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<https://doi.org/10.13028/j61r-ks88>. Retrieved from https://escholarship.umassmed.edu/gsbs_diss/1033

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CHANGING TRENDS IN THE LANDSCAPE OF PATIENTS HOSPITALIZED WITH
ACUTE MYOCARDIAL INFARCTION (2001 to 2011): THE WORCESTER HEART
ATTACK STUDY

A Masters Thesis Presented

By

REGINO MERCADO-LUBO

Submitted to the Faculty of the
University of Massachusetts Graduate School of Biomedical Sciences, Worcester in
partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN CLINICAL INVESTIGATION

June 28, 2019

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Dean of the Graduate School of Biomedical Sciences

Master of Science Degree in Clinical Investigation (MSCI)

June 28, 2019

ACKNOWLEDGEMENT

I would like to express my appreciation to my thesis advisor, Dr. Robert Goldberg, for his support and the mentorship he provided to me, from the time I was considering applying to the MSCI program, through to completion of this degree. His meticulous scrutiny and timely advice throughout my time in the MSCI program were instrumental in my development as a clinical investigator. I would also like to thank the members of my Master's Thesis Committee, Dr. Sharina Person, Dr. Joel Gore and Dr. William Jesdale, for their guidance and participation in my thesis review process.

Finally, I owe a deep sense of gratitude to long-time mentor, Dr. Beth McCormick, for her continuous support and dedication to my personal and intellectual growth, during the time I have worked under her guidance. Her intellectual heft and scientific integrity are only second to her genuinely good nature, and I am truly fortunate to have the opportunity to work with her.

ABSTRACT

Background: During the past several decades, novel diagnostic tools, interventional approaches, and population-wide changes in the major coronary risk factors have occurred. However, few studies have examined relatively recent trends in the demographic characteristics, clinical profile, and the short-term outcomes of patients hospitalized for acute myocardial infarction (AMI) from the more generalizable perspective of a population-based investigation.

Methods: We examined decade long trends (2001 to 2011) in patient's demographic and clinical characteristics, treatment practices, and hospital outcomes among residents of the Worcester metropolitan area hospitalized with an initial AMI (n = 3,730) at all 11 greater Worcester medical centers during 2001, 2003, 2005, 2007, 2009, and 2011.

Results: The average age of the study population was 68.5 years and 56.9% were men. Patients hospitalized with a first AMI during the most recent study years were significantly younger (mean age = 69.9 years in 2001/03; 65.2 years in 2009/11), had lower serum troponin levels, and experienced a shorter hospital stay compared with patients hospitalized during the earliest study years. Hospitalized patients were more likely to received evidence-based medical management practices during the years under study. Multivariable-adjusted regression models showed a considerable decline over-time in the hospital death rate and a significant reduction in the proportion of patients who developed atrial fibrillation, heart failure, and ventricular fibrillation during their acute hospitalization.

Conclusions: These results highlight the changing nature of patients hospitalized with an incident AMI, and reinforce the need for surveillance of AMI at the community level.

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ABBREVIATIONS

AMI - Acute myocardial infarction

WHAS - Worcester Heart Attack Study

ICD - International Classification of Disease

SMSA - Worcester standard metropolitan statistical area

CKD - Chronic kidney disease

COPD - Chronic obstructive pulmonary disease

PVD - Peripheral vascular disease

eGFR - Estimated glomerular filtration rate

PCI - Percutaneous Coronary Intervention

CABG - Coronary artery bypass grafting

ACE - Angiotensin-converting-enzyme

ARBs - Angiotensin II receptor blocker

STEMI - ST-segment elevation myocardial infarction

NON-STEMI - non-ST-segment elevation myocardial infarction

CHAPTER I

INTRODUCTION

Despite more than 50 years of significant therapeutic advances and population-wide lifestyle changes in several predisposing factors, acute myocardial infarction (AMI) continues to be a major cause of morbidity and mortality, being responsible for more than 150,000 deaths and nearly one million hospitalizations annually in the U.S.^{1, 2}.

