LONG-TERM SURVIVAL AND PROGNOSTIC FACTORS IN PATIENTS WITH ACUTE

DECOMPENSATED HEART FAILURE ACCORDING TO EJECTION FRACTION

FINDINGS: A POPULATION-BASED PERSPECTIVE

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A Master Thesis Presented
By

Andrew H. Coles, PhD

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August 18, 2014

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DEDICATION

I would like to dedicate this thesis work to my mom Ann Coles and my deceased
grandfather Michael Comperchio. Without their love, support, and encouragement, this
work would not have been possible.

ACKNOWLEDGEMENTS

SUMMARY

Limited data exists describing the long-term prognosis of patients with acute decompensated heart failure (ADHF) further stratified according to currently recommended ejection fraction (EF) findings. In addition, little is known about the magnitude of, and factors associated with, long-term prognosis for these patients. Based on previously validated and clinically relevant criteria, we defined HF-REF as patients with an EF value ≤40%, HF-PEF was defined as an EF value $\geq$ 50%, and HF-BREF was defined as patients with an EF value during their index hospitalization between 41 and 49%. The hospital medical records of residents of the Worcester (MA) metropolitan area who were discharged after ADHF from all 11 medical centers in central Massachusetts during the 5 study years of 1995, 2000, 2002, 2004, and 2006 were reviewed. Follow-up was completed through 2011 for all patient cohorts.

The average age of this population was 75 years, the majority was white, and 44% were men. Patients with HF-PEF experienced higher post discharge survival rates than patients with either HF-REF or HF-BREF at 1, 2, and 5-years after discharge. Advanced age and lower estimated glomerular filtration rate findings at the time of hospital admission were important predictors of 1-year death rates, irrespective of EF findings. Previously diagnosed chronic obstructive pulmonary disease, chronic kidney disease, and atrial fibrillation were associated with a poor prognosis in patients with PEF and REF whereas a history of diabetes was an important prognostic factor for patients with REF and BREF.

In conclusion, although improvements in 1-year post-discharge survival were observed for patients in each of the 3 EF groups examined to varying degrees, the post-

discharge prognosis of all patients with ADHF remains guarded. In addition, we observed differences in several prognostic factors between patients with ADHF with varying EF findings, which have implications for more refined treatment and surveillance plans for these patients.

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PREFACE

Data from the WHFS (Worcester Heart Failure Study), an observational study of all residents of the Worcester metropolitan area hospitalized at all 11 medical centers in central MA with acute heart failure between 1995 and 2006, were used to perform the analyses outlined herein.

Dr. Coles wrote and designed the analyses outlined in this thesis. Darleen Lessard MS and Dr. Mayra Tizminitesky provided assistance with respect to of the analyses performed. Jerry Gurwitz MD, Chad Darling MD, Kim Fisher MD, Joel Gore, MD, Mayra Tizminitesky MD/PhD, and Robert Goldberg PhD provided editorial assistance.

CHAPTER 1

INTRODUCTION

1.1 Forward

Cardiovascular disease (CVD) is a leading cause of death worldwide and is associated with a substantial economic and healthcare burden [1,2]. Within the broad CVD umbrella are five major conditions including stroke, coronary heart disease, arrhythmias, heart valve problems, and congestive heart failure. This thesis will focus on heart failure (HF), and in particular, acute decompensated heart failure. Approximately 5.8 million American men and women have HF and there are 23 million cases worldwide [3]. The HF epidemic is associated with substantial economic costs and high mortality, costing nearly $30 billion per year in healthcare services, medications, and lost productivity in 2013 [2,4]. A recent epidemiological study has reported that less than 1 in 3 patients with HF discharged from the hospital survive to 5-years [5]. In addition to the high mortality associated with HF, it is the leading cause of hospitalizations in the elderly accounting for approximately one million hospitalizations annually [4,6,7]. Controversy currently exists as to the long-term prognosis of patients with HF divided into various ejection fraction (EF) strata. This thesis describes the long-term prognosis, and the risk factors that are associated with death at 1-year, of patients with HF divided into three EF strata representing reduced (HF-REF; EF≤40%), borderline (HF-BREF; EF=41-49%), and preserved (HF-PEF; EF$\geq$50%) EF measurements.

1.2 Diagnosis, classification, and lifetime risk of heart failure

Acute decompensated heart failure (ADHF) is an increasingly prevalent complex

clinical syndrome resulting from impairment in either ventricular filling or ejection of

blood from the heart [8,9,10]. There is no single diagnostic test for this condition and

the clinical diagnosis of ADHF is based on medical history and physical examination

findings [11]. The main symptoms of ADHF are fatigue and dyspnea, which limit

exercise tolerance, and fluid retention, which can result in pulmonary congestion or

peripheral edema [11]. However, the signs and symptoms of ADHF are not specific and

may be absent at presentation [11]. The Framingham HF criteria is used for the

diagnosis of HF and patients must have 2 major criteria or 1 major and 2 minor criteria

present to be considered as having HF (Table 1.1) [12]. The diagnosis of HF also

involves the collection of information by a chest x-ray, echocardiogram, and blood tests

for specific biomarkers [11]. This data is used to stage HF using either the New York

Heart Association classification or American College of Cardiology schemas (Table 1.2)

[9,10,13].

An echocardiogram is utilized to determine the ejection fraction (EF), or pumping

capacity of the heart, which is used to differentiate patients with ADHF into varying

strata. These groups have typically included patients with , reduced HF, HF-REF [14],

and those with preserved HF, HF-PEF [15,16]. Studies that have examined EF and its

association with short and long-term prognosis in patients with ADHF have, however,

been inconsistent with the EF cutpoints used, making comparisons between studies

difficult [3,5,17,18,19,20,21]. The 2013 AHA/ACC guidelines have attempted to clarify

this concern by proposing three groups based on EF findings [4]. These groups are

defined as reduced (EF$\leq$40%, HF-REF), borderline (EF=41-49%, HF-BREF), and

preserved HF (EF>50%, HF-PEF) [4]. In the current work we will use the 2013

AHA/ACC definitions for these three EF strata [4]. Blood tests for specific biomarkers,

such as BNP/NT-proBNP and troponins, are being increasingly used by clinicians to

assist in the diagnosis and selection of treatments for patients with, or suspected to

have, HF [4,22,23,24,25,26,27,28].

Table 1.1: Framingham Heart Failure Criteria
**2 major or 1 major and 2 minor criteria needed for heart failure to be present.

Major Criteria
Paroxysmal nocturnal dyspnea or
orthopnea
Neck vein distension
Rales
Cardiomegaly
Acute pulmonary edema
S3 gallop
Increased venous pressure ($\geq$16cm water)
Circulation time ($\geq$25 seconds)
Hepatojugular reflux

Minor Criteria
Ankle edema
Night cough
Dyspnea on excertion
Hepatomegaly
Plueral effusion
Vital capacity decreased one-third of maximum
Tachycardia ($\geq$120 beats/minute)

Major or minor criterion
Weight loss ($\geq$4.5kg) in 5 days in response to treatment

Table 1.2: Comparison between the NYHA and ACC/AHA classifications of heart failure severity.

