, lower use of medications and interventional cardiac procedures in older patients may be due to the higher rates of complications in these patients,[114,116] which may make both physicians and patients more reluctant to use these interventions. Since older patients have been generally excluded from, or were included in small numbers, in earlier clinical trials, the evidence of effectiveness of these treatments in these individuals is limited. Based on these and other considerations, physicians may be reluctant to treat elderly patients more aggressively. It is also possible that some physicians believe that age is a contraindication to some medications in patients who have suffered an ACS. On the other hand, the American College of Cardiology/ American Heart Association and European guidelines emphasize that all medications that are used for the management of patients with an ACS should not be differentially utilized on the basis of age.[62,63,112] Inasmuch, physicians should prescribe these medications to older patients when there are no contraindications present as often as they do to younger patients with proper precautions noted (e.g., starting with lower doses and monitoring closely for toxicity).

Our results suggest that women were less likely to be treated with beta blockers and multiple medications among younger patients only**,** particularly in patients with NSTEMI/UA. This finding is consistent with a study of 1,059 patients with AMI in the Hospital In-Patient Enquiry (HIPE) that was conducted between 1992 and 1994. In this study, in younger patients (<65 years), women were significantly less likely to receive thrombolytic therapy compared with men but there were no sex differences in the administration of thrombolytic agents in older patients.[117] Other previous studies have not examined sex differences in treatment practices stratified according to age in patients with an ACS; therefore, it is difficult to compare their results with those of the present study. For example**,** in the HELIOS study which included 1,840 patients with AMI admitted to 31 hospitals in Greece during the mid -2000s, women were less likely to be treated with aspirin, beta blockers, and statins, but were more likely to be treated with

ACE inhibitors/ARBs, than men during hospitalization for AMI.[87] A recent report from the large AMIS Plus registry in Switzerland showed that women were approximately one-third less likely to undergo PCI than men between 1997 and 2006, though the investigators did not examine whether sex differences in the administration of these procedures remained during the period under study.[81]

In contrast, several studies have found that there were no differences between men and women in the use of several cardiac medications and interventional procedures in patients hospitalized with acute coronary disease.[17,83,87,28] For example, findings from the MITRA (Maximal Individual The Rapy of Acute myocardial infarction) registry in Germany showed that there were no differences between men and women with regards to the receipt of aspirin, beta blockers, and ACE inhibitors during the first 48 hours of hospitalization in patients hospitalized with AMI.[86] Some of the discrepancies observed with regards to these study findings may be partially attributed to the different demographic and clinical characteristics of the respective study populations, time period under study, and the fact that none of these studies simultaneously examined age and sex differences in the receipt of these treatment regimens as we did in the present study.

The reasons for underutilization of beta blockers and multiple effective cardiac medications in younger women are unclear. This may be partially explained by the fact that younger women have lower incidence rates of ACS, and are more likely to experience atypical symptoms[115], particularly in patients with UA, which makes their diagnosis and management more challenging. In addition, younger women may be less likely to be cared for by a cardiologist during their hospitalization[96], which can contribute to underutilization of effective medications. Finally, younger women have been shown to be more likely to develop important clinical complications than younger men during hospitalization[117], which could prevent younger women from receiving these medications. More studies need to be carried out to understand the reasons for the underutilization of effective treatment regimens in younger women.[94] Educational campaigns should continue to target older patients and younger women with regards to the receipt of effective cardiac treatments in the setting of an ACS as contemporary gaps in their more optimal management continue to remain.

Trends in Age and Sex differences in Hospital Treatment Practices

In examining changing trends in the utilization of evidence -based medications and interventional procedures, our results suggest that age and sex gaps in the utilization of most medications have not changed significantly over time. Our findings are consistent with the findings from the Nationwide Inpatient Sample which found that women were less likely to undergo CABG surgery than men between 1995 and 2001 and disparities in the use of this procedure remained over time.[17] These and other findings suggest the need for greater understanding of the reasons underlying these treatment disparities and for the development of educational interventions and targeted programs to enhance the more optimal treatment of these high risk patients.

Study Strengths and Limitations

The GRACE study is the largest multinational registry to include the complete spectrum of patients hospitalized with an ACS. Standardized criteria are employed for defining ACS and hospital outcomes and rigorous quality control and audit measures are employed. ”Real-life” observational studies such as GRACE provide data on a heterogeneous population of patients that includes groups who are often under-represented in randomized trials, including women and the elderly.[8]

On the other hand, as an observational study, GRACE is subject to certain inherent limitations and potential biases that must be kept in mind in interpreting the study results. Treatments were given according to individual physicians’ decisions and not through the use of standardized treatment protocols. While currently recommended criteria were utilized to characterize patients who were eligible for the receipt of the cardiac medications examined, due to our reliance on data obtained from medical records, questions might be raised about our ability to characterize patient’s eligibility status. Furthermore, we did not have information available on several patient associated characteristics (e.g., socioeconomic status, patient preferences) which may have confounded some of the observed associations. Moreover, an important shortcoming of data from large population registries is the inability to grasp nuances, subtleties, or unrecorded factors which may affect individual patient care and management choices. For example, it is possible that our data may actually represent reasonable or even good patient care and patient’s choices.

3.5 Conclusions

The results of the present study demonstrate that the utilization of evidence- based medications and use of CABG or PCI in the setting of ACS has significantly increased over the period under study. Despite these encouraging trends, important gaps in the use of these treatment modalities persist in elderly patients and younger women. Given ongoing demographic changes in economically developed and developing countries, resulting in more women and elderly patients seeking treatment for cardiovascular disease, the underlying reasons for differences in the use of effective treatment modalities by age and sex need to be more fully elucidated to narrow current treatment disparities.

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Table 3.1 Baseline Characteristics of Patients Hospitalized with an Acute Coronary Syndrome According to Age and Sex

	Men					Women				
Characteristic	<65y (n=17302)	65-74y (n=8504)	75-84y (n=5890)	≥ 85y (n=1454)	P value	<65y (n=5254)	65-74y (n=4414)	75-84y (n=4880)	≥ 85y (n=2174)	P value
Age, mean(SD)†, yrs	53.8(7.6)	69.9(2.9)	79.3(2.8)	88.7(3.1)		54.8(7.6)	70.5(2.8)	79.7 (2.8)	89.2(3.4)	
Geographic region										
Australia/NewZealand/ Canada	2197(12.7)	1161(13.7)	924(15.7)	195(13.4)	<0.001	680(12.9)	571(12.9)	767(15.7)	269(12.4)	<0.001
Europe	8092(46.8)	4024(47.3)	2629(44.6)	549(37.8)	<0.001	1997(38.0)	1935(44.3)	2100(43.0)	743(34.2)	<0.001
South America	3913(22.6)	1893(22.3)	1016(17.3)	166(11.4)	<0.001	1416(27.0)	1015(23.0)	729(16.2)	299(13.8)	<0.001
US	3100(17.9)	1426(16.8)	1321(22.4)	544(37.4)	<0.001	1161(22.1)	875(23.0)	1221(25.1)	867(39.7)	<0.001
Teaching hospital	1207(80.8)	5795(80.4)	3834(77.3)	859(69.8)	<0.001	3499(81.5)	2848(80.8)	3013(76.2)	1293(70.3)	<0.001
Co-morbidity (n,%)										
Angina	8304(48.2)	4893(57.8)	3387(57.9)	775(53.7)	<0.001	2936(56.1)	2576(58.6)	2668(54.8)	1007(46.7)	<0.001
Atrial fibrillation	489(2.9)	715(8.5)	895(15.4)	294(20.4)	<0.001	132(2.5)	384(8.8)	673(14.0)	389(18.1)	<0.001
Diabetes	3325(19.3)	2387(28.2)	1565(26.7)	331(22.9)	<0.001	1475(28.2)	1451(33.0)	1412(29.1)	456(21.1)	<0.001
Heart failure	772(4.5)	879(10.4)	928(16.0)	366(25.5)	<0.001	369(7.1)	535(12.2)	907(18.7)	589(27.3)	<0.001
Hypertension	8704(50.6)	5354(63.4)	3882(66.4)	945(65.4)	<0.001	3315(63.4)	3312(75.3)	3717(76.5)	1609(74.3)	<0.001
Kidney disease	764(4.4)	673(8.0)	807(13.8)	265(18.3)	<0.001	304(5.8)	315(7.2)	481(9.9)	248(11.5)	<0.001
MI	4687(27.2)	2987(35.3)	2259(38.6)	620(42.9)	<0.001	1299(24.9)	1251(28.5)	1487(30.6)	696(32.2)	<0.001
TIA/Stroke	705(4.1)	798(9.5)	806(13.8)	231(16.0)	<0.001	323(6.2)	410(9.4)	619(12.8)	349(16.2)	<0.001
*#Co-morbidity**										
0	4039(23.9)	988(12.0)	510(9.0)	99(7.0)	<0.001	822(16.0)	386(9.0)	340(7.1)	169(8.0)	<0.001
1	5548(32.8)	2186(26.5)	1293(22.8)	308(21.8)		1478(28.7)	983(22.8)	1054(22.1)	494(23.3)	

2	4647(27.5)	2665(32.3)	1755(30.9)	405(28.7)		1544(30.0)	1487(34.5)	1572(33.0)	612(28.9)	
≥ 3	2659(15.8)	2418(29.2)	2123(37.3)	593(42.5)		1299(25.3)	1453(33.7)	1797(37.8)	845(39.8)	
Current smoking	7756(46.0)	1726(20.9)	626(10.9)	77(5.5)	<0.001	1891(36.9)	606(14.0)	324(6.8)	56(2.6)	<0.001

†SD: Standard deviation

*Co-morbidities include angina/MI, atrial fibrillation, diabetes, heart failure, hypertension, kidney disease, TIA/Stroke

Table 3.2 Clinical Presentation at the Time of Hospital Admission According to Age and Sex