A limited number of longitudinal, community-based, observational studies have described changes over time in the clinical epidemiology and outcomes of patients hospitalized with AMI in the U.S.³. Investigators from the Worcester Heart Attack Study have described multi-decade long trends in the epidemiology of AMI among residents of the Worcester, Massachusetts, metropolitan area hospitalized with AMI at all central Massachusetts medical centers on an approximate biennial basis^{4, 5}, while the Minnesota Heart Survey has monitored trends in the magnitude of AMI and out-of-hospital cardiac deaths among residents of the seven county Minneapolis/St. Paul metropolitan area between 1980 and 2002^{6, 7}. The Rochester Epidemiology Project, through use of a comprehensive medical records linkage system, has examined the occurrence and outcomes of AMI among residents of Olmsted County, Minnesota on an annual basis between 1966 and 2012^{8, 9}.

The introduction of newer diagnostic tools and laboratory biomarkers, new cardiac therapies and interventional approaches, as well as population-wide changes in

the major coronary predisposing factors have impacted the descriptive epidemiology of AMI and its in-hospital and post-discharge outcomes. However, few relatively recent data exist describing the potentially changing landscape of AMI at the community level.

The primary objective of this population-based study was to describe decade long trends in the sociodemographic and clinical characteristics, hospital management practices, and in-hospital clinical outcomes among residents of central Massachusetts hospitalized with a first AMI at all 11 metropolitan Worcester medical centers on a biennial basis between 2001 and 2011^{5, 10-12}.

CHAPTER II

METHODS

A. Study population.

Details of the Worcester Heart Attack Study have been previously described¹⁰. Briefly, residents of the Worcester metropolitan area hospitalized with a primary or secondary discharge diagnosis of AMI (International Classification of Disease [ICD-9] code 410) at all 11 Worcester standard metropolitan statistical area (SMSA) hospitals during 2001, 2003, 2005, 2007, 2009, and 2011 comprised the study population.

B. Data collection.

The medical records of residents of central Massachusetts hospitalized with a possible AMI were individually reviewed and validated according to pre-established criteria¹⁰⁻¹³. In brief, these criteria included a clinical history of prolonged chest pain not relieved by rest or use of nitrates, serum enzyme level elevations in excess of the upper limit of normal as specified by the laboratory at each hospital, and serial electrocardiographic tracings during hospitalization showing changes in the ST-segment typical of AMI. At least two of these three criteria needed to be satisfied for study inclusion. Additionally, sociodemographic, medical history, and clinical data were abstracted from the hospital medical records of geographically eligible patients by trained study physicians and nurses. Information was collected about patient's age, sex, co-morbidities (e.g., angina, diabetes, heart failure, hypertension, or stroke), AMI type (ST-segment elevation vs. non-

ST-segment elevation), and occurrence of clinically significant hospital complications including atrial fibrillation, heart failure, cardiogenic shock, and hospital survival status^{4, 5, 10, 11}. Patients with a history of AMI were excluded from the present study in order to provide descriptive insights to the natural history of AMI among patients with a first confirmed AMI. Information was collected about the prescribing of different cardiac medications including the hospital use of aspirin, angiotensin-converting enzyme inhibitors, beta blockers, calcium antagonists, diuretics, lipid-lowering agents, and thrombolytic therapy. Data were also collected about the receipt of various coronary diagnostic and interventional procedures including cardiac catheterization, percutaneous transluminal coronary intervention, and coronary artery bypass graft surgery.

C. Data analysis.

To facilitate the interpretation of decade long trends in the descriptive epidemiology of AMI, the 6 one-year study years were aggregated into 3 two-year time periods. These aggregated periods consisted of 2001 and 2003, 2005 and 2007, and 2009 and 2011. Differences in the distribution of various demographic factors, medical history, physiologic findings, clinical characteristics, and treatment practices among patients hospitalized with an initial AMI during the years under study were examined with chi-square tests for trends and analysis of variance for discrete and continuous variables respectively. To assess changes over time in the occurrence of important clinical complications and in-hospital case-fatality rates, while controlling for several potentially

confounding demographic and clinical factors of prognostic importance, several logistic multivariable adjusted regression analyses were performed.