NYHA Functional Classification	Description	ACC/AHA Stages of Heart Failure	Description
Class I	Normal physical activity, no dyspnea on excertion	Stage A	At high risk for HF, no symptoms
Class II	Slight limitation of physical activity	Stage B	Structural heart disease present, no symptoms
Class III	Less than ordinary activity causes fatigue	Stage C	Structural disease with prior or current symptoms
Class IV	Any physical activity causes discomfort	Stage D	Refractory symptoms to therapy, requires special interventions

The lifetime risk for developing HF for a middle aged American man or woman (aged 45 years) through 75 years of age differs by gender and race/ethnic group; ranging from 20-46% [29,30,31]. A number of individual, and potentially modifiable, risk factors for developing HF have been identified. Major risk factors for HF include hypertension, diabetes mellitus, the metabolic syndrome, and atherosclerotic disease [3,4]. The etiology of HF has been categorized in clinical trials and routine practice as either ischemic or non-ischemic cardiomyopathy, with the terms dilated cardiomyopathy (DCM) and non-ischemic cardiomyopathy being used interchangeably in these settings [32].

1.3 Pathophysiology and medical management of heart failure.

1.3.1 Models of HF development and progression

Current understanding of HF pathophysiology combines several traditional models to explain the complex biological alterations seen in HF and to guide therapeutic interventions (Figure 1.1) [8,9,15,16,33]. Two major models used to describe the abnormalities seen in HF are the hemodynamic model and the neurohormonal model [34,35,36]. The hemodynamic model explains the effects of an altered load on ventricular filling and is the rationale for the use of vasodilators and inotropic agents. In the neurohormonal model, the impact on HF development of the renin-angiotensin-aldosterone axis and sympathetic nervous system are explained as is the rationale for the use of selected medications including angiotensin-converting-enzyme (ACE)

inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone

inhibitors in patients with HF [37].

Figure 1.1: Pathophysiology of acute decompensated heart failure.
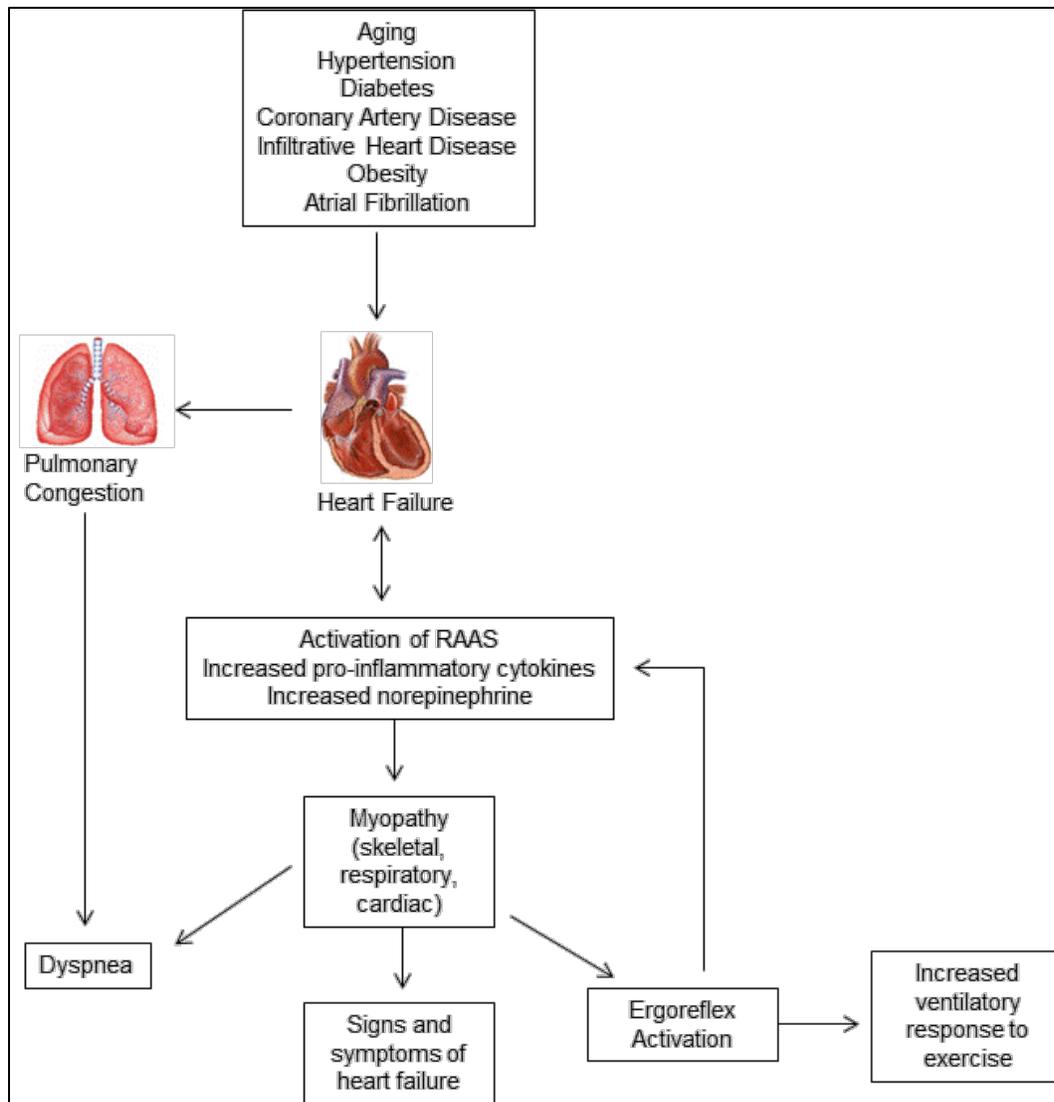
Another model for HF development and progression is left ventricular remodeling, which describes the mechanical, nuerohormonal, and genetic factors that converge to alter ventricular size, shape, and ultimately function [9,38,39]. A variety of treatments can induce reverse remodeling in which treatment promotes a return to a more normal ventricular size and shape [9].

Diastolic heart failure, also termed HF-PEF, occurs when the heart contracts normally, but the relaxation is abnormal resulting in limited cardiac output especially during exercise [16]. Ventricular pressure becomes elevated leading to pulmonary congestion, dyspnea, and edema similar to what is seen in patients with HF-REF [9]. However, in contrast to what occurs in HF-REF, clinical trial data have shown a lack of significant benefit from neurohormonal antagonists suggesting that this may not be a significant mechanism for the development of HF-PEF [8,16]. Recent studies into the pathophysiological mechanisms underlying HF-PEF suggest that it may be a heterogeneous disorder resulting from many pathophysiological processes distinct from HF-REF [40,41]. These advances have led to better patient related outcomes, but further work is needed to improve our understanding of HF pathophysiology, especially that of HF-PEF, in order to better treat these patients [16].

1.3.2 Medical management of HF with reduced EF

The primary goals of treatment are to improve survival, alleviate symptoms, avoid hospital admissions, slow the progression of disease, and to minimize the magnitude and impact of risk factors [4,9]. Current evidence-based guidelines have been developed for the treatment of patients with HF-REF only and include medications,

surgical interventions, and use of implantable devices [4]. In addition to medical and

surgical interventions to treat patients with HF, lifestyle modifications; such as sodium

restriction, weight monitoring, moderation of alcohol intake, and exercise, and improved

healthcare organization and delivery, have also been suggested to improve patient

related outcomes [1,4,8,33,42,43,44]. Several non-pharmacologic, non-surgical, and

non-device treatments have been proposed and advocated, but the evidence base to

support these interventions is limited [4,14].

1.3.3 Medical management of HF with preserved EF

There are currently little evidence-based guidelines directing therapy for patients

with HF-PEF and the guidelines that do exist are based primarily on consensus opinion.

Despite the limited efficacy in RCTs involving HF-PEF patients treated with the standard

HF-REF medications, many practitioners believe that similar pathophysiologic

processes are occurring in both patient groups and thus similar drugs could be used for

treatment. However, one exception are calcium channel blockers which have been

reported to improve exercise capacity, peak diastolic filling, exercise time, and

congestive HF score in two very small clinical studies of patients with HF-PEF

[40,45,46].