	Men				P value	Women				P value
	<65y	65-74y	75-84y	≥ 85y		<65y	65-74y	75-84y	≥ 85y	
Pre-hospital Delay , min*	160(84-365)	180(93-392)	180(95-392)	177(90-275)	0.17	180(95-420)	195(100-435)	191(100-442)	190(93-460)	<0.001
Systolic BP, mmHg	139(120-156)	140(120-160)	140(120-160)	137(120-160)	<0.001	140(120-160)	145(127-166)	144(125-165)	140(120-163)	<0.001
Diastolic BP, mmHg	80(70-93)	80(70-89)	77(66-89)	74(63-85)	<0.001	80(79-90)	80(70-90)	80(66-90)	74(60-87)	<0.001
Pulse, beats/min	75(70-89)	75(63-92)	77(64-92)	80(66-96)	<0.001	78(66-90)	78(67-91)	80(68-96)	84(70-100)	<0.001
Creatinine, mg/dl	1.0(0.9-1.2)	1.1(0.9-1.5)	1.2(1.0-1.5)	1.4(1.1-1.7)	<0.001	0.9(0.7-1.0)	0.9(0.8-1.1)	1.0(0.9-1.3)	1.1(0.9-1.5)	<0.001
Cholesterol, mg/dl	195(165-228)	178(151-199)	169(140-199)	164(138-195)	<0.001	198(166-234)	194(165-227)	190(160-223)	182(152-217)	<0.001
Triglycerides, mg/dl	145(102-155)	123(87-144)	108(79-146)	94(69-128)	<0.001	135(94-196)	127(92-178)	115(83-160)	103(74-146)	<0.001
Glucose, mg/dl	120(102-155)	127(104-174)	130(106-174)	134(109-177)	<0.001	122(100-169)	131(105-182)	130(106-178)	135(111-179)	<0.001
BMI, kg/m2	27.5(24.9-30.6)	26.0(24.5-8.5)	26.0(23.8-8.5)	24.7(22.7-7.3)	<0.001	27.5(24.2-32.0)	27.0(23.9-0.9)	25.8(23.0-29.3)	23.9(21.1-27.2)	<0.001
Killip class (n,%)										
I	15459(91.0)	6904(83.1)	4308(75.0)	950(66.3)	<0.001	4603(89.6)	3439(79.7)	3417(71.4)	1310(61.7)	<0.001
II	1141(6.7)	1020(12.3)	1040(18.1)	339(23.7)		375(7.3)	645(15.0)	940(19.6)	538(25.3)	
III	264(1.6)	300(3.6)	327(5.7)	120(8.4)		121(2.4)	191(4.4)	362(7.6)	234(11.0)	

IV	121(0.7)	84(1.0)	68(1.2)	23(1.6)		39(0.7)	40(0.9)	67(1.4)	43(2.0)	
Admission Diagnosis (n,%)										
STEMI	3914(44.3)	2854(33.6)	1833(31.1)	483(33.2)	<0.001	1567(29.8)	1307(29.6)	1566(32.1)	775(35.7)	<0.001
NSTEMI/UA	4846(55.7)	5650(66.4)	4058(68.9)	971(66.8)		3687(70.2)	3107(70.4)	3305(67.9)	1399(64.3)	

STEMI: ST segment elevation MI; NSTEMI: Non ST segment elevation MI; UA: Unstable angina; BMI: Body mass index.

*pre-hospital delay was defined as the duration of time from the onset of symptoms suggestive of ACS to hospital arrival; continuous variables: medians and inter-quartiles ranges.

Table 3.3 Utilization of Cardiac Medications and Procedures in Eligible Patients during Hospitalization According to Age and Sex

	Men				P values	Women				P values
	<65y	65-74y	75-84y	≥ 85y		<65y	65-74y	75-84y	≥ 85y	
Aspirin (n,%)	14785(96.7)	6491(96.1)	4088(95.1)	940(94.0)	<0.001	4335(96.2)	3356(95.8)	3411(94.2)	1413(92.1)	<0.001
ACE inhibitors or ARBs (n,%)	10027(69.0)	5088(73.3)	3359(73.2)	724(67.0)	<0.001	2935(67.9)	2625(73.6)	2875(73.7)	1096(68.7)	<0.001
Beta blockers (n,%)	11897(92.5)	4896(88.9)	2889(86.5)	592(86.6)	<0.001	3503(89.7)	2491(87.3)	2409(86.8)	889(87.5)	0.003
Statins (n,%)	12657(74.2)	5679(68.0)	3561(61.7)	699(50.0)	<0.001	3600(69.5)	2825(65.2)	2835(59.6)	918(43.9)	<0.001
CABG (n,%)	910(5.3)	536(6.4)	281(4.8)	23(1.6)	<0.001	257(5.0)	207(4.8)	147(3.1)	11(0.5)	<0.001
PCI (n,%)	8514(49.6)	3458(41.0)	1920(32.8)	285(19.8)	<0.001	1941(37.3)	1447(33.0)	1308(27.1)	299(13.9)	<0.001
CABG or PCI (n,%)	9286(54.4)	3951(47.0)	2176(37.3)	305(21.2)	<0.001	2174(42.0)	1634(37.5)	1446(30.0)	309(14.5)	<0.001

ACE: Angiotensin converting enzyme; ARBs: Angiotensin II Receptor Blockers; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

Table 3.4 Odds Ratios (95% CIs) for the Utilization of Medications and Procedures in Eligible Patients Hospitalized with an Acute Coronary Syndrome According to Age and Sex

	Men				Women				P value§	P value†
	<65y	65-74y	75-84y	≥ 85y	<65y	65-74y	75-84y	≥ 85y		
Aspirin										
All patients	1.00	0.86(0.72-1.04)	0.84(0.68-1.03)	0.72(0.51-1.01)	0.80(0.65-0.99)	0.86(0.68-1.09)	0.68(0.55-0.84)	0.46(0.36-0.59)	0.27	0.57
NSTEMI/UA	1.00	0.88(0.70-1.11)	0.81(0.63-1.05)	0.67(0.45-1.00)	0.87(0.67-1.13)	0.86(0.64-1.14)	0.70(0.54-0.91)	0.48(0.35-0.66)	0.76	0.25
STEMI	1.00	0.82(0.60-1.13)	0.90(0.62-1.33)	0.84(0.44-1.61)	0.70(0.49-1.01)	0.91(0.58-1.43)	0.63(0.44-0.90)	0.40(0.27-0.61)	0.22	0.48
ACE inhibitors/ARBs										
All patients	1.00	1.09 (1.00-1.17)	1.01(0.93-1.11)	0.71(0.61-0.84)	0.83(0.76-0.91)	0.90(0.82-0.99)	0.89(0.81-0.98)	0.63(0.55-0.72)	0.81	0.20
NSTEMI/UA	1.00	1.09 (1.00-1.20)	1.05(0.95-1.17)	0.79(0.65-0.95)	0.81(0.73-90)	0.90(0.80-1.01)	0.92(0.82-1.03)	0.71(0.60-0.83)	0.76	0.31
STEMI	1.00	1.26 (1.09-1.45)	1.15(0.97-1.37)	0.68(0.51-0.90)	1.04(0.87-1.24)	1.09(0.89-1.33)	0.99(0.83-1.20)	0.59(0.47-0.75)	0.47	0.08
Beta blockers										
All patients	1.00	0.66(0.59-0.75)	0.52(0.45-0.60)	0.53(0.40-0.69)	0.67(0.58-0.78)	0.54(0.46-0.63)	0.53(0.45-0.62)	0.52(0.41-0.65)	0.003	0.80
NSTEMI/UA	1.00	0.66(0.57-0.77)	0.54(0.46-0.64)	0.68(0.49-0.95)	0.66(0.56-0.78)	0.52(0.44-0.62)	0.56(0.47-0.67)	0.55(0.42-0.73)	0.008	0.90
STEMI	1.00	0.76(0.59-0.99)	0.53(0.40-0.71)	0.30(0.19-0.50)	0.87(0.62-1.21)	0.79(0.54-1.15)	0.52(0.37-0.72)	0.48(0.30-0.76)	0.45	0.88
Statins										

All patients	1.00	0.72(0.67-0.77)	0.49(0.45-0.54)	0.29(0.25-0.33)	0.82(0.75-0.90)	0.68(0.62-0.75)	0.44(0.40-0.48)	0.22(0.19-0.25)	0.06	0.67
NSTEMI/UA	1.00	0.74(0.68-0.81)	0.52(0.47-0.58)	0.31(0.26-0.37)	0.82(0.74-0.92)	0.72(0.64-0.80)	0.47(0.42-0.53)	0.24(0.21-0.27)	0.12	0.81
STEMI	1.00	0.70(0.62-0.80)	0.47(0.41-0.54)	0.26(0.20-0.33)	0.88(0.75-1.04)	0.65(0.55-0.77)	0.41(0.35-0.48)	0.20(0.16-0.24)	0.75	0.21
CABG/ PCI										
All patients	1.00	0.79(0.74-0.84)	0.53(0.49-0.57)	0.21(0.18-0.25)	0.64(0.59-0.70)	0.57(0.52-0.62)	0.38(0.35-0.42)	0.13(0.11-0.15)	0.12	0.46
NSTEMI/UA	1.00	0.82(0.75-0.89)	0.58(0.53-0.64)	0.21(0.17-0.26)	0.63(0.57-0.69)	0.58(0.52-0.64)	0.41(0.36-0.45)	0.13(0.10-0.16)	0.29	0.67
STEMI	1.00	0.82(0.73-0.92)	0.50(0.44-0.57)	0.22(0.17-0.28)	0.75(0.65-0.87)	0.62(0.53-0.72)	0.37(0.32-0.42)	0.13(0.11-0.17)	0.67	0.80
≥3 medications										
All patients	1.00	0.71(0.63-0.80)	0.60(0.52-0.69)	0.35(0.25-0.45)	0.76(0.67-0.86)	0.69(0.60-0.81)	0.58(0.50-0.67)	0.29(0.23-0.35)	0.046	0.42
NSTEMI/UA	1.00	0.72(0.63-0.83)	0.58(0.49-0.68)	0.37(0.27-0.50)	0.75(0.65-0.87)	0.71(0.59-0.84)	0.58(0.49-0.68)	0.29(0.23-0.37)	0.051	0.37
STEMI	1.00	0.75(0.60-0.94)	0.72(0.54-0.96)	0.34(0.21-0.56)	0.95(0.72-1.25)	0.79(0.57-1.09)	0.68(0.50-0.94)	0.32(0.21-0.46)	0.97	0.57

STEMI: ST segment elevation MI; NSTEMI: Non ST segment elevation MI; UA: Unstable angina

§ p values for interactions between age and sex

† p values for 3-way interactions among age, sex, and study period

Model 3 adjusted for study period (1999-2001, 2002-2003, 2004-2005, and 2006-2007), geographic region, type of hospital (teaching vs. others), history of heart failure, hypertension, or diabetes, and GRACE risk model factors: systolic blood pressure, initial serum creatinine, heart rate, cardiac enzyme, Killip class, ST-segment deviation, and cardiac arrest at the time of hospital arrival.