CHAPTER III

RESULTS

A. Study population.

The present report is based on the 3,730 residents of the Worcester metropolitan area who satisfied the diagnostic criteria for an initial AMI in the 6 calendar years examined. The mean age of study patients was 68.5 years, 43.1% were women, and 89.9% were white.

Patients hospitalized with a first AMI during the most recent study years were significantly younger compared with patients who had been hospitalized in the earliest study years (Table 1). There were a greater proportion of individuals with previously diagnosed anemia, chronic kidney disease, hyperlipidemia, hypertension, and peripheral vascular disease during the most recent as compared with earlier study years. A modest decrease in mean systolic blood pressure and estimated glomerular filtration rate (eGFR) values was observed over time. There was a decline in the mean serum Troponin levels at the time of hospital admission as well as in the average length of hospital stay during the decade long period under study (Table 1).

B. Trends in hospital medication practices and coronary interventions.

The in-hospital use of aspirin and lipid lowering agents increased markedly during the years under study (Figure 1). A statistically significant, but inconsistent, increase in the use of beta blockers was observed during the years under study while there was a marked

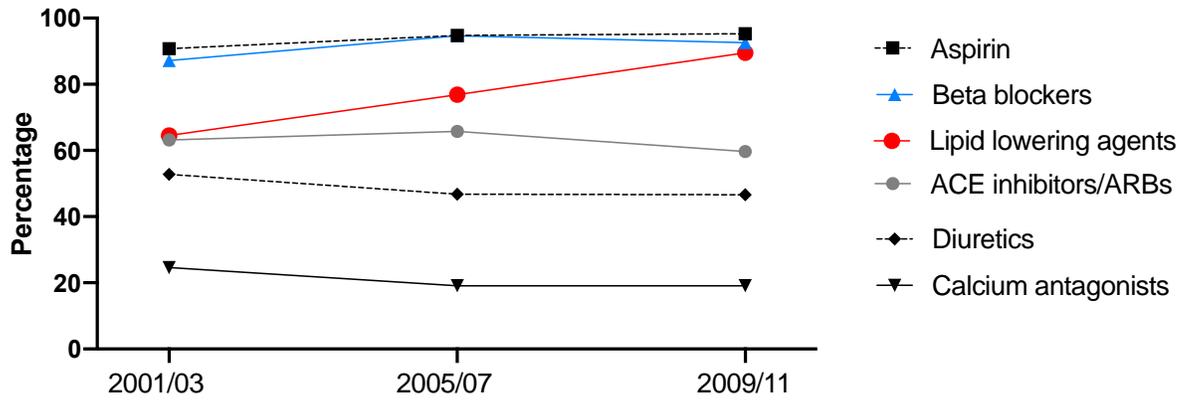
Table 1
Characteristics of Patients Hospitalized with an Initial Acute Myocardial Infarction According to Time Period of Hospitalization

Characteristic	2001/03 (n = 1,547)	2005/07 (n = 1,170)	2009/11 (n = 1,013)	<i>P value</i>
Age (yrs), mean	69.9	69.3	65.2	
Age, years (%)				
<55	17.8	19.1	22.0	
55 - 64	17.5	16.8	21.5	
65 - 74	20.9	17.9	19.9	
75 - 84	27.2	27.1	18.3	
≥85	16.7	19.1	18.3	< 0.001
Male, %	56.9	54.9	59.1	0.09
White, %	87.9	90.6	91.9	< 0.001
Medical History %				
Angina	16.7	8.9	4.1	< 0.001
Anemia	4.5	11.8	10.0	< 0.001
CKD	11.8	17.5	18.0	<0.001
COPD	15.0	16.5	12.2	<0.005
Diabetes	28.0	28.8	31.7	0.33
Heart Failure	15.0	16.5	12.2	<0.005
Hyperlipidemia	44.2	55.6	65.6	< 0.001
Hypertension	65.0	70.6	69.6	<.01
PVD	11.6	16.3	16.3	< 0.001
Stroke	9.3	9.2	7.5	0.42
Laboratory/Physiologic Findings				
Systolic BP in (mean, mmHg)	143.2	142.1	140.4	0.08
Diastolic BP (mean, mmHg)	78.8	78.2	79.0	0.08
eGFR	59.7	62.1	53.9	< 0.001
Serum Glucose (mean, mg/dl)	168.6	163.3	166.9	0.20
ST-segment elevation, %	38.5	35.4	34.5	0.08
Troponin I, Mean	34.3	11.7	9.4	<0.001
Length of stay, (Mean, days)	5.9	5.7	4.6	<0.001

(CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease)

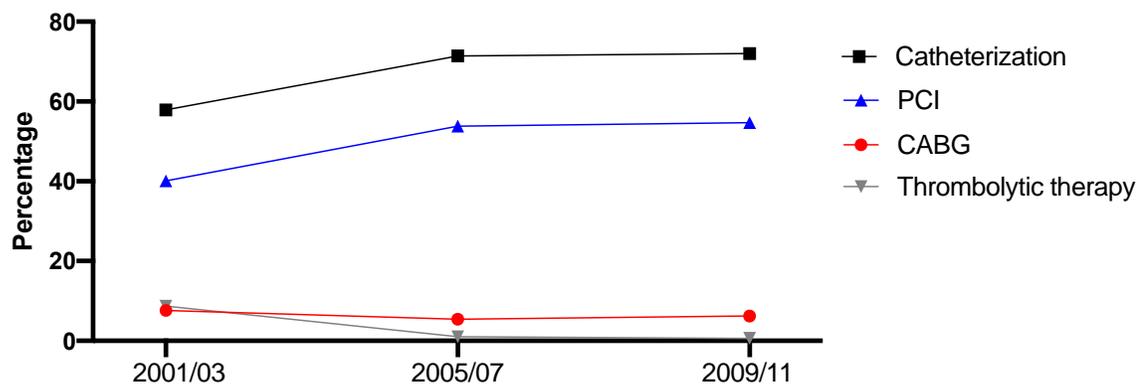
decrease in the use of calcium channel blockers, diuretics, and thrombolytic therapy over time; the use of angiotensin-converting enzyme inhibitors remained essentially unchanged during the period under study (Figure 1). The proportion of patients who underwent diagnostic cardiac catheterization and a percutaneous coronary intervention (PCI) increased markedly between 2001 and 2011. In 2009/11, the percentage of hospitalized patients that received diagnostic catheterization or a percutaneous coronary intervention was 72.0% and 54.7%, respectively (Figure 2). Moreover, changes over time in the utilization of coronary revascularization procedures following a diagnostic cardiac catheterization were observed (Figure 3). The proportion of patients who underwent a subsequent PCI increased significantly over time, while the proportion of patients who underwent coronary artery bypass surgery during their acute hospitalization declined over time (Figure 3).

Figure 1
Changing Trends in Hospital Medication Practices.



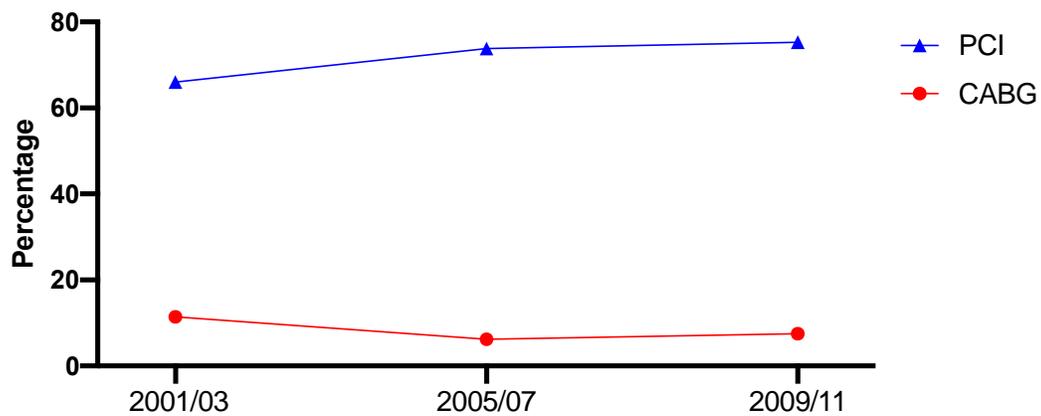
(ACE = angiotensin-converting-enzyme; ARBs = angiotensin II receptor blocker)