1.4 Long-term prognosis of patients with acute decompensated heart failure

A number of studies have utilized data from registries, RCTs, and community-

based cohort studies to examine the in-hospital, short, and long-term prognosis of

patients with ADHF [44]. An observational study of 4,537 residents of Olmsted County,

Minnesota who were discharged from the Mayo Clinic and the Olmsted Medical Center with a first diagnosis of HF between 1979 and 2000 found that the 5-year age-adjusted survival was worse among men than women (RR 1.33; 95% CI, 1.24-1.43) [47]. In addition, while long-term survival improved for all groups over this period, it improved the most among men and younger patients [47]. Similar studies conducted in Ontario [48] between 1997-2007 and Scotland [49] between 1986-2003 of patients with HF were consistent with the Olmsted County results, finding that survival after HF is very poor but has been improving over time. In the population-based Worcester Heart Failure Study, fewer than 1 in 3 patients discharged with ADHF in 2004 survived more than 5 years. On the other hand, 5 year survival rates improved between 1995 and 2004, increasing from 20% in 1995 to 29% in 2004 [5,50]. The overall conclusions from these studies and others [51] suggest that patients with HF have a poor long-term survival, which has slightly improved over time.

The previously cited studies did not, however, stratify patients based on EF findings. A limited number of studies in the 1990's and 2000's that did stratify patients by EF findings observed that those with a preserved EF had a better prognosis than those with a reduced EF [17,52,53]. A large population based cohort of patients with a discharge diagnosis of HF from 103 hospitals as part of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study in Ontario, Canada between 1999 and 2001 were studied to determine which EF group had a better prognosis [17]. The cohort was stratified into three EF groups, less than 40% for the reduced EF group, 40-50% for the borderline EF group, and greater than 50% for the preserved EF group; only the two extreme groups were studied in detail, however. This study found that

patients with reduced and preserved EF had similar 1-year survival and hospital readmission rates. The 1-year unadjusted mortality rate for the HF-REF group was 26% versus 22% for the HF-PEF group (p=0.07) and the readmission rate at 1-year was 16. % for the HF-REF group and 14% for the HF-PEF group (p=0.09) [17]. After multivariable adjustment, the mortality rate hazard ratio was 1.13 (95% CI 0.94-1.36) [17], suggesting that the HF-PEF and HF-REF groups had a similar mortality experience.

More recently, two papers examined trends in long-term mortality in patients with either preserved or reduced EF HF. The first study was a meta-analysis that compiled data from 31 RCTs and observational studies conducted through 2008 with an EF of 50% differentiating the HF-PEF from the HF-REF group [52]. In this meta-analysis, the HF-PEF group had a 32% lower risk of dying from all causes over three years than the HF-REF group, with mortality increasing when EF findings fell below 40% [52]. The second paper summarized the findings from RCTs that enrolled patients with HF-REF and/or HF-PEF [53]. Results from this review were consistent with the meta-analysis findings suggesting that patients with HF-PEF have a better prognosis than patients with HF-REF [53]. The controversy that remains from these few reports highlights the necessity of further population based observational studies with broad generalizability to determine which patients ,experience higher death rates and /or other outcomes of long-term importance and require more aggressive surveillance and/or tailored treatment approaches.

1.5 Factors associated with post-hospital discharge mortality among patients with ADHF.

A number of factors have been identified in association with post-hospital discharge mortality among patients with ADHF. In this work, we will focus on those factors that are associated with mortality at 1-year post-hospital discharge due to the high incidence of death at this time point (see previous section).   Factors that have been reported in the literature include older age, male gender, hyponatremia, lower systolic blood pressure, a higher urea nitrogen level, and several comorbid conditions (cerebrovascular disease, COPD, hepatic cirrhosis, dementia, and cancer) [54,55,56,57,58,59,60]. In addition to these variables, lower EF findings have also been found to predict poor long-term survival in the CHARM study for both the composite outcome of re-hospitalization and all-cause death and the single outcome of death at 2-years after hospital discharge [61]. The CHARM study also identified diabetes as an important prognostic factor of death in patients with HF [61], as well as a low BMI, low diastolic BP, and a prior heart attack. Reduced renal function has been associated with increased all-cause mortality [58,59].

A number of groups have also stratified patients with HF based on EF findings into two main groups, preserved and reduced EF HF, and examined factors associated with mortality in these patients [17,62,63,64,65,66]. These studies did not, however, use consistent definitions of HF-PEF or HF-REF, making comparisons between studies difficult. In addition, prior studies did not examine the newly identified HF-BREF group [4]. A number of these studies used data from clinical trials making the generalizability to patients encountered in clinical practice less likely [63,65]. The factors that were

found to be important in predicting long-term all-cause mortality depended to some extent on whether the patient had either HF-PEF or HF-REF, but several were in common. Predictors of all-cause mortality for patients with HF-REF were low systolic and diastolic BP, older age, hyponatremia, renal dysfunction, and peripheral vascular disease [17,62]. For patients with HF-PEF, factors associated with an increased risk of dying after being discharged from the hospital after ADHF were older age, peripheral vascular disease, hyponatremia, renal dysfunction, low diastolic BP, diabetes, COPD, low glomerular filtration rate, and anemia [17,62,65]. The impact of atrial fibrillation (AF) on mortality of the HF-REF and HF-PEF groups was also examined recently and was shown to adversely impact mortality and the rates of re-hospitalization in both groups [67].

1.6 Observational studies and the Worcester Heart Failure Study (WHFS)

Randomized clinical trials (RCTs) are the most rigorous study design to establish causation and drug efficacy. However, RCTs have a number of limitations; they use a study population with a number of inclusion and exclusion criteria that could decrease the generalizability of the findings, they typically exclude patients with multiple comorbidities, and in some cases it is not ethical to conduct them, such as to determine if a risk factor is an important cause of a disease [68]. Observational studies provide a better understanding of what occurs in usual clinical practice and answers questions pertaining to the "typical" patient better than an RCT [68]. However, they cannot prove causation by themselves, which is a major limitation inherent in the use of these designs. A good example of a prospective observational study is the Worcester Heart

Failure Study (WHFS) [69,70].

The WHFS cohort is derived from all residents of the greater Worcester metropolitan area who had a discharge diagnosis of HF from any of the 11 medical centers in central MA during the four study years of 1995, 2000, 2002, and 2004 (Chapter 4 includes the fifth study year of 2006). A more detailed discussion of this study is presented in Chapter 2: Methods. In brief, the medical records of patients with primary and/or secondary International Classification of Diseases, 9th Revision (ICD-9) discharge diagnoses indicating the presence of HF were reviewed by trained nurse and physician reviewers. The present study population used for all analyses in this thesis was restricted to individuals who had undergone a clinically indicated echocardiogram during their index ADHF-related hospitalization.

1.7 Objectives of this thesis

There are three main objectives of this thesis using data from the WHFS. These are to: 1) describe the characteristics of the three EF subtypes of ADHF; 2) examine the long-term outcomes of ADHF stratified by three EF strata; and 3) determine the prognostic factors that are associated with mortality at 1-year for the three EF subtypes. The first two objectives will be addressed in chapter 3 and the third objective will be addressed in chapter 4.