Figure 3.1 Proportion of Patients Hospitalized with an Acute Coronary Syndrome Treated with ≥3 Cardiac Medications according to Age and Sex by Study Period

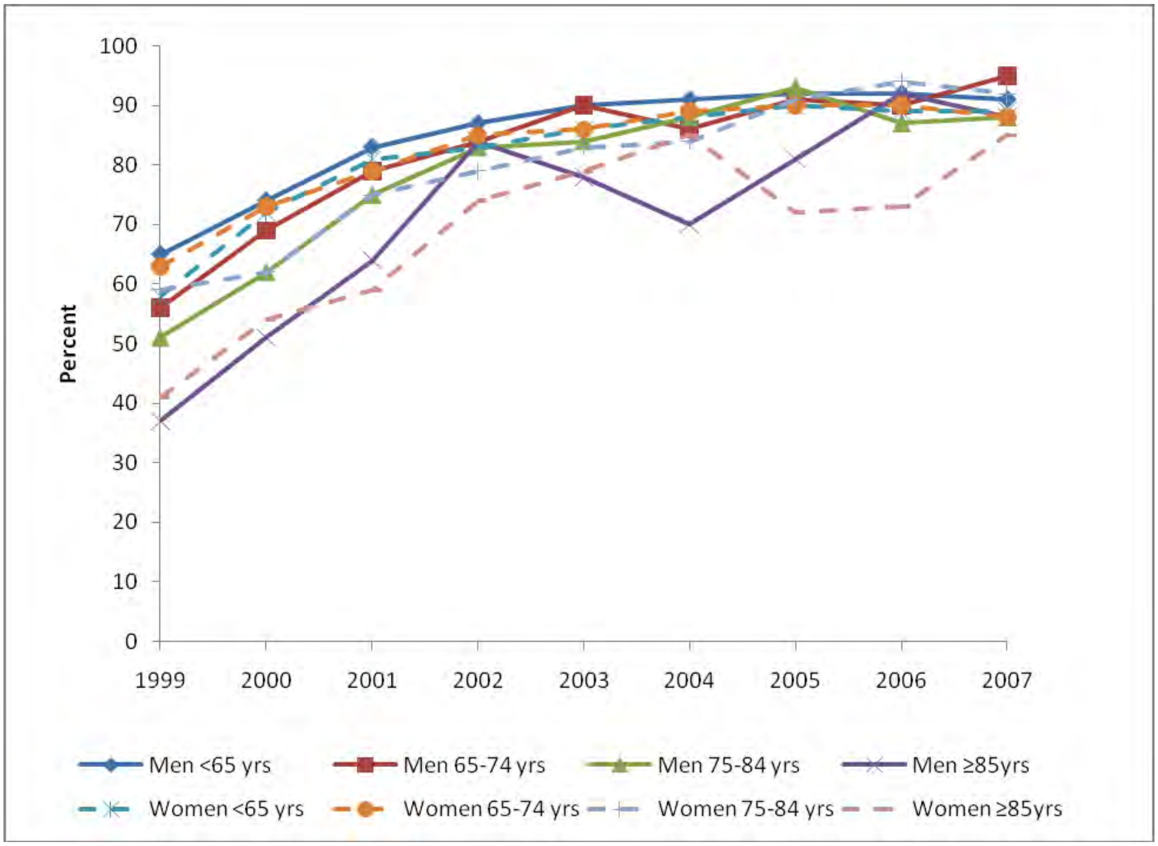
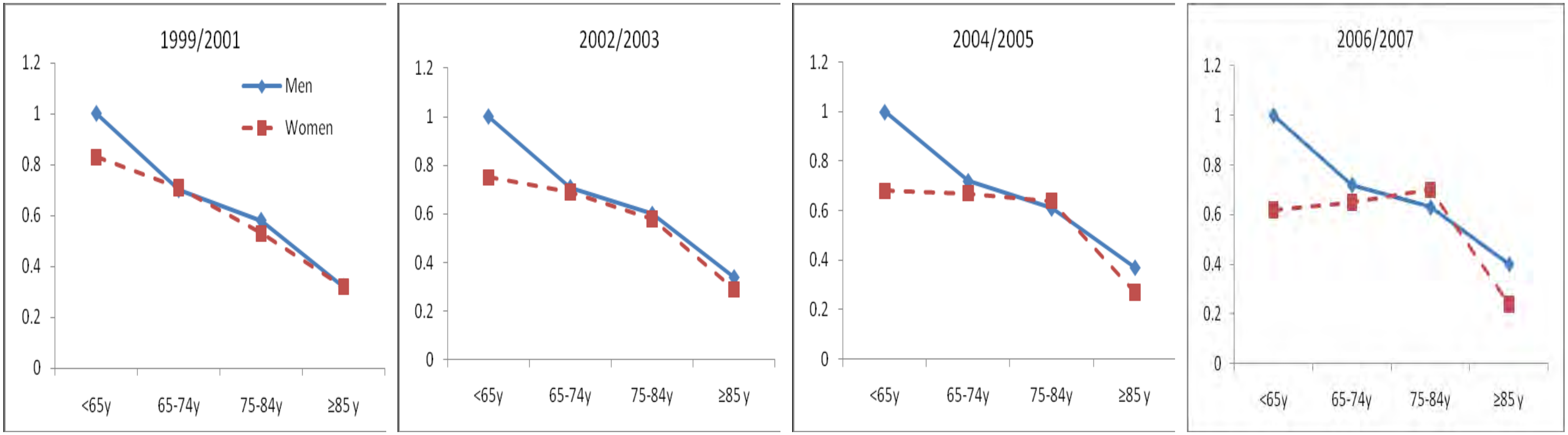


Figure 3.2 Odd Ratios for the Utilization of ≥ 3 Cardiac Medications in Eligible Patients According to Age, Sex, and Study Period



CHAPTER IV

Age and Sex Differences in Short-term Outcomes, and Changing Trends, in Patients Hospitalized with Acute Myocardial Infarction

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Abstract

Background

Despite declines in in-hospital complications and short-term death rates in patients with acute myocardial infarction (AMI), several patient groups remain at increased risk for these adverse outcomes, including women and the elderly. However, recent trends in age and sex differences in short-term outcomes associated with AMI remain unexplored. The objectives of this study were to examine the overall magnitude, and changing trends, of age and sex differences in short-term outcomes in patients hospitalized with AMI.

Methods

The study population consisted of 13,663 residents of the Worcester, MA, metropolitan area hospitalized at all greater Worcester medical centers for AMI between 1975 and 2005.

Results

In comparison with men <65 years, patients in various older age-sex strata were significantly more likely to develop atrial fibrillation, cardiogenic shock, heart failure, and to die during hospitalization and in the first 30 days after admission. The odds of developing these hospital complications and dying increased with advancing age. There was a significant interaction between age and sex in relation to the development of several of these outcomes; in patients <65 years, women were more likely to develop these complications and die compared with men, but in patients ≥ 65 years, there were no significant sex differences. These age and sex differences have not changed significantly over time.

Conclusions

Younger women and the elderly were more likely to have adverse outcomes than younger men. More targeted treatment approaches during hospitalization for AMI for younger women and older patients are needed to improve their hospital prognosis.

Word count: 249

Key words: Acute myocardial infarction, hospital complications, hospital mortality, age and sex differences.

4.1 Introduction

Over the past several decades, dramatic advances in the medical management of patients hospitalized with acute myocardial infarction (AMI) have been accompanied by reductions in in-hospital complications and short-term death rates. Despite encouraging declines in population death rates from coronary heart disease (CHD) in the U.S., and hospital mortality from AMI since the late 1960's, several patient groups remain at increased risk for dying after AMI, including women and the elderly.

Previous studies examining age and sex differences in the development of hospital complications and risk of dying in the setting of AMI have shown inconsistent results. [51,81,85,86,93-95] Some studies found that older persons and women had higher hospital complication and mortality rates compared to younger individuals and men, respectively. [51,91,93-95,118,119] On the other hand, several studies have failed to find any association between the risk of developing clinically significant hospital complications and/or dying between men and women of varying ages.[81,85,86,120] Furthermore, there are a distinct lack of data from a broader community perspective that has examined changing, and contemporary, associations between age/sex and short-term hospital outcomes in patients hospitalized with AMI as well as the interaction between age and sex in relation to these endpoints. Moreover, few population-based studies have examined whether differences in hospital outcomes observed in prior studies according to age and sex have changed over time or whether important gaps in these endpoints continue to exist.[91,121]

The objectives of the present study were to examine age and sex differences, and changing trends over an extended period (1975-2005), in important hospital complications as well as short-term (in-hospital and 30-day) mortality in patients hospitalized with AMI. Data from the population-based Worcester Heart Attack Study were utilized for this investigation.[2,6,105,122]

4.2 Methods

The Worcester Heart Attack Study is an ongoing population-based investigation that is examining long-term trends in the incidence, hospital, and post-discharge case-fatality rates of AMI among residents of the Worcester metropolitan area (2000 census estimate = 478,000) hospitalized at all 16 greater Worcester medical centers in 15 biennial periods between 1975 and 2005. [2,6,105,122] Fewer hospitals (n=11) have been included during recent study years due to hospital closures, mergers, and conversion to chronic care facilities. The details of this study have been described previously.[105,122] In brief, the medical records of patients hospitalized for possible AMI were individually reviewed and a diagnosis of AMI was validated according to predefined criteria.[105,122] Patients who developed AMI secondary to an interventional procedure or surgery were excluded from the study sample.

Data Collection

Information about demographic characteristics, medical history, clinical presentation, hospital treatment approaches, clinical complications, and hospital discharge status were abstracted from the hospital medical records of patients with confirmed AMI by trained study physicians and nurses. Age was categorized into three strata, which was used previously in the literature, for purposes of analysis: <65 years, 65-74 years, and ≥75 years. Development of hospital complications and short-term (in-hospital and 30 day) mortality were the primary study outcomes. The criteria for atrial fibrillation included the documentation of atrial fibrillation in the physicians' progress notes, based on the review of hospital medical records, or occurrence of typical electrocardiographic changes consistent with a diagnosis of atrial fibrillation.[100] Heart failure was considered to be present when there was clinical or radiographic evidence of pulmonary edema or bilateral basilar rales with an S3 gallop.[101] Cardiogenic shock was defined as a systolic blood pressure of less than 80 mm Hg in the absence of hypovolemia and associated with cyanosis, cold extremities, changes in mental status, persistent oliguria, or congestive heart failure.[102] The occurrence of acute stroke was defined as the development of neurologic changes consistent with the presence of a stroke based on information contained in medical records and reviewed by our team of nurse and physician abstractors.[99] Patients with a validated diagnosis of AMI discharged from all metropolitan Worcester hospitals were followed on an annual basis through the review of records for additional hospitalizations and search of death certificates at state and local Divisions of Vital Statistics. Some form of additional follow-up has been obtained for more than 99% of discharged hospital survivors from the cohorts included to date with follow-up completed through 2008.