Figure 2
Changing Trends in Hospital Coronary Diagnostic and Revascularization Procedures



(CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention)

Figure 3
Changing Trends in Hospital Coronary Revascularization Procedures following Cardiac Catheterization



(CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention)

C. Trends in hospital clinical complications and case-fatality rates.

Changes over time in the occurrence of several major in-hospital complications and all-cause in-hospital mortality were evaluated. We observed a progressive decline in the proportion of patients who developed ventricular fibrillation, atrial fibrillation, or heart failure during the years under study as well as a marked decrease in hospital death rates (Table 2). No significant changes in the occurrence of cardiogenic shock or stroke during the patient's acute hospitalization were found (Table 2).

Both crude and multivariable adjusted regression analyses were performed to more systematically examine trends in hospital death rates and in the occurrence of the major clinical complications examined while controlling for a number of potentially confounding demographic and clinical factors of prognostic importance (Table 5).

Results of the unadjusted analysis (model 1) showed significant declines over time in the odds of dying in the hospital while declines in the odds of developing atrial fibrillation, heart failure, and ventricular fibrillation were also noted. These results essentially remained after adjusting for patient demographic characteristics, occurrence of concomitant clinical complications, as well as AMI type (STEMI vs NON-STEMI) and duration of the acute hospitalization (regression models 2 and 3) (Table 3).

Table 2
Frequency of clinical outcomes according to time period of hospitalization

Complications	2001/03 (n = 1,547) %	2005/07 (n = 1,170) %	2009/11 (n = 1,013) %	<i>P value</i>
Atrial Fibrillation	21.7	21.5	15.1	0.003
Cardiogenic Shock	4.9	6.1	4.6	0.87
Death	9.6	9.8	6.5	0.003
Heart Failure	34.4	33.9	28.2	0.014
Stroke	1.7	0.6	1.8	0.88
Ventricular Fibrillation	4.8	3.8	2.6	0.013

Table 3
Multivariable-adjusted Risk of in-hospital outcomes

Outcomes	2001/03 *	2005/07	2009/11	2005/07	2009/11	2005/07	2009/11
		Model 1 OR (95% CI)		Model 2 OR (95% CI)		Model 3 OR (95% CI)	
Atrial Fibrillation	1	0.99 (0.82, 1.19)	0.65 (0.52, 0.80)	0.98 (0.799, 1.19)	0.71 (0.56, 0.89)	1.07 (0.87, 1.32)	0.81 (0.64, 1.03)
Cardiogenic Shock	1	1.27 (0.91, 1.77)	0.95 (0.65, 1.38)	1.27 (0.90, 1.79)	0.97 (0.66, 1.43)	1.51 (1.06, 2.15)	1.25 (0.83, 1.87)
Death	1	1.03 (0.80, 1.33)	0.66 (0.49, 0.89)	1.02 (0.77, 1.34)	0.76 (0.55, 1.05)	1.02 (0.78, 1.34)	0.76 (0.55, 1.05)
Heart Failure	1	0.98 (0.84, 1.15)	0.75 (0.63, 0.89)	0.91 (0.76, 1.09)	0.81 (0.66, 0.98)	1.02 (0.84, 1.23)	0.95 (0.77, 1.17)
Stroke	1	0.35 (0.15, 0.81)	1.05 (0.57, 1.93)	0.37 (0.16, 0.88)	1.39 (0.73, 2.66)	0.37 (0.16, 0.88)	1.39 (0.73, 2.66)
Ventricular Fibrillation	1	0.80 (0.54, 1.16)	0.52 (0.33, 0.82)	0.82 (0.56, 1.21)	0.52 (0.33, 0.83)	0.88 (0.60, 1.30)	0.60 (0.38, 0.97)

* Referent period

Model 1: Unadjusted

Model 2: Adjusted for age, gender, race and medical history of: anemia, COPD, heart failure, hyperlipidemia, hypertension, PVD.