CHAPTER 2

METHODS

Study population

The study population consisted of adult residents of the Worcester (MA) metropolitan area (2000 census estimate = 478,000) who survived hospitalization for ADHF at all 11 central Massachusetts medical centers during the 4 study years of 1995, 2000, 2002, and 2004 (2006 was added in chapter 4). These particular years were selected for detailed study due to funding availability and to provide insights into decade long trends in the clinical epidemiology of ADHF. The present study population was restricted to individuals who had undergone a clinically indicated echocardiogram during their index ADHF-related hospitalization. Details of the Worcester Heart Failure Study (WHFS) have been described previously [5,70,71].

In brief, the hospital medical records of patients with primary and/or secondary International Classification of Diseases, 9th Revision (ICD-9), discharge diagnoses indicating the presence of HF were reviewed in a retrospective manner by trained nurse and physician reviewers. Patients with a discharge diagnosis of HF (ICD-9 code 428) comprised the primary diagnostic rubric reviewed. In addition, the medical records of patients with discharge diagnoses of hypertensive heart and renal disease, acute cor pulmonale, cardiomyopathy, pulmonary congestion, acute lung edema, and respiratory abnormalities were also reviewed to identify patients who may have had new-onset ADHF. Confirmation of the diagnosis of HF, based on use of the Framingham criteria, included the presence of 2 major criteria or the presence of 1 major and 2 minor criteria

[3]. Patients in whom ADHF developed secondary to admission for another acute illness (e.g., acute myocardial infarction), or after an interventional procedure (e.g., coronary artery bypass surgery), were excluded.

Data Collection

Information was collected about patient's demographic characteristics, medical history, clinical characteristics, and laboratory test results through the review of information contained in hospital medical records. This included information about patient's age, sex, race, prior comorbidities (e.g., angina, diabetes, hypertension, and stroke), and clinical characteristics. Based on the review of medical record data, EF findings during the patient's index hospitalization for ADHF were recorded in 37% of the overall study cohort. Based on previously validated and clinically relevant criteria, we defined HF-REF as patients with an EF value ≤40%, HF-PEF was defined as an EF value $\geq$ 50%, and HF-BREF was defined as patients with an EF value during their index hospitalization between 41 and 49% [3,4,72,73,74].

Physician's progress notes were reviewed, in addition to the daily medication logs, for the prescribing of selected medications at the time of hospital discharge. We examined the hospital use of cardiac medications that have been shown to be of benefit in improving the long-term prognosis of patients with ADHF, namely angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and aldosterone inhibitors. In addition, we examined the use of medications shown to be effective in improving patient's symptomatic status (digoxin, diuretics) and selected cardiac medications (lipid-lowering agents, nitrates) [15]. Long-term survival

status was obtained by the review of medical records at all participating medical centers for further hospitalizations or medical care contacts and review of social security death index and statewide death certificates. Follow-up was completed through the end of 2009 for all patient cohorts.

Data Analysis

We examined differences in the characteristics of patients with EF values $\leq$40%, 41-49%, and $\geq$50% using *ANOVA* and chi-square tests for continuous and discrete variables, respectively. A life-table approach was used to examine long-term mortality following discharge from all central Massachusetts hospitals, including patients with varying lengths of long-term follow-up. Post-discharge case-fatality rates, multivariable adjusted relative risks (RRs), and accompanying 95% confidence intervals (CIs) were calculated in a standard manner. Multivariable adjusted logistic regression analyses were used to examine the association between EF findings and 1 and 2-year post-discharge mortality while controlling for several clinical and demographic factors of prognostic importance including age, sex, history of previously diagnosed atrial fibrillation, diabetes, chronic lung disease, renal failure, and HF, and serum glucose findings during the acute hospitalization. The factors chosen for inclusion in the regression models were based on established predictors of mortality in the published literature and differences between groups at baseline as defined by a p value <0.15. We did not control for the receipt of various cardiac medications during the patient's index hospitalization in these regression analyses due to the potential for confounding by treatment indication and lack of more detailed information about the timing of therapy

administration relative to the onset of ADHF. The post-discharge mortality time points

chosen for analysis were selected because of the high death rates observed in patients

with ADHF during the first several years after hospital discharge. The Committee for

the Protection of Human Subjects in Research at the University of Massachusetts

Medical School approved this study.

CHAPTER 3

Long-Term Survival for Patients with Acute Decompensated Heart Failure According to Ejection Fraction Findings

Background: Limited data exists about the long-term prognosis of patients with acute decompensated heart failure (ADHF) further stratified according to ejection fraction (EF) findings.

Methods and Results: The primary objective of this population-based observational study was to characterize and compare trends in long-term prognosis after an episode of ADHF across 3 EF strata. Hospital medical records were reviewed for 3,604 residents of the Worcester (MA) metropolitan area who were discharged after ADHF from all 11 medical centers in central Massachusetts during 1995, 2000, 2002, and 2004 and had EF measurements during their index hospitalization. The average age of this population was 75 years, the majority was white, and 44% were men. Approximately 49% of the population had preserved EF HF (HF-PEF) ($\geq$50%), 37% had reduced EF HF (HF-REF) ($\leq$40%), and 14% had borderline EF HF (41-49%) (HF-BREF). Patients with HF-PEF experienced higher post discharge survival rates than patients with either HF-REF or HF-BREF at 1, 2, and 5-years after discharge from all central Massachusetts medical centers. While prognosis at 1-year after hospital discharge improved for all patient groups during the years under study, especially for those with HF-REF and HF-PEF, these encouraging trends declined with increasing duration of follow-up.

Conclusion: In conclusion, although improvements in 1-year post-discharge survival were observed for patients in each of the 3 EF groups examined to varying degrees, the post-discharge prognosis of all patients with ADHF remains guarded.

INTRODUCTION

Acute decompensated heart failure (ADHF) is an increasingly prevalent clinical syndrome which is associated with reduced quality of life, a high rate of hospital readmissions, and a poor long-term prognosis [73]. One year all-cause death rates among patients with ADHF have been reported to be as high as 35% [3,4,75,76]. Hospital readmission rates are also very high in these patients, with approximately one half of patients with ADHF being readmitted to the hospital within the first 6 months after discharge [6].

In order to optimize the medical management of patients with ADHF, and more fully understand and describe the epidemiology of this clinical syndrome, the most recent American Heart Association/American College of Cardiology (AHA/ACC) guidelines identified 3 groupings based on ejection fraction (EF) findings to further stratify patients with HF into varying at risk groups. These groups are defined as those with reduced (EF$\leq$40%, HF-REF), borderline (EF=41-49%, HF-BREF), and preserved HF (EF$\geq$50%, HF-PEF) [4]. Although the long-term prognosis of patients discharged from the hospital after ADHF has been characterized in several longitudinal studies [3,5,17,18,19,20,21], including our community-wide study of residents of central Massachusetts [5,13], decade long trends in the long-term mortality of patients

discharged from the hospital after ADHF, further stratified according to contemporary EF criteria, have not been described.

The primary objective of this study was to describe and compare the long-term post-discharge prognosis of patients hospitalized with ADHF across several EF strata and over time. Data from the population-based Worcester Heart Failure Study were used for this investigation [4,5,13-15].

RESULTS

Study population characteristics

Our study population consisted of 3,604 residents of the Worcester metropolitan area who were hospitalized at all central Massachusetts medical centers with ADHF during the 4 years under study and had EF data available. Their average age was approximately 75 years, the vast majority was Caucasian, 44% were male, and the majority had a prior history of HF (59%). In this population, 36.9% (n=1,479) were classified as having HF-REF (average EF=26.7%), 49.4% (n=1,779) were classified as having HF-PEF (average EF=59.9%), and the remaining 13.7% (n=346) were classified as having HF-BREF (average EF=43.6%).