Candidate variables considered as potential confounders of the association between age/sex and the outcomes under study were chosen based on findings from prior studies including study year, which was grouped into 7 periods (1975/1978, 1981/1984, 1986/1988, 1990/1993, 1995/1997, 1999/2001 and 2003/2005) for ease of analysis, race (white vs. non-white), marital status (single, married, divorced, widowed), comorbidities (e.g., atrial fibrillation, diabetes, hypertension, stroke, heart failure), chest pain symptoms, AMI order (initial vs. prior), type (Q wave vs. non–Q wave) and location (anterior vs. other), and receipt of cardiac procedures during hospitalization (PCI, CABG), and length of stay.[98] Information on pre-hospital delay was recorded beginning in 1986, information on do not resuscitate (DNR) status was recorded beginning in 1991, data on body mass index (BMI) was collected beginning in 1995, and information about whether the AMI was a non–ST-segment elevation myocardial infarction (NSTEMI) or an ST-segment elevation myocardial infarction (STEMI) was recorded beginning in 1997.

Data Analysis

Categorical data were summarized as percentages and were compared between patients of various age strata (<65, 65-74 and ≥75 years) and both sexes using the chi-square test. Continuous variables were presented as medians (inter-quartile range, IQR) and were tested for possible differences according to age and sex using the Kruskal-Wallis test.

We examined the possible association between age/sex and various hospital outcomes using logistic regression models. Model 1 included age, sex, and study year. Model 2 further adjusted for race, marital status, and medical history of cardiovascular disease. Model 3 further adjusted for the presence of chest pain, AMI-associated characteristics, cardiac procedures, and length of stay**.** This approach allowed us to examine the contributions of various potentially confounding factors to observed age and sex differences in our principal study outcomes. To test whether any age or sex differences in our hospital endpoints have changed over time, 2-way and 3-way interaction terms between age, sex, and study year were created and included in each regression model. Likelihood ratio tests were used to test the nested models with and without interaction terms. A similar process was performed to examine the association between age/sex and 30-day mortality using Cox regression models. The proportional hazards assumption was checked graphically and satisfied. Further analyses in patients, who had information available on duration of pre-hospital delay after the onset of acute coronary symptoms, DNR status, and STEMI/NSTEMI, were also carried out in additional regression models. Random effect models were used to assess whether the different patient clusters within hospital affected our observed results. All analyses were performed using STATA 10.0.

4.3 Results

The study sample consisted of 13,663 residents of the Worcester metropolitan area hospitalized with validated AMI at all greater Worcester medical centers in 15 study years between 1975 and 2005. The average age of this patient population, which was comprised of approximately three- fifths men, was 69 years; 36% of patients were <65 years (75% men vs. 25% women), 26% were between the ages of 65- 74 years (59% men vs. 41% women), and 38% were ≥ 75 years (42% men vs. 58% women). Women were considerably older than men at the time of hospital admission for AMI (means: 74 years vs. 66 years).

Baseline Characteristics

Baseline characteristics of patients hospitalized with AMI according to age and sex are shown in Table 4.1. The proportion of patients with a history of atrial fibrillation, heart failure, hypertension, and stroke was higher in older patients in both sexes. Within the same age strata, women were more likely to have a previous history of hypertension, heart failure, and diabetes, but were less likely to have a history of atrial fibrillation, than men (Table 4.1).

The proportion of patients with an initial and Q-wave MI was lower in older patients in both sexes (Table 4.1). The proportion of STEMI patients decreased with advancing age in men, but not in women. Within the same age strata, women were more likely to have an initial and anterior MI than men. Among patients <75 years, women were less likely to have a Q-wave MI than men, but in older patients these proportions were similar (34%). Among patients < 75 years, women were less likely to develop a STEMI than men, but among older patients, women were more likely to have a STEMI than men (Table 4.1).

The proportion of patients reporting shortness of breath and fatigue was higher in older patients in both sexes (Table 4.1). Within the same age strata, women were more likely to report nausea and fatigue than men. Among patients >65 years, women were less likely to report chest pain than men; however, among patients younger than 65 years, identical proportions of men and women reported chest pain (28%). The proportion of patients with a DNR order in their hospital medical records was higher in older patients; within the same age strata, women were more likely to have a DNR order than men (Table 4.1).

Heart rate and serum glucose levels were higher in older patients in both sexes; on the other hand, serum levels of cholesterol, LDL and triglycerides, GFR, and patient's BMI were lower in older women and men (Table 4.1). Within the same age strata, women were more likely to have a higher heart rate, serum cholesterol, triglycerides, and glucose levels, but lower diastolic blood pressure and GFR, than men. The proportions of patients undergoing angioplasty during hospitalization were lower in older patients in both sexes; within the same age groups, women were less likely to undergo coronary angioplasty and CABG during hospitalization (Table 4.1).

Hospital Complications and Death According to Age and Sex

Unadjusted Analyses

Overall, older patients were more likely to have developed atrial fibrillation, cardiogenic shock, and heart failure than younger patients. Within the same age groups, women were more likely to have developed heart failure and stroke than men (Table 4.2). Hospital and 30-day case-fatality rates were higher in older patients; within the same age strata, women were more likely to have died during hospitalization or during the first 30 days after hospital admission than men (Table 4.2).

In examining trends in hospital mortality according to age and sex, declining trends in hospital mortality were observed for all groups (Figure 4.1). Between 1975/1978 and 2003/2005, the greatest absolute decline in hospital mortality was observed in women ≥ 75 years (43% vs. 13%), followed by men 75 years and older (31% vs. 13%), men 65-74 years (23% vs. 8%), women 65-74 years (26% vs. 12%), women < 65 years (14% vs. 5%), and men <65 years (9% vs. 2%).

Multivariable Adjusted Analyses

Hospital Complications

For atrial fibrillation, the overall odds of developing this complication increased with advancing age in both men and women (Table 4.3). Compared with men < 65 years, other age- sex groups were significantly more likely to develop atrial fibrillation in all 3 regression models with the exception of women <65 years. There was no evidence of an interaction between age and sex in relation to the development of this arrhythmia. The non- significant 2-way and 3-way interactions among age, sex, and study year indicated that age and sex differences in the risk of developing atrial fibrillation in patients hospitalized with AMI have been relatively unchanged over time (Table 4.3, Figure 4.2).

For heart failure, the overall odds of developing this clinical syndrome increased with advancing age in both men and women (Table 4.3). Compared with men < 65 years, other age- sex groups were significantly more likely to have developed heart failure in all 3 regression models. There were significant interactions between age and sex in relation to the development of heart failure in our unadjusted model and in the model adjusted for marital status and medical history (Model 1, 2, Table 4.3); however, the interaction between age and sex became non-significant when the regression model was further adjusted for clinical presentation, cardiac procedures, and length of hospital stay (Model 3, Table 4.3). The non- significant 2-way and 3-way interactions among age, sex, and study year indicated that age and sex differences in heart failure have been relatively unchanged over time (Table 4.3, Figure 4.3).

For cardiogenic shock, the overall odds of developing this complication increased with advancing age in men but not in women (Table 4.3). Compared with men < 65 years, other age and sex groups were significantly more likely to have developed cardiogenic shock in all 3 regression models. There were significant interactions between age and sex in relation to the development of cardiogenic shock; in patients <65 years, women were more likely to have developed cardiogenic shock compared with men (Adjusted OR: 1.77, 97% CI: 1.31-2.41, model 3), but in patients ≥ 65 years, there was no significant difference between men and women in the risk of developing cardiogenic shock (Table 4.3). The non- significant 2-way and 3-way interactions among age, sex, and study year indicated that age and sex differences in cardiogenic shock have been relatively unchanged over time (Table 4.3, Figure 4.4).

Due to the small number of acute stroke events, no multivariable regression analysis was performed for this study outcome.

Short-Term Mortality

Overall, the odds of dying during hospitalization, and the risk of dying during the first 30 days after admission, increased with advancing age in both men and women (Table 4.3). Compared with men < 65 years, other age and sex groups experienced significantly higher short-term death rates in all 3 regression models. There was a significant interaction between age and sex in relation to short-term mortality; among patients <65 years, women had significantly higher in-hospital mortality (Adjusted OR:

1.62, 97% CI: 1.23-2.14, model 3) and 30-day mortality compared to men (Adjusted HR: 1.72, 97% CI: 1.32-2.24, model 3); however, among patients ≥ 65 years, there were no significant differences in the risk of short-term mortality between men and women (Table 4.3). The non- significant 2-way and 3-way interactions among age, sex, and study year indicated that age and sex differences in short-term (in-hospital and 30-day) mortality have been relatively unchanged over time (Table 4.3, Figure 4.5).

Further regression analyses performed in patients who had information available on pre-hospital delay, DNR status, and STEMI/NSTEMI provided relatively similar results. Random effect models assessing the effects of patient clusters within hospital provided similar results and did not change our conclusions.

4.4 Discussions

In this study of more than 13,000 residents of a large central New England metropolitan area hospitalized with AMI, we found that, compared with men <65 years, older men and women were more likely to develop atrial fibrillation, cardiogenic shock, and heart failure, and were more likely to have died during hospitalization and in the first 30 days after admission, for AMI. There was a significant interaction between age and sex in relation to the development of these important hospital complications and death; in patients <65 years, women were more likely to develop these complications and to die compared with men, but in patients ≥ 65 years, there were no significant differences between men and women in the occurrence of these outcomes. These age and sex differences have not changed significantly over the past 3 decades.