Model 3: Adjusted for characteristics in Model 2 plus type of AMI and hospital length of stay

(COPD = Chronic Obstructive Pulmonary Disease; PVD = Peripheral artery disease)

CHAPTER IV

DISCUSSION

The results of our large population-based study highlight the changing landscape of patients hospitalized with AMI at all teaching and community medical centers in central Massachusetts. We found significant changes in the demographic characteristics, clinical profile, and in-hospital management of patients who were hospitalized with a first AMI. Moreover, encouraging declines in the proportion of patients who died or experienced major clinical complications during their acute hospitalization were observed.

Changes in patient's demographic and clinical characteristics. Residents of the Worcester metropolitan area hospitalized with an independently confirmed initial AMI during the most recent study years were significantly younger and more likely to be men compared with patients hospitalized during the initial years under investigation. The average age of patients who had been hospitalized with AMI in 2009/11 was nearly 5 years younger than the average age of patients hospitalized in 2001/03. Furthermore, approximately two thirds of the patients hospitalized in 2009 and 2011 were less than 75 years old compared with slightly more than one half of the patients hospitalized in prior study years, reflecting a relatively dramatic shift in the age distribution of patients hospitalized with a first AMI.

This shift to a younger age at the time of diagnosis in our patient population is in contrast to those observed in the Cardiovascular Research Network ¹⁴, in which there were no

significant changes in the age profile of patients hospitalized with a first AMI between 2000 and 2008. Similarly, investigators from the Rochester Epidemiology project reported little change in the age distribution of patients hospitalized with a first AMI between 1987 and 2006 ¹⁵.

While the reasons underlying differences in the findings between the current study and other population-based studies are unknown, we believe they could be due, in part, to the introduction of novel biomarkers and the use of more sensitive diagnostic tests as well as differences in the sociodemographic and clinical characteristics of the respective study populations. If real, these changes could be a result of a worsening of the coronary risk factor profile among residents of the Worcester metropolitan area during the years under study, creating a younger vulnerable population at risk for acute coronary disease. However, we lack data to examine this and related hypotheses and further research needs to be done to determine the factors underlying these troubling findings.

There have also been marked changes over time in the occurrence of clinically important chronic diseases in our patient population. We observed increases in the proportion of patients previously diagnosed with anemia, chronic kidney disease, hyperlipidemia, hypertension, and peripheral vascular disease. This shift in patient profile toward the admission of predominantly younger patients with a greater prevalence of serious comorbidities could be secondary to changes in clinical-guidelines for the identification of patients with various chronic conditions that took place during the years under study.

New hypertension guidelines for the classification, prevention, and management of patients with elevated blood pressure were updated in 2003 while revised cholesterol guidelines management were released in 2004^{16, 17}. These updates could have potentially increased disease awareness among practicing physicians, leading to increases in detection and diagnosis. These trends could also be the result of meaningful changes in patient's comorbidity profiles. The observed increases in various comorbidities in our study population were similar to those observed in by the Cardiovascular research Network (CVRN) in which significant increases over time in the proportion of patients diagnosed with hypertension and dyslipidemia were observed¹⁸, but in partial contrast with those noted in the Minnesota Heart Survey in which the proportion of patients hospitalized with an incident AMI with previously diagnosed hypertension markedly declined⁶. We observed a steady decline in the average length of hospital stay for residents of the Worcester metropolitan area hospitalized with a first AMI over time, most likely due to improved treatment strategies and cost considerations¹⁹.

We found that patients with an incident AMI were more likely to have developed a Non-ST-segment elevation myocardial infarction diagnosed during the years under study. These results are in contrast with some population-based studies¹⁴, but are consistent with trends observed in the Rochester epidemiology project during a relatively similar study period⁸. Our data also show that the levels of Troponin I decreased considerably among patients hospitalized with a first AMI between 2001 and 2011. Although this could be an artifact created by the introduction of high-sensitivity troponin assays and

new test guidelines, the lower serum troponin levels observed in our patient population over time and the increasing proportion of smaller infarcts, as reflected by patient's serial ECG findings, may be suggestive of a progressive decline in the severity of patients hospitalized with a first AMI at all medical centers in central Massachusetts during the decade long period under study.