Patients with HF-REF were slightly younger, predominantly male, had the greatest co-morbid disease burden, and presented with lower systolic blood pressures, but higher BUN and serum hematocrit levels, than did patients with either HF-BREF or HF-PEF (Table 3.1). They were also less likely to have a history of chronic lung disease, but were more likely to have a history of previously diagnosed coronary heart disease, chronic kidney disease, and HF.

Patients with HF-PEF were generally older, mostly female, and presented with higher estimated glomerular filtration rate findings at the time of hospital admission than patients in the other EF strata. Patients with HF-PEF were also more likely to have presented with a first episode of ADHF and to have a history of chronic lung disease and hypertension (Table 3.1).

Patients with HF-BREF were slightly older than patients with HF-REF and included a higher percentage of women. In addition, they included a greater percentage of patients with previously diagnosed peripheral vascular disease compared to patients with either HF-REF or HF-PEF (Table 3.1).

Hospital Medication Prescribing Practices

Overall, as well as over time, patients with ADHF and reduced EF findings were more likely than those with preserved EF findings to have received ACE inhibitors/ARBs, lipid lowering agents, nitrates, diuretics, and digoxin at the time of hospital discharge (Figure 3.1). Diuretics were prescribed the most to patients with HF-REF and to a similar extent in the other two categories in 2004 (Figure 3.1B). Patients with HF-PEF were more likely to have been prescribed calcium channel blockers but were less likely to have received combinations of ACE/ARBs, beta-blockers, and aldosterone inhibitors in comparison to those with either HF-REF or HF-BREF (Figures 3.1A and D).

Post-Hospital Discharge Prognosis

Overall, the case-fatality rates at 1, 2, and 5 years after hospital discharge were approximately 35%, 49%, and 71% for patients with HF-REF; 27%, 42%, and 70% for those with HF-BREF; and 30%, 43%, and 69% for patients with HF-PEF, respectively (Table 3.2 and Figure 3.2). The overall median survival times were approximately 1.9 years for patients with HF-REF, 2.1 years for those with HF-BREF, and 2.3 years for patients with HF-PEF (Figure 3.2).

At 1, 2, and 5 years after hospital discharge, patients with HF-BREF had the highest crude relative risk (RR) of dying compared with patients in the other two groups (Table 3). After adjustment for a variety of important demographic and clinical variables, the poorer long-term prognosis for patients with HF-BREF, and for those with HF-REF, remained though these differences were no longer statistically significant at 5 years after hospital discharge (Table 3.3).

Trends in post-discharge survival

The 1-year post-hospital discharge survival rates improved for all patients discharged from greater Worcester medical centers during the years under study, though these trends were only statistically significant for patients with HF-REF in 2004 as compared to those discharged in 1995 (Table 3.4). However, lesser degrees of improvement in survival were observed at 2 years after hospital discharge for patients discharged in 2004 compared with those discharged in 1995 (Table 3.4).

DISCUSSION

The results of this community-wide study suggest that patients with HF-PEF experienced a better prognosis after hospital discharge compared to patients discharged after HF-REF or HF-BREF. While encouraging increases in 1 year survival were observed in all patient groups during the years under study, especially for those with HF-REF and HF-PEF, these trends were attenuated during subsequent years of follow-up and death rates after hospital discharge remained high in all groups. We observed differences in the characteristics of patients with ADHF with preserved, mildly impaired, or reduced EF values and the prescription of evidence-based cardiac medications at discharge increased over time for all patient groups.

Study population characteristics

The baseline characteristics of our 3 ADHF groups were consistent with the results of previous observational studies and clinical trials [20,21,53]. We found that patients with lower EF findings had a higher burden of several pre-existing cardiovascular diseases and were primarily male. In contrast, patients presenting with preserved EF findings were typically older, mostly female, and had a higher prevalence of previously diagnosed hypertension and COPD [53].

A limited number of prior investigations have examined the characteristics of patients with borderline EF values [20,21,53]. We found that patients with HF-BREF were most similar to those with HF-REF. This could reflect the inexact science and measurement of EF assessment or that patients with HF-BREF represent a distinct ADHF subtype.

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Long-term prognosis of patients with ADHF according to EF findings

To date, no studies of patients with ADHF have examined trends in long-term prognosis using current ACC/AHA cut points for EF values [3]. The studies that have examined the long-term prognosis of patients with ADHF further stratified according to EF findings have used different cut points, some defining HF-PEF as >50% whereas others have used a cut point of >40%, making comparisons between studies difficult [53].

Despite these limitations, data from observational studies have suggested that HF patients with preserved EF have a better long-term prognosis than patients with reduced EF findings [53,77]. The DIG [78] and CHARM [79,80] clinical trials found that patients with HF-PEF experienced lower all-cause death rates compared to patients with reduced EF findings. However, the DIG-PEF trial used an EF cutpoint >45% [78] to define patients with HF-PEF whereas the CHARM-Preserved trial used an EF cutpoint >40% [79] to characterize patients with preserved EF findings.

The finding that patients with preserved EF have a better long-term prognosis than our other comparison groups is consistent with a meta-analysis that pooled data from 31 cohort studies and clinical trials [52]. However, a study examining differences in the long-term survival of approximately 6,000 patients from Olmsted County, Minnesota with HF-REF or HF-PEF found that patients with HF-PEF had only a marginally better prognosis at 1 and 5 years after hospital discharge [74]. A Canadian study examining 30-day and 1-year mortality rates of 2,802 patients with incident ADHF found no differences in these rates between patients with HF-REF and HF-PEF [17].

Additionally, similar death rates at 3 months after hospital discharge were observed among 20,118 HF patients with reduced EF and 21,149 patients with preserved EF in the OPTIMIZE-HF registry [18].

One possible explanation for these disparate results is that there have been considerable improvements in the treatment of patients with HF-REF over time. This hypothesis is consistent with a recent study from Olmsted County, Minnesota that examined longitudinal changes in EF values in 1,233 patients with newly diagnosed HF between 1984 and 2009 [81]. Average EF values decreased by nearly 6% over a 5 year period for patients with HF-PEF whereas patients with HF-REF had EF measurements that increased by nearly 7% over time, with greater increases in EF findings observed in patients treated with evidence-based therapies.

The results from our population-based study in residents of central Massachusetts suggest that patients with HF-REF and HF-PEF experience different survival rates during the first several years after hospital discharge, with patients with HF-PEF faring slightly better than those with HF-REF; only patients with HF-REF and HF-PEF exhibited improvements in 1-year survival after hospital discharge for ADHF during the years under study. None of the patient subgroups examined demonstrated significant increases in post-discharge survival thereafter. One reason for the increases in 1-year survival observed for patients with HF-REF may be due in part to the enhanced management of these patients based upon evidence-based guidelines.

Medication Prescribing Practices

Little data exists describing differences in the prescribing of cardiac medications to patients with ADHF with preserved, mildly reduced, or reduced EF values. Current treatment guidelines are designed to treat patients with HF-REF [3] at the time of hospital discharge, but few, if any, recommendations exist to treat patients with either preserved, or mildly reduced, EF findings. In our patient cohort, approximately 30% of patients with HF-REF were not prescribed ACEI/ARBs and almost 25% were not prescribed a beta-blocker at the time of hospital discharge, even during the most recent year under study (2004). Further studies remain needed to better understand patient and provider level barriers to potential gaps in the use of evidence-based treatments and whether these findings are evident in more recent cohorts of patients hospitalized with ADHF.