Our results are consistent with the findings from previous studies[51,91,93] which have shown that older persons were significantly more likely to develop clinically significant complications and to die than younger individuals in patients hospitalized with AMI and age was a more important predictor of poor hospital prognosis than sex. For example, a retrospective cohort study that included more than 17,000 patients in the Analysis of Delay in AMI register (ARIAM) in 119 Spanish hospitals between 1995 and 2001, found that the risk of developing various hospital complications, including heart failure, shock, and stroke, and dying increased significantly with advancing age.[51] Older patients are more likely to have additional comorbidities present, including diabetes, hypertension, and heart failure,[20,39,52] at the time of their AMI which may increase their risk of adverse outcomes. In addition, previous studies have shown that older patients were less likely to be treated with effective medications and cardiac procedures[51,113] that may have contributed to their higher risk of hospital complications and dying. Other factors such as prolonged delay in seeking medical care,[8-10] limited health care access, cognitive impairment, and frailty may have contributed to the adverse outcomes noted in older persons.

Sex differences in hospital complications and short-term mortality were found in our study in patients < 65 years, but not in patients ≥65 years, a finding which is consistent with the results of previous studies. [94,103,117,119,123,124] For example, findings from the Swedish National Acute Myocardial Infarction of approximately 350,000 patients aged 30 to 89 years over the period 1987-1995 demonstrated higher early mortality rates in women than men but only in patients <70 years.[123] Similarly, a recent publication from the National Registry of Myocardial Infarction (NRMI), that included approximately 360,000 patients from 2000 and 2006, found that in patients <70 years, women had a higher hospital death rate than men; in older patients, however, women had either a similar (among STEMI patients) or lower hospital death rate (among NSTEMI patients) compared with men.[103]

The reasons for worse short-term outcomes in younger women hospitalized with AMI are unclear. This may be partially explained by the fact that women are more likely to have additional comorbidities present, such as diabetes and heart failure, than men, and differences in these and other important prognostic factors are likely to be more pronounced in younger than in older individuals.[123] In addition, young women have been shown to be less likely to be treated with effective medications[117,121] compared with young men, which can contribute to the worse outcomes noted in younger women. However, a previous analysis in approximately 380,000 patients included in the NRMI suggested that the differences in medical history, clinical severity of the infarction, and early management accounted only for about one third of the differences in early mortality observed between men and women.[94] Moreover, in the present study, we found that women were more likely to develop clinical complications than men in younger patients only, while there was no sex difference in the frequency of these complications in older patients, which could explain the excess mortality observed in younger women than men. The fact that men may be more likely to die out-of-hospital from coronary disease than women, and that this sex difference may be larger in younger than in older patients,[123] could contribute to higher in-hospital mortality rates in younger women hospitalized with

AMI compared with men. More studies need to be done to further understand the reasons behind the greater risk of adverse outcomes noted in younger women hospitalized with AMI.

In examining whether age and sex differences in various short-term outcomes have changed over time, our results suggest that age and sex differences in hospital complications and deaths have not changed significantly over time with the exception of cardiogenic shock. On the other hand, a recent publication from the NRMI that included approximately 910,000 patients with AMI between 1994 and 2006 demonstrated that sex differences in hospital mortality have narrowed over time.[121] Differences between these studies may be due to the characteristics of the respective study samples, inclusion/exclusion criteria, sample size, and periods under study.

Our findings showed that although hospital mortality associated with AMI has decreased over time (21% in 1975/1978 vs. 9% in 2003/2005), age and sex differences in important clinical complications and mortality have not changed significantly over time; younger women and the elderly are still at higher risk for these adverse outcomes than younger men. Inasmuch, greater use of prevention programs and effective cardiac treatment regimens for younger women and the elderly are needed to improve their short-term outcomes.

Study Strengths and Limitations

This study has several strengths including its population-based design that captured all validated cases of AMI occurring among unselected residents of the Worcester metropolitan area hospitalized at all Central Massachusetts medical centers over a 30 year period. However, several limitations need to be kept in mind in interpreting the present findings. First, the majority of the study population was white; therefore, the generalizability of our findings to other race/ethnic groups is limited. We did not have information available on several patient associated characteristics (e.g., socioeconomic status, psychological factors) which may have confounded some of the observed associations. Finally, since patients who died out of the hospital from AMI were not included, the findings only apply to patients hospitalized with AMI; the direction and magnitude of the associations between age/sex and these outcomes in patients who died before reaching the hospital may be different from those who are hospitalized.

4.5 Conclusions

Our results suggest that younger women and the elderly were more likely to experience adverse short-term outcomes in the setting of AMI compared with younger men and these differences have relatively unchanged over time. Future studies should focus on investigating the reasons for these differences in order to optimize the treatment of these high risk groups and improve their short-term prognosis.

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Table 4.1. Baseline Characteristics of Patients with Acute Myocardial Infarction (AMI) According to Age and Sex

	Men				Women			
Characteristics	<65 y (n=3,657)	65-74y (n=2,103)	≥ 75y (n=2,205)	P-value	<65y (n=1,202)	65-74y (n=1,453)	≥ 75y (n=3,004)	P-value
Mean age ± SD, years	53.4±8.5	69.6±2.9	81.6±5.1		55.0±8.8	70.0±2.8	83.0±5.6	
White, n (%)	3,294(93.5)	1,926(95.4)	2,090(97.6)	<0.001	1,073(92.0)	1,315(94.6)	2,822(96.8)	<0.001
Marital status, n (%)								
Single	436(12.1)	202(9.7)	163(7.5)	<0.001	136(11.6)	139(9.7)	325(11.1)	<0.001
Married	2,798(77.4)	1,598(77.1)	1,435(66.1)		727(61.8)	654(45.8)	723(24.6)	
Divorced	198(8.3)	107(5.2)	58(2.7)		158(13.4)	94(6.6)	78(2.7)	
Widowed	81(2.2)	166(8.0)	514(23.7)		156(13.2)	540(37.8)	1,814(61.6)	
Medical History, n (%)								
Atrial fibrillation	56(2.7)	140(11.2)	312(19.7)	<0.001	17(2.4)	77(8.8)	377(17.5)	<0.001
Hypertension	1,668(45.6)	1,163(55.3)	1,315(59.6)	<0.001	647(53.9)	984(67.7)	2,074(69.1)	<0.001
Heart failure	217(5.9)	337(16.0)	622(28.2)	<0.001	144(12.0)	308(21.2)	971(32.3)	<0.001
Diabetes	703(19.2)	637(30.3)	639(29.0)	<0.001	401(33.4)	560(38.5)	887(29.5)	<0.001
Stroke	134(3.7)	216(10.3)	349(15.8)	<0.001	78(6.5)	159(10.9)	394(13.1)	<0.001

CABG	112(3.1)	131(6.2)	217(9.8)	<0.001	53(4.4)	68(4.7)	106(3.5)	0.135
AMI characteristics, n (%)								
Initial	2,627(72.1)	1,252(59.7)	1,275(58.0)	<0.001	879(73.3)	953(65.7)	1,883(62.8)	<0.001
Q-wave	1,889(55.4)	857(44.1)	662(33.5)	<0.001	517(46.7)	542(40.0)	917(34.3)	<0.001
Anterior	1,129(33.2)	717(36.8)	653(33.1)	0.015	416(37.7)	528(38.9)	953(35.8)	0.128
STEMI*	664(18.2)	301(14.3)	289(13.1)	<0.001	209(17.4)	169(11.6)	437(14.6)	<0.001
Clinical symptoms, n (%)								
Chest pain	1,018(28.0)	495(23.8)	627(29.1)	<0.001	333(28.1)	294(20.6)	724(24.7)	<0.001
Shortness of breath	673(18.4)	404(19.2)	616(27.9)	<0.001	253(21.1)	310(21.3)	858(28.6)	<0.001
Nausea	480(13.1)	198(9.4)	235(10.7)	<0.001	203(16.9)	168(11.6)	407(13.6)	<0.001
Diaphoresis	661(18.1)	267(12.7)	320(14.5)	<0.001	196(16.3)	192(13.2)	394(13.1)	0.019
Fatigue	142(3.9)	95(4.5)	182(8.3)	<0.001	55(4.6)	88(6.1)	348(11.6)	<0.001
DNR order, n (%)*	53(2.8)	122(11.2)	472(33.1)	<0.001	47(7.4)	113(15.5)	900(45.7)	<0.001
Pre-hospital delay (hour)*, median (IQR)	1.9(1.0- 4.1)	2.0(1- 4.5)	2.5(1.2-5.1)	<0.001	2.0(1.0-4.7)	2.4(1.3-5.5)	2.3(1.2-5.0)	0.018
Clinical parameters on admission, median (IQR)								
Heart rate(beats/min)	80(67-94)	81(67-100)	87(71-102)	<0.001	83(70-99)	84(72-102)	88(74-105)	<0.001
Systolic BP, mmHg	141(122-161.5)	142(121-160)	140(117-160)	0.051	142(121-164)	143(120-170)	141(120-165)	0.82

Diastolic BP, mmHg	84(70-98)	80(67-91)	73.5(61-86)	<0.001	80(64-92)	77(64-90)	70(57.5-86)	<0.001
BMI(kg/m2)*	28.6(25.7-32.3)	27.3(24.4-30.3)	25.6(23.1-28.0)	<0.001	28.1(24.5-33.1)	27.3(23.0-32.1)	24.6(21.3-28.3)	<0.001
Laboratory findings on admission, median (IQR)								
Cholesterol(mg/dl)	210(178-246)	192(162-230)	177.5(147-214)	<0.001	220(181-259)	221(183-260)	204(166-240)	<0.001
LDL(mg/dl)	115(94-142)	105(82-124)	97(75-121)	<0.001	111(87-142)	107(84-141)	102(78-133)	<0.004
Triglyceride(mg/dl)	134(95-194)	115(85-177)	98(67-136)	<0.001	139(93-197)	129(94-198)	105(76-152)	<0.001
Glucose(mg/dl)	134(112-178)	151(119-209)	150(120-209)	<0.001	146(116-238)	163(125-247)	161(126-228)	0.024
GFR	80(66-92)	64(49-79)	52(37-68)	<0.001	69(50-83)	58(43-67)	46(33-62)	<0.001
In-hospital Procedures, n (%)								
PCI	812(22.2)	308(14.7)	235(10.7)	<0.001	235(19.6)	196(13.5)	268(8.9)	<0.001
CABG	147(4.0)	107(5.1)	69(3.1)	<0.001	44(3.7)	61(4.2)	47(1.6)	<0.001
Length of stay (day), median (IQR)	8(4-13)	8(5-14)	7(4-12)	<0.001	8(4-14)	9(5-14)	7(4-11)	<0.001

IQR: Inter quartile range; LDL, low-density lipoprotein; GFR, glomerular filtration rate; PCI: Percutaneous coronary intervention; CABG: Coronary Artery Bypass Graft

*Information on pre-hospital delay, DNR status, BMI and STEMI was recorded beginning in 1986, 1991, 1995 and 1997, respectively.