Trends in hospital medication practices and coronary interventions. A number of community-based studies, including previous reports from the Worcester Heart Attack Study^{4, 5, 7, 14}, as well as large-scale coronary disease registries¹⁸, have shown evidence of a progressive and sustained increase over time in the prescribing of effective cardiac therapies in patients hospitalized with AMI during the past two decades. We observed progressive increases in the percentage of patients receiving effective in-hospital therapies for AMI including aspirin, beta-blockers, and lipid lowering medications. These data demonstrate the increasing adherence of health care providers in central Massachusetts to guideline-recommended medications. Moreover, a gradual reduction in the utilization of cardiac medications with questionable therapeutic value or a narrow therapeutic/toxic ratio was also observed (e.g., calcium channel blockers and digoxin).

Increases over the decade long period under study in the proportion of patients that underwent nonsurgical revascularization and diagnostic procedures were observed. These findings are consistent with evidence-based guidelines for the management of patients hospitalized with AMI, which recommend early percutaneous coronary intervention as

the preferred reperfusion therapy and the use of CABG as an alternative for patients with cardiogenic shock, high-risk anatomy, or a failed PCI. As new treatment recommendations and approaches evolve further over time, it remains of importance to monitor trends in the management of patients hospitalized with AMI and factors associated with different treatment approaches and patient's long-term outcomes.

Trends in hospital clinical complications and death. A marked change over time in the occurrence of clinically important AMI related complications was observed in our patient population. We found a significant reduction in the proportion of patients who developed atrial fibrillation, heart failure, and ventricular fibrillation following an incident AMI. These meaningful changes in important and serious clinical complications are consistent with the trends reported in several large population-based studies including the New Jersey Myocardial Infarction Data Acquisition System (MIDAS) and the OACIS prospective study^{20,21, 22}.

We also documented a significant increase in the in-hospital survival of patients hospitalized with AMI in the Worcester metropolitan area, a finding consistent with prior reports from this study during earlier time periods^{4, 5}. These findings are also consistent with those derived from population-based studies in Northern California and Minneapolis/St Paul, Minnesota^{7, 14}. Several studies in Canada, European countries, and Australia have also shown increases over time in the short-term survival rates of patients hospitalized with AMI²³⁻²⁵.

The encouraging declines in the hospital death rate of patients who had been hospitalized with an initial AMI observed over the past several decades could be a result of declines in the occurrence of common AMI complications, changes in the severity of the acute coronary episode, as well as due to the increased use of effective cardiac interventions and medications during the years under study.

Study Strengths and limitations

The strengths of the present investigation include the study of a large community-based population of patients hospitalized with a confirmed initial AMI at all central Massachusetts medical centers, and an examination of decade long trends in the occurrence of patient's demographic characteristics, therapeutic interventions, and in-hospital outcomes. The study was carried out in men and women of all ages from a well-defined metropolitan area with demographic characteristics similar to U.S. residents. However, this study has several limitations, which must be kept in mind when interpreting our study results. Our study cohorts were comprised largely of Caucasians and thus may lack generalizability to other race/ethnic groups. The present study only included patients who were hospitalized with a first AMI. The influence of possible changes over time in the magnitude of out-of-hospital deaths due to cardiac disease or changes in the occurrence of silent unrecognized AMIs on the characteristics and outcomes of patients hospitalized with AMI remains unknown.

Conclusions. The results of this community-based study highlight the changing nature of the demographic characteristics, clinical landscape, and management of patients hospitalized with incident AMI at all medical centers in central Massachusetts. Disconcertingly, and meriting further surveillance, we observed a shift to a younger age at the time of first AMI diagnosis in our patient population. On the other hand, concomitant with progressive increases in the proportion of patients receiving effective evidence-based in-hospital therapies and coronary revascularization procedures, we observed a gradual decline in the occurrence of serious AMI complications and hospital deaths, highlighting the importance of AMI surveillance at the community level.

CHAPTER V

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