Current recommendations for the treatment of patients with HF-PEF are to control their blood pressure and volume status [3]. In addition, data from randomized clinical trials have demonstrated a lack of efficacy for the use of ARBs in HF patients with preserved EF [79,82] and the results from a single randomized trial failed to show any efficacy for ACE-inhibitors [83]. We observed an increase during the years under study in the prescribing of calcium channel blockers to patients with HF-PEF. Several clinical trials have demonstrated an improvement in exercise tolerance and HF related symptoms for patients with HF-PEF treated with verapamil [45]. However, no data currently exists that suggest that calcium channel blockers improve mortality in patients with HF-PEF [40,46].

We were unable to find any published studies that examined the medications that were prescribed to ADHF patients with borderline EF findings at discharge from the

hospital. Our study suggests that patients with HF-BREF are being treated similarly to those with preserved EF in the community setting. There remains an ongoing need for the development of better evidence-based guidelines to treat patients with HF-PEF and HF-BREF beyond current measures of blood pressure and volume control to address the poor long-term prognosis these and all patients with ADHF face.

Study Strengths and Limitations

Our study has several strengths including its population-based design and ability to examine trends in long-term prognosis over a decade long period in patients from 3 EF strata. Since this New England community is predominately white, however, the generalizability of our findings to patients of other race/ethnicities may be limited. We did not collect information on patient's socioeconomic or cognitive status or other factors that have been shown to affect long-term prognosis after ADHF. Additionally, data were not collected on patient's adherence to any prescribed treatments or lifestyle practice changes after being discharged from the hospital. We only had a single measurement of EF for each patient and only 2 out of every 5 patients had their EF assessed acutely. We could not account for the impact of potentially changing EF values on observed long-term mortality patterns and more contemporary data are needed to extend the present findings.

CONCLUSIONS

Despite encouraging trends in survival after the first year after hospital discharge for residents of central Massachusetts discharged from all area medical centers after

ADHF, the long-term death rates in these patients remain extremely high. Patients with varying EF findings had different demographic and clinical characteristics that need to be taken into account when treating these patients. Finally, the prescribing of effective cardiac medications increased over time for all patient groups. This may have, in part, contributed to the observed improvements in post-discharge survival observed across all EF strata. Additional clinical and epidemiologic research utilizing contemporary EF criteria remains needed to improve the long-term prognosis of patients who develop ADHF.

Table 3.1

Demographic and clinical characteristics of patients

with acute decompensated heart failure according to ejection fraction (EF) findings

	Ejection Fraction (%)			
	≤40	41-49	≥50	
Variable	(n=1,479)	(n=346)	(n=1,779)	p-value
Age (mean yrs, SD)	73.7 ± 12.8	76.1 ± 11.4	76.5 ± 11.9	<0.01
Men	836 ± 56.5%	157 ± 45.4%	594 ± 33.4%	<0.01
White	1373 ± 92.8%	319 ± 92.2%	1660 ± 93.3%	0.72
Length of stay (days) (mean, SD)	7.0 ± 7.3	7.2 ± 7.5	7.6 ± 8.9	0.10
Hypertension	973 ± 65.8%	250 ± 72.3%	1257 ± 70.7%	<0.01
Atrial fibrillation	515 ± 34.8%	118 ± 34.1%	635 ± 35.7%	0.80
Diabetes mellitus	593 ± 40.1%	129 ± 37.3%	610 ± 34.3%	<0.01
Coronary heart disease	827 ± 56.0%	189 ± 54.6%	776 ± 43.6%	<0.01
Chronic obstructive pulmonary disease	412 ± 27.9%	112 ± 32.4%	604 ± 34.0%	<0.01
Peripheral vascular disease	299 ± 20.2%	75 ± 21.7%	320 ± 18.0%	0.13
Stroke	186 ± 12.6%	51 ± 14.7%	212 ± 11.9%	0.34
Chronic kidney disease	407 ± 27.5%	86 ± 24.9%	386 ± 21.7%	<0.01

Heart failure	939 ± 63.5%	200 ± 57.8%	978 ± 55.0%	<0.01
Body mass index (kg/m^2)	27.5 ± 6.9%	27.9 ± 6.8%	28.7 ± 7.9%	<0.01
Glomerular filtration rate (mL/min/1.73 m^2)	51.1 ± 23.2%	50.8 ± 23.2%	53.7 ± 24.0%	<0.01
Systolic BP (mm Hg)	139.8 ± 30.9%	150.6 ± 33.0%	148.1 ± 32.5%	<0.01
Diastolic BP (mm Hg)	77.6 ± 19.5%	78.0 ± 18.6%	74.3 ± 19.7%	<0.01
Glucose (mg/dL)	160.0 ± 70.8%	162.4 ± 76.7%	155.0 ± 66.3%	0.06
Total cholesterol (mg/dL)	155.4 ± 42.6%	154.9 ± 38.8%	162.1 ± 44.2%	0.11
Blood urea nitrogen (mg/dL)	33.8 ± 22.6%	31.1 ± 20.5%	30.0 ± 19.7%	<0.01
Serum sodium (mEq/L)	137.2 ± 5.4%	138.0 ± 4.3%	137.5 ± 6.2%	0.48
Hematocrit (%)	37.2 ± 6.5%	36.1 ± 6.6%	35.9 ± 12.2%	<0.01

Table 3.2

Changes over time in post-discharge case-fatality rates according to ejection fraction (EF) findings

Ejection Fraction

Period	1-year			2-years			5-years		
	≤40%	41-49%	>50%	≤40%	41-49%	>50%	≤40%	41-49%	>50%
Overall	34.8%	26.7%	29.9%	48.9%	41.6%	43.3%	71.1%	69.5%	68.7%
1995	40.4%	25.4%	35.0%	55.7%	38.8%	46.5%	76.2%	68.7%	70.7%
2000	35.7%	31.3%	30.4%	52.2%	50.6%	46.7%	74.7%	77.1%	71.5%
2002	32.6%	21.7%	28.9%	44.4%	35.1%	41.2%	67.7%	65.0%	66.9%
2004	32.6%	28.7%	29.1%	45.9%	42.5%	41.9%	67.9%	67.8%	67.6%

Table 3.3

Relative risk (RRs) for dying after hospital discharge according to ejection fraction (EF) findings

	1-year		2-years		5-years	
		Mutivariable		Mutivariable		Mutivariable
	Crude RR	adjusted RR*	Crude RR	adjusted RR	Crude RR	adjusted RR
HF-REF	1.12	1.17	1.10	1.17	1.03	1.02
(EF≤40%)	(1.02, 1.22)[0]	(1.07, 1.28)	(1.03, 1.18)	(1.09, 1.24)	(0.99,1.08)	(0.99, 1.05)
HF-BREF	1.25	1.37	1.22	1.36	1.06	1.04
(EF=41-49%)	(1.04, 1.49)	(1.14, 1.65)	(1.06, 1.40)	(1.20, 1.55)	(0.97,1.16)	(0.98, 1.10)
HF-PEF**	1.0	1.0	1.0	1.0	1.0	1.0
(EF≥50%)						

* Controlling for age, sex, history of atrial fibrillation, diabetes, chronic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, and heart failure, and serum glucose levels during hospitalization.