Table 4.2 Overall Hospital Complication and Death Rates in Patients with Acute Myocardial Infarction According to Age and Sex

	Men				Women			
Complications, n(%)	<65y	65-74y	≥ 75y	P-value	<65y	65-74y	≥ 75y	P value
Atrial fibrillation	300(8.2)	391(18.6)	578(26.2)	<0.001	104(8.7)	228(15.7)	739(24.6)	<0.001
Heart failure	807(22.1)	838(39.9)	1,110(50.3)	<0.001	370(30.8)	633(43.6)	1,633(54.4)	<0.001
Cardiogenic shock	159(4.4)	149(7.1)	174(7.9)	<0.001	81(6.7)	109(7.5)	232(7.7)	0.55
Stroke†	6(0.3)	5(0.4)	13(0.8)	<0.001	2(0.3)	11(1.1)	21(1.0)	<0.001
In-hospital mortality	201(5.5)	285(13.6)	462(21.0)	<0.001	102(8.5)	221(15.2)	676(22.5)	<0.001
30-day mortality from admission	426(11.7)	417(19.8)	694(31.5)	<0.001	188(15.6)	298(20.5)	1,007(33.5)	<0.001

† Information on the occurrence of stroke was recorded beginning in 1986.

Table 4.3 Overall Age and Sex Differences in Short-Term Outcomes in Patients with Acute Myocardial Infarction

	Men			Women			P values†	P values‡
	<65y	65-74y	≥ 75y	<65y	65-74y	≥ 75y		
Hospital Complications				Odd Ratios (95%CI)				
Atrial Fibrillation								
Model 1	1.00	2.56(2.18-3.01)	3.93(3.37-4.57)	1.07(0.85-1.35)	2.09(1.73-2.51)	3.16(3.12-4.17)	0.19	0.27
Model 2	1.00	2.46(2.09-2.91)	3.52(3.00-4.14)	1.02(0.80-1.29)	1.98(1.54-2.32)	2.98(2.52-3.53)	0.17	0.28
Model 3	1.00	2.37(1.98-2.84)	3.49(2.93-4.17)	1.02(0.79-1.32)	1.79(1.47-2.25)	2.98(2.47-3.58)	0.18	0.31
Heart Failure								
Model 1	1.00	2.37(2.10-2.67)	3.82(3.40-4.29)	1.60(1.38-1.85)	2.87(2.43-3.15)	4.49(4.03-5.00)	0.002	0.52
Model 2	1.00	1.98(1.76-2.26)	2.75(2.42-3.11)	1.33(1.14-1.56)	1.97(1.70-2.28)	2.86(2.51-3.26)	0.013	0.61
Model 3	1.00	1.84(1.61-2.11)	2.49(2.17-2.86)	1.31(1.11-1.54)	1.87(1.60-2.19)	2.67(2.30-3.07)	0.07	0.26
Cardiogenic Shock								
Model 1	1.00	1.69(1.34-2.13)	1.99(1.59-2.48)	1.59(1.20-2.09)	1.80(1.40-2.31)	1.94(1.57-2.39)	0.020	0.22
Model 2	1.00	1.63(1.28-2.06)	1.88(1.48-2.38)	1.51(1.13-2.01)	1.66(1.26-2.18)	1.75(1.37-2.25)	0.029	0.09

Model 3	1.00	1.83(1.41-2.37)	2.57(1.98-3.32)	1.77(1.31-2.41)	2.11(1.57-2.82)	2.42(1.85-3.18)	0.006	0.35
Hospital Mortality								
Model 1	1.00	2.80(2.32-3.39)	5.47(2.57-6.53)	1.63(1.27-2.09)	3.25(2.65-3.98)	5.97(5.04-7.07)	0.023	0.36
Model 2	1.00	2.62(2.16-3.19)	4.83(4.00-5.84)	1.57(1.21-2.03)	2.84(2.29-3.53)	5.02(4.13-6.10)	0.022	0.37
Model 3	1.00	2.67(2.16-3.30)	5.46(4.46-6.70)	1.62(1.23-2.14)	3.08(2.44-3.90)	5.56(4.50-6.87)	0.018	0.56
30-day mortality				Hazard Ratios (95%CI)				
Model 1	1.00	2.87(2.39-3.45)	5.37(4.53-6.36)	1.67(1.31-2.13)	2.96(2.42-3.62)	5.76(4.90-6.77)	0.004	0.84
Model 2	1.00	2.64(2.19-3.20)	4.53(3.79-5.14)	1.57(1.22-2.01)	2.49(2.01-3.07)	4.53(3.77-5.44)	0.003	0.94
Model 3	1.00	2.85(2.34-3.47)	5.28(4.38-6.37)	1.72(1.32-2.24)	2.91(2.34-3.65)	5.29(4.36-6.42)	0.016	0.99

† p values for interaction between age and sex
‡ p values for 3-way interaction among age, sex, and study period
Model 1: Included age, sex, and interaction between age, sex, and study period
Model 2: Further adjusted for marital status and medical history of hypertension, diabetes, CABG, stroke, and heart failure
Model 3: Further adjusted for chest pain and AMI characteristics (Q wave vs. non-Q wave; initial AMI vs. recurrent AMI, anterior AMI vs. non-anterior AMI), cardiac procedures, and length of stay.

Figure 4. 1 Hospital Case- Fatality Rates According to Age, Sex, and Study Period

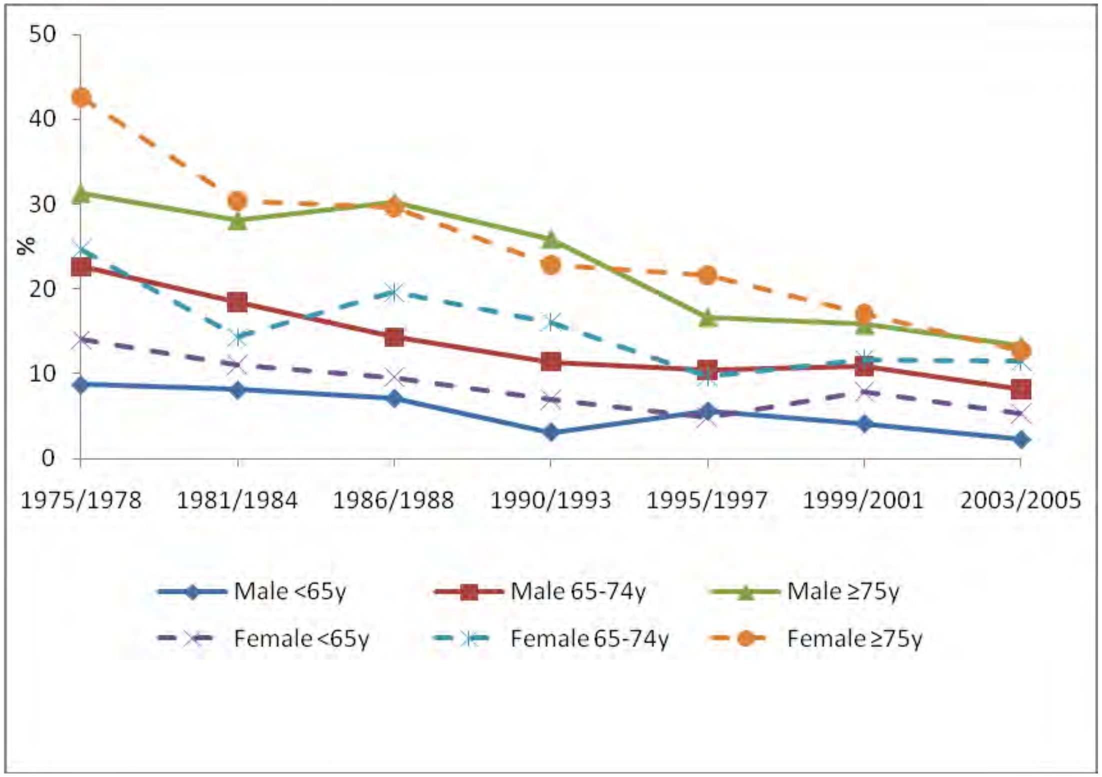


Figure 4.2 Adjusted Odds Ratios of Developing Atrial Fibrillation According to Age, Sex, and Study Period