** Referent group

[0] 95% confidence intervals

Table 3.4

Changes over time in crude and multivariable adjusted relative risk (RRs) for dying

at 1 and 2 years after hospital discharge according to ejection fraction (EF) findings

	EF≤40%		EF=41-49%		EF≥50%	
1-Year	Crude RR	Adjusted RR*	Crude RR	Adjusted RR	Crude RR	Adjusted RR
2000	0.74	0.69	1.30	0.91	0.73	0.69
	$(0.51-1.07)^0$	(0.50-0.97)	(0.51-3.30)	(0.37-2.28)	(0.47-1.14)	(0.45-1.07)
2002	0.63	0.58	1.48	0.87	0.62	0.58
	(0.36-1.10)	(0.35-0.96)	(0.37-5.99)	(0.22-3.46)	(0.32-1.22)	(0.30-1.11)
2004	0.55	0.48	1.69	0.84	0.53	0.48
	(0.26-1.14)	(0.25-0.94)	(0.26-10.87)	(0.13-5.23)	(0.22-1.31)	(0.20-1.15)
2-Years						
2000	0.85	0.92	1.53	1.24	0.95	0.89
	(0.64-1.11)	(0.77-1.09)	(0.78-3.02)	(0.67-2.32)	(0.67-1.35)	(0.64-1.24)
2002	0.78	0.88	1.90	1.38	0.93	0.84
	(0.52-1.17)	(0.68-1.14)	(0.69-5.24)	(0.54-3.52)	(0.55-1.57)	(0.51-1.38)
2004	0.72	0.84	2.35	1.54	0.90	0.79

(0.42-1.24)   (0.60-1.19)   (0.61-9.11)   (0.44-5.36)   (0.45-1.83)   (0.40-1.54)

* Controlling for age, sex, history of atrial fibrillation, diabetes, chronic heart disease, chronic obstructive pulmonary

disease, chronic kidney disease, and heart failure, and serum glucose levels during hospitalization.

[0] 95% confidence interval

1995 is the referent year for all regression analyses

Figure 3.1: Trends in Treatment Practices According to Ejection Fraction Findings

A - Disease-modifying Medications (ACE/ARBs, Beta-blockers)
B - Symptom-modifying Medications (Diuretics, Digoxin)
C - Cardiac Medications (Lipid lowering agents, Nitrates)
D - Combined Medications (ACE/ARBs, Beta-blockers, aldosterone inhibitors)

■ HF-REF (EF<40%)   ■ HF-BREF (EF=41-49%)   □ HF-PEF (EF≥50%)
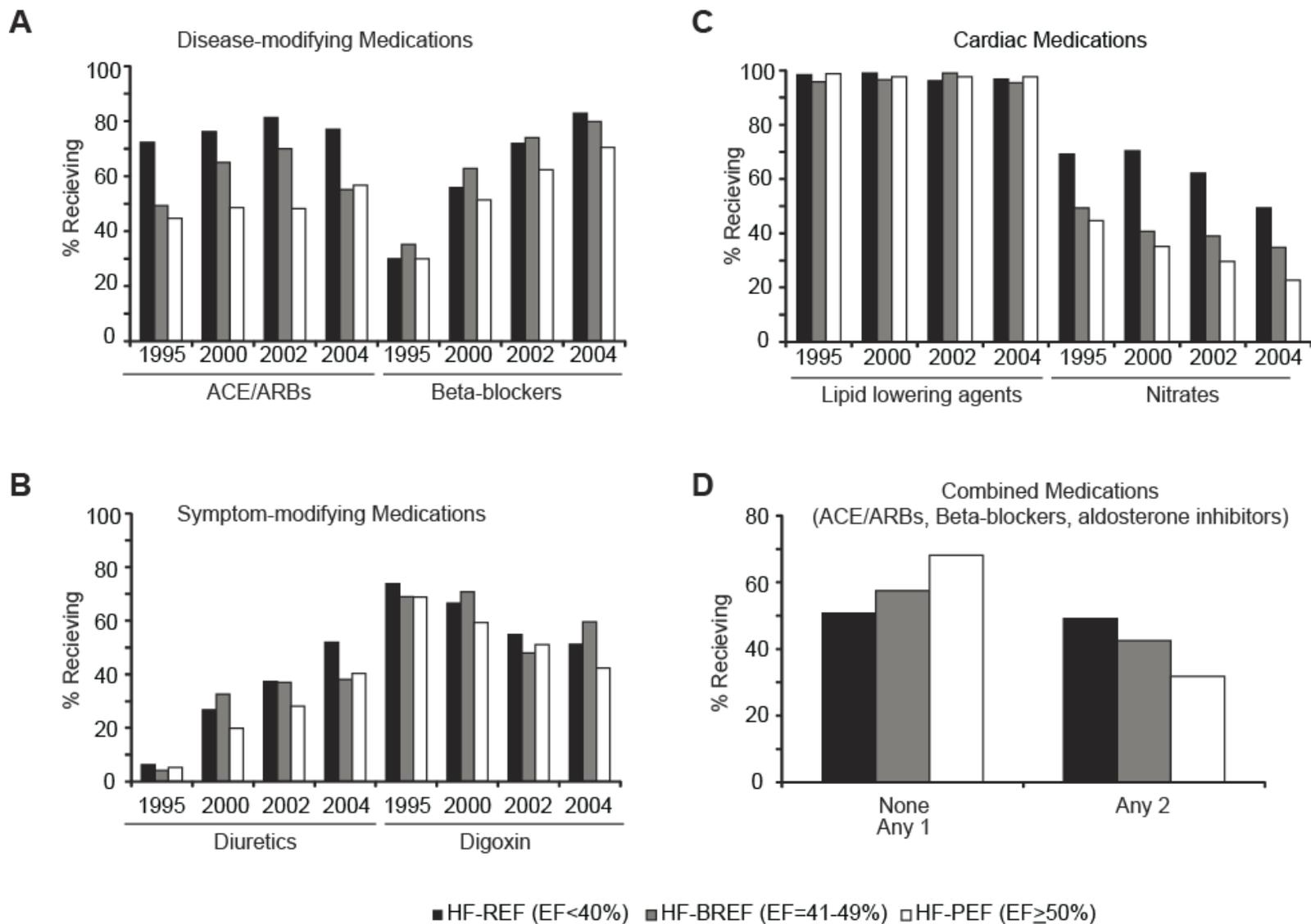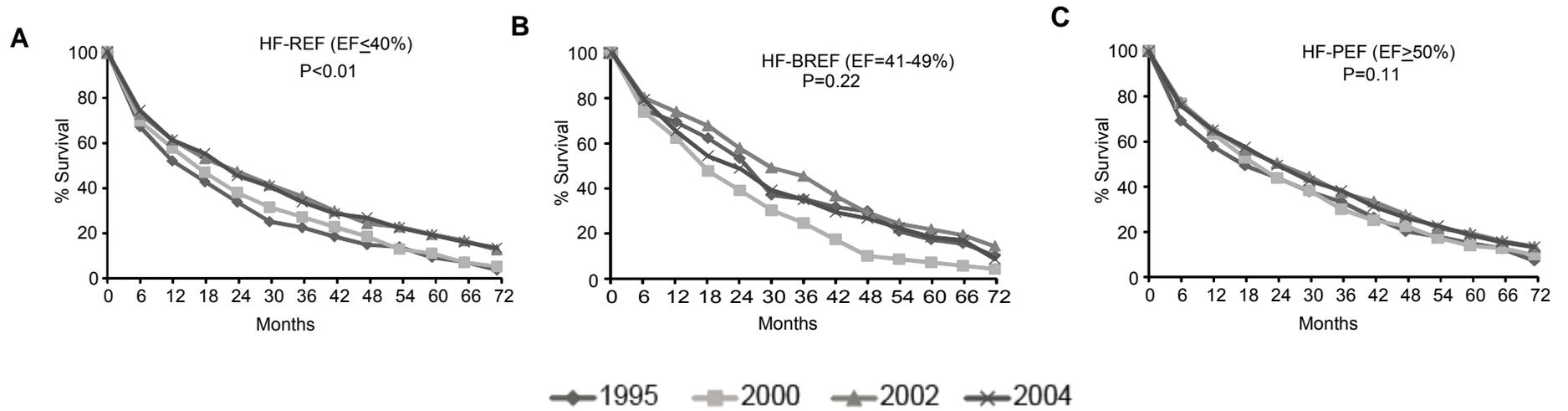
44

Figure 3.2: Trends in Post-Discharge Survival Rates According to Ejection Fraction Findings

CHAPTER 4

Magnitude of and prognostic factors associated with post-discharge mortality after hospitalization for acute decompensated heart failure according to ejection fraction findings.