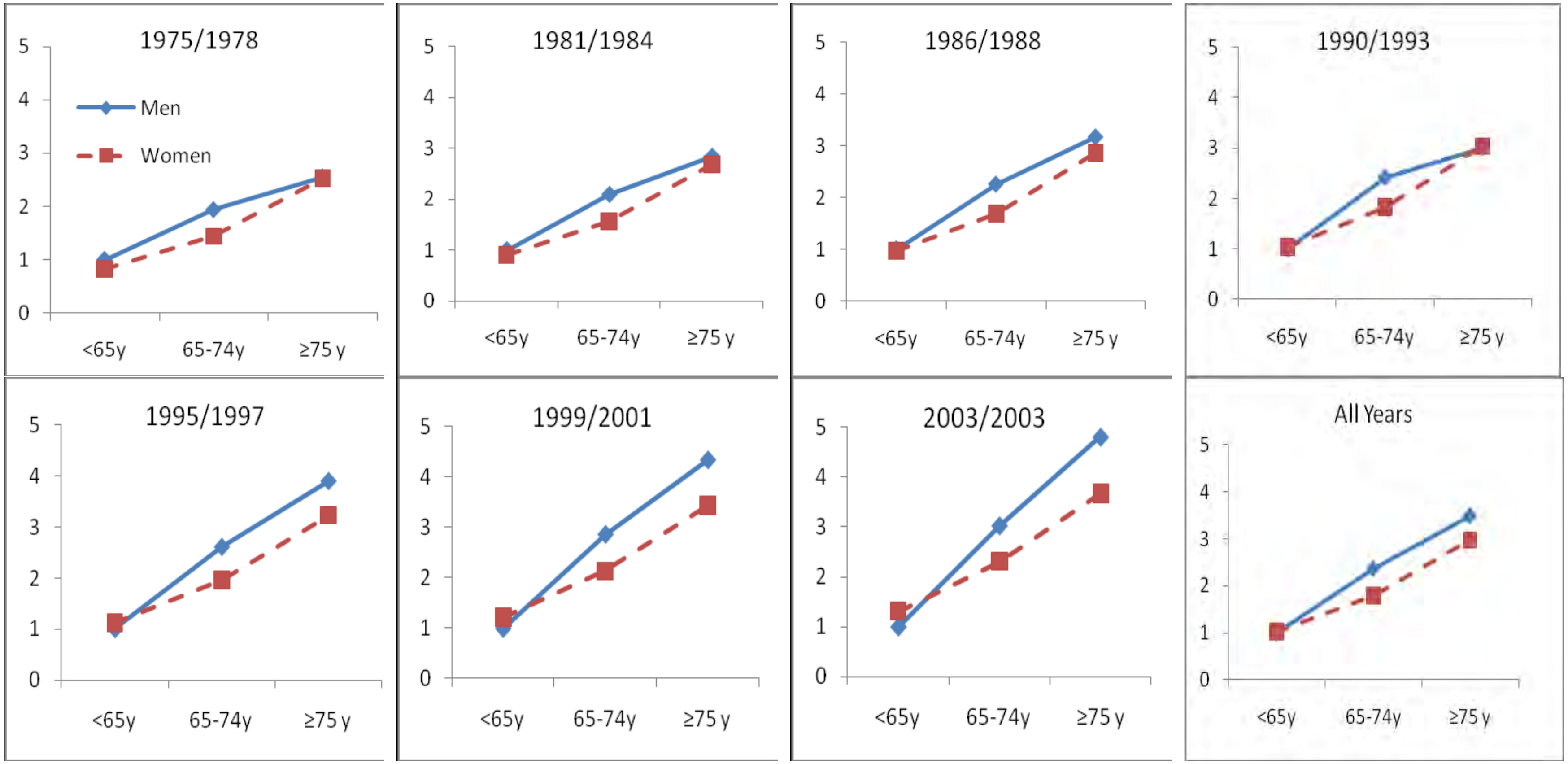


Figure 4.3 Adjusted Odds Ratios of Developing Heart Failure According to Age, Sex, and Study Period

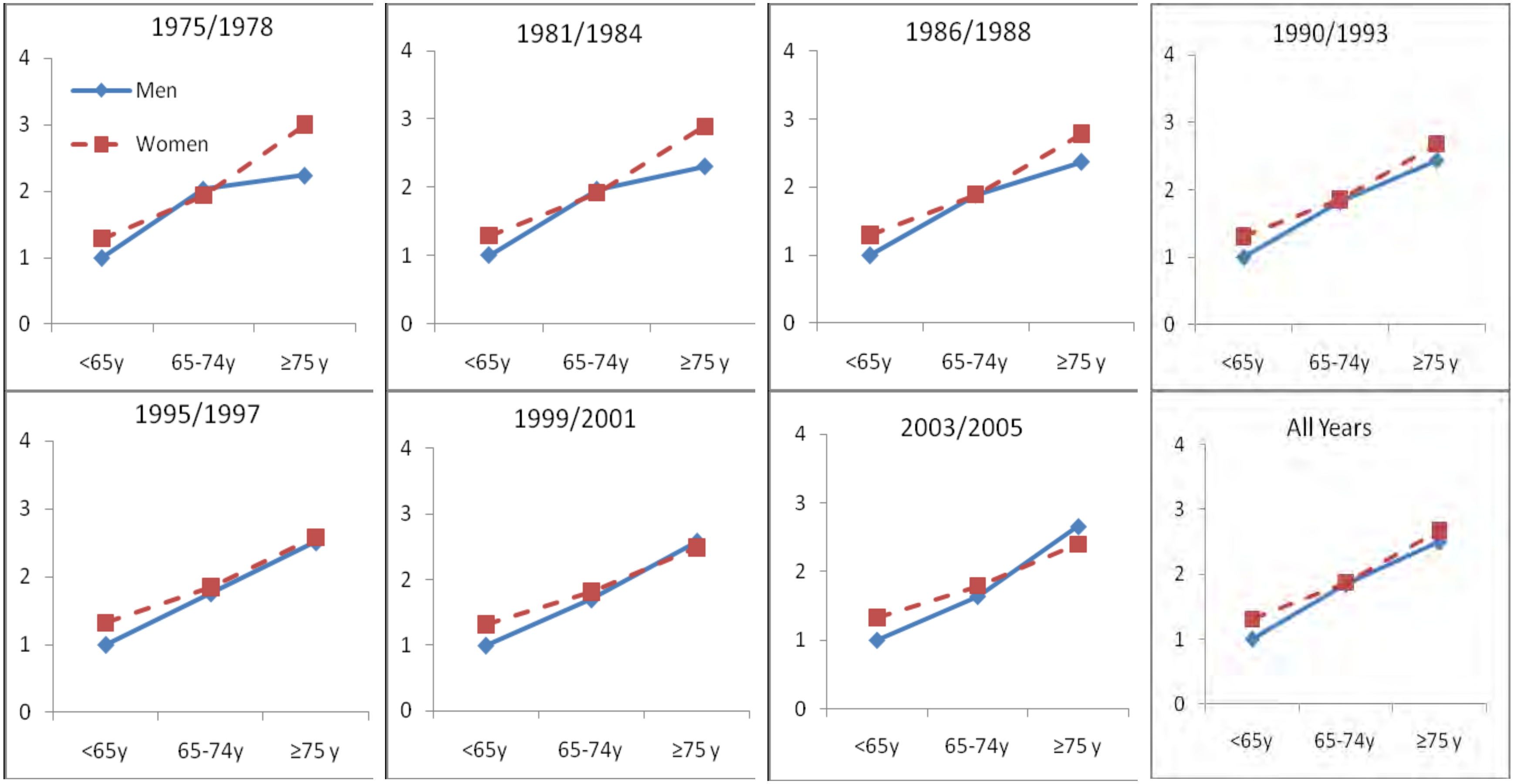


Figure 4.4 Adjusted Odds Ratios of Developing Cardiogenic Shock According to Age, Sex, and Study Period

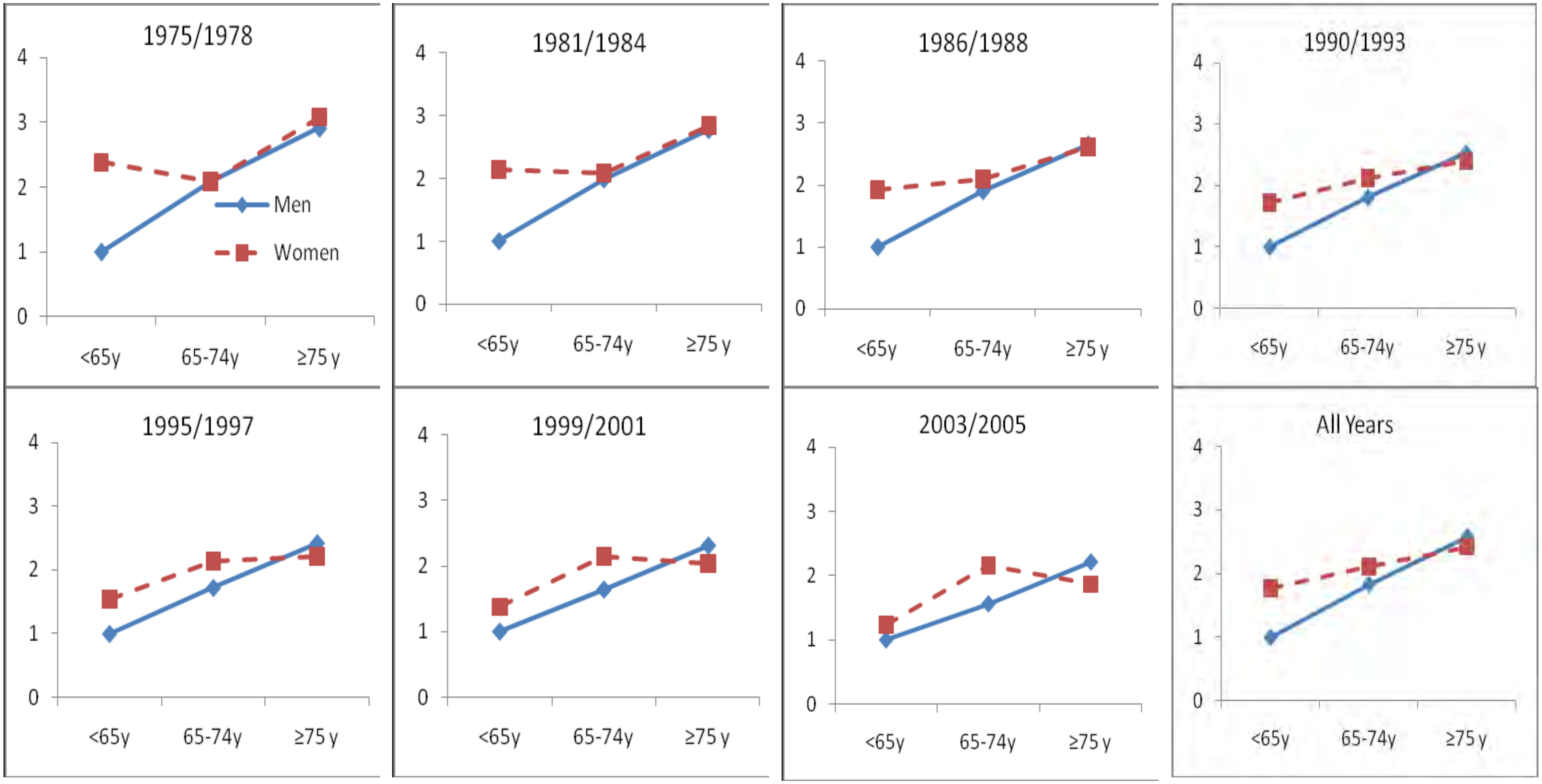
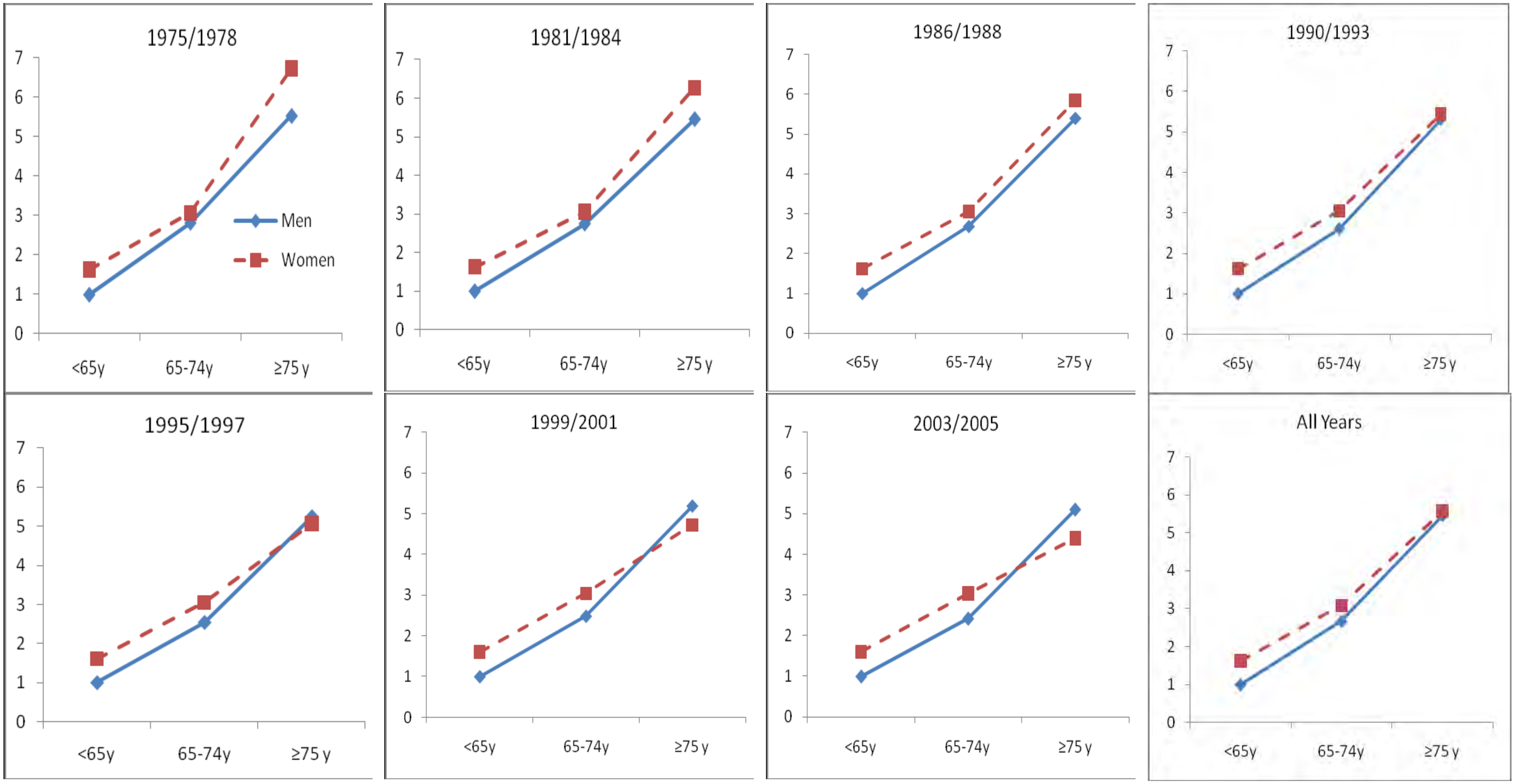


Figure 4.5 Adjusted Odds Ratios of In-Hospital Mortality According to Age, Sex, and Study Period



CHAPTER V

Conclusions

5.1 Summary of Findings

The objectives of this dissertation were to examine age and sex differences, and changing trends therein, in duration of pre-hospital delay, hospital management practices, and short-term outcomes in patients hospitalized with an ACS/AMI.

In examining changing trends in duration of pre-hospital delay in nearly 6,000 residents of a large central New England metropolitan area hospitalized with AMI between 1986 and 2005 (chapter II), we found that in overall patient's care seeking behavior after the onset of acute coronary symptoms has been relatively unchanged over the past 2 decades. In examining the association between age/sex and duration of pre-hospital delay, as compared with younger men, other age/sex groups were significantly more likely to delay seeking medical care after the onset of symptoms suggestive of AMI, with the exception of women < 65 years. There was an interaction between age and sex in relation to duration of pre-hospital delay. These age and sex differences have narrowed over time which has been largely explained by changes in patient's comorbidity profile and AMI associated characteristics.

In examining changing trends in the use of evidence-based medications in more than 50,000 patients hospitalized with an ACS between 1999 and 2007 in the large multinational GRACE study (chapter III), we found a marked increase in the hospital use of several key evidence-based cardiac medications, CABG surgery, and PCI in men and women of various age strata. In comparison with men <65 years, patients in other age-sex strata were less likely to be treated with these medications and cardiac procedures. There was some evidence, however, which suggested that there were interactions between age and sex with the use of beta blockers and multiple medications in that younger women were less likely to be treated with these medications during hospitalization for an ACS compared with younger men. Despite encouraging increases in prescribing practices over time, age and sex differences with regards to the prescribing of most effective cardiac therapies have not changed significantly during the period under study with the exception of beta blockers.

In examining changing trends in short-term outcomes in more than 13,000 residents of a large central New England metropolitan area hospitalized with AMI between 1975 and 2005 (chapter IV), we found declines in the frequency of important hospital complications, and increases in short-term survival, for all patients. In comparison with men <65 years, older men and women were more likely to develop atrial fibrillation, cardiogenic shock, and heart failure, and were more likely to have died during hospitalization and in the first 30 days after admission. There was a significant interaction between age and sex in relation to the development of these important hospital complications and death; in patients <65 years, women were more likely to develop these complications and to die compared with men; on the other hand, in patients ≥ 65 years, there were no significant differences between men and women in the occurrence of these outcomes. These age and sex differences have not changed significantly over the past 3 decades.

These findings suggest that the elderly were more likely to experience longer pre-hospital delay, were less likely to be treated with evidence-based treatments during hospitalization for acute coronary disease, and were more likely to develop adverse outcomes compared to younger persons. Younger women were less likely to be treated with effective treatments and were more likely to develop adverse outcomes compared with younger men. That may be partially explained by the differences in clinical presentation, coping mechanism when having symptoms suggestive of ACS/AMI, medical history, medical management practices between older and younger patients, and between men and women at younger age. Thus, more studies are needed to fully understand the reasons of these differences in order to design effective interventions aiming at narrowing these gaps. The elderly and younger women with ACS/AMI should receive more intentions with regards to both prevention and treatment to improve these outcomes.

5.2 Strengths and Limitations

A particular strength of the dissertation was the use of data from two large population-based and multinational registries of patients with ACS/AMI, which provide long-term and contemporary data on patients hospitalized with an ACS/AMI. On the other hand, as with all observational studies, the WHAS and the GRACE project are subject to certain inherent limitations and potential biases.

This WHAS has several strengths including its population-based design that captured all validated cases of AMI occurring among unselected residents of the Worcester metropolitan area hospitalized at all Central Massachusetts medical centers over a 30 year period. However, several limitations need to be kept in mind in the findings of this community-wide investigation. First, a considerable proportion of patients had data missing on pre-hospital delay; therefore, our findings should be interpreted with caution. Second, information about pre-hospital delay was abstracted from hospital medical records whose documentation may have varied over time and according to patient's demographic characteristics. In addition, the majority of the study population was White; therefore, the generalizability of our findings may be limited. We did not have information available on several patient associated characteristics (e.g., socioeconomic status) which may have confounded some of the observed associations, nor did we have information on the reasons why patients delayed seeking medical care. Finally, since patients who died out of the hospital from AMI were not included, the findings may only apply to patients hospitalized with AMI.

The GRACE study is the largest multinational registry to include the complete spectrum of patients hospitalized with an ACS. Standardized criteria are employed for defining ACS and hospital outcomes and rigorous quality control and audit measures are employed. ”Real-life” observational studies such as GRACE provide data on a heterogeneous population of patients that includes groups who are often under-represented in randomized trials, including women and the elderly.[8] On the other hand, as an observational study, GRACE is subject to certain inherent limitations and potential biases that must be kept in mind in interpreting the study results. Treatments were given according to individual physicians' decisions and not through the use of standardized treatment protocols. While currently recommended criteria were utilized to characterize patients who were eligible for the receipt of the cardiac medications examined, due to our reliance on data obtained from medical records, questions might be raised about our ability to characterize patient's eligibility status. Furthermore, we did not have information available on several patient associated characteristics (e.g., socioeconomic status, patient preferences) which may have confounded some of the observed associations.

5.3 Implications and Future Research Directions

Our results reinforce the need for the development of intervention programs to educate patients about the importance of seeking medical care promptly after the onset of symptoms suggestive of AMI since the prompt seeking of medical care is associated with the receipt of coronary reperfusion therapy and is crucial to reducing mortality and the risk of serious clinical complications in these patients. Moreover, since older men and women were at greatest risk for prolonged delay, interventions designed to reduce pre-hospital delay might be primarily focused on older men and women. Further qualitative studies might also be carried out in older men and women to identify the reasons why these high risk groups fail to react promptly to their symptoms of acute coronary disease focusing on their levels of cognition, knowledge, and attitudes toward health care.

In examining changing trends in the utilization of evidence -based medications and interventional procedures, our results suggest that age and sex gaps in the utilization of most medications have not changed significantly over time with the exception of beta blockers and the use of multiple medications. These findings suggest the need for greater understanding of the reasons underlying these treatment disparities and for the development of educational interventions and targeted programs to enhance the more optimal treatment of these high risk patients. Educational campaigns should continue to target older patients and younger women with respect to the receipt of effective cardiac treatments in the setting of an ACS since contemporary gaps in their more optimal management continue to remain.

Our findings showed that although hospital mortality associated with AMI has decreased over time, age and sex differences in important clinical complications and mortality have not changed significantly; younger women and the elderly are still at higher risk for these adverse outcomes than younger men. More studies need to be done to further understand the reasons behind the greater risk of adverse outcomes noted in younger women hospitalized with acute coronary diseases. Inasmuch, greater use of prevention programs and effective cardiac treatment regimens for younger women and the elderly are needed to improve their short-term outcomes.

In conclusion, the findings of this dissertation provide useful and contemporary information regarding age and sex differences in patients hospitalized with an ACS/AMI with regards to duration of pre-hospital delay, hospital management practices, and short-term outcomes. These data can inform the design of appropriate public health interventions and clinical guidelines to improve the short as well as long-term outcomes of all persons hospitalized with ACS/AMI.

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