Background: Limited data exist, particularly from the more generalizable perspective of a population-based investigation, about the magnitude of, and factors associated with, long-term prognosis in patients discharged from the hospital after acute decompensated heart failure (ADHF) further stratified according to currently recommended ejection fraction (EF) findings.

Methods: The hospital medical records of residents of the Worcester (MA) metropolitan area who were discharged after ADHF from all 11 medical centers in central Massachusetts during the 5 study years of 1995, 2000, 2002, 2004, and 2006 were reviewed. Follow-up was completed through 2011 for all patient cohorts.

Results: The average age of the 4,293 study patients was 75 years, the majority (93%) were Caucasian, and 44% were men. Of these, 35% (n=1,680) had reduced (REF; EF≤40%), 13% (n=377) had borderline (BREF; EF=41-49%), and 52% (n=2,236) had preserved EF findings (PEF; EF≥50%). One and two year post discharge death rates were 34% and 53%, 27% and 46%, and 27% and 48% for patients with REF, BREF, and PEF, respectively. Advanced age and lower estimated glomerular filtration rate findings at the time of hospital admission were important predictors of 1-year death rates, irrespective of EF findings. Previously diagnosed chronic obstructive pulmonary

disease, chronic kidney disease, and atrial fibrillation were associated with a poor prognosis in patients with PEF and REF whereas a history of diabetes was an important prognostic factor for patients with REF and BREF.

Conclusion: We observed differences in several prognostic factors between patients with ADHF with varying EF findings, which have implications for more refined treatment plans for these patients.

INTRODUCTION

Acute decompensated heart failure (ADHF) is a world-wide epidemic that affects nearly 6 million adult Americans and results in a substantial number of deaths annually [3,4,73,75,76]. Given the aging of the American population, it is predicted that the number of adult U.S. men and women who will be diagnosed with ADHF will increase to approximately 8 million by 2030 [84].

In order to better understand and characterize the epidemiology of this increasingly prevalent clinical syndrome, a classification scheme for heart failure has been recently created based on ejection fraction (EF) findings [4]. The 2013 American Heart Association/American College of Cardiology (AHA/ACC) guidelines defined three EF strata [4]. This new classification schema was recommended since several research groups had utilized different EF cut-offs for differentiating patients with preserved (PEF) from those with reduced ejection fraction (REF) findings, producing varying study results and difficulties in interpretation. Furthermore, little data exist on the prognosis, or factors associated with poor long-term prognosis, of patients with

borderline reduced EF values (BREF), especially from the more generalizable

perspective of a population-based investigation.

Several epidemiological studies have identified a number of important prognostic

factors that are associated with poor long-term outcomes for patients with ADHF

including advanced age, male sex, hyponatremia, lower systolic blood pressure, poorer

kidney function, and several comorbid conditions [17,20,54,55,56,57,58,59,60,85].

However, many of these earlier studies examined the role of various prognostic factors

in patients with heart failure that had not been stratified according to EF findings and,

among those that did [17,62,63,64,65,66], none used the 2013 AHA/ACC guidelines

recommending specific EF cutpoints [4].

The objectives of the present community-wide study were to describe long-term

death rates and factors associated with all-cause mortality among patients with ADHF

further categorized into currently recommended EF strata. Data from the population-

based Worcester Heart Failure Study were used for this investigation [5,19,70,86].

RESULTS

Study population characteristics

During the 5 periods under study, a total of 4,293 residents of central

Massachusetts were discharged from all 11 metropolitan Worcester medical centers

after ADHF and had echocardiography results available for their index hospitalization.

The average age of this population was approximately 75 years, the majority were

Caucasian, and about 56% were women (Table 4.1). In this population, 39% (n=1,680)

of patients were considered to have REF (EF≤40%), 9% (n=377) had BREF (EF=41-49%), and 52% (n=2,236) were classified as having PEF (EF≥50%).

Post Discharge Mortality

Thirty four percent (n=571) of the patients with REF, 27% (n=101) of the patients with BREF, and 27% (n=613) of the patients with PEF died during the first year after hospital discharge for ADHF. These death rates increased to 53%, 46%, and 48%, at 2 years after hospital discharge for our respective comparison groups. The median survival time was 2.2, 2.3, and 2.7 years after hospital discharge for patients with REF, BREF, and PEF, respectively.

Characteristics of Deceased Patients

In comparing the characteristics of patients with REF who died during the first year after hospital discharge to patients with REF that survived this high risk period, patients that died were older, had longer stays in the hospital during their index hospitalization, lower BMIs, and lower blood pressures and estimated glomerular filtration rate (eGFR) findings at the time of hospital admission (Table 4.1). In addition, deceased patients with REF were more likely to have previously diagnosed chronic kidney disease (CKD), coronary heart disease, chronic obstructive pulmonary disease (COPD), atrial fibrillation, and HF. Patients with BREF who died during the first year after discharge were older and had longer hospital stays than those that lived (Table 4.1). In addition, they had higher frequencies of previously diagnosed COPD, atrial fibrillation, and heart failure (HF), but lower rates of hypertension and peripheral

vascular disease (PVD). Patients with PEF who died during the first year after discharge were older, had longer hospital stays, lower eGFR and hematocrit findings, but lower serum sodium levels at the time of hospital admission in comparison to those that lived (Table 4.1). In addition, they had higher rates of previously diagnosed CKD and atrial fibrillation, but lower rates of previously diagnosed hypertension. Across all EF strata, patients who died during the first year after hospital discharge were significantly older than those who survived this high risk period (Table 4.1).

Predictors of 1-year Mortality for Patients with ADHF according to EF strata

After adjusting for several important clinical and demographic factors, several factors were associated with a poorer prognosis during the first year after hospital discharge for all study patients (Table 4.2). Advanced age, a prior history of CKD, and atrial fibrillation were important predictors of 1-year mortality for patients with ADHF, irrespective of EF findings. A prior history of COPD was an important predictor of mortality for patients with either PEF or REF whereas a history of diabetes was associated with higher 1 year death rates in patients with REF. A lower ($<30L/min/1.73m^2$) eGFR was associated with higher one year death rates after hospital discharge for patients with ADHF, irrespective of EF results (Table 4.2).

Impact of Age on Post Discharge Prognostic Factors

Cox proportional hazard regression models demonstrated advanced age to be a highly significant prognostic factor for patients in all EF strata (Table 4.2). In our study population, 45% of patients with REF, 36% of patients with BREF, and 34% of patients

with PEF were <75 years old (Table 4.1). Therefore, we further divided patients in the three EF strata into two age groups, <75 and ≥75 years, for purposes of examining whether there were differences in various prognostic factors between younger and older patients hospitalized with ADHF(Table 4.3).

The important prognostic factors that were associated with increased mortality during the first year after hospital discharge for ADHF for comparatively younger patients with REF included previously diagnosed diabetes, COPD, CKD, low eGFR values. In contrast, predictors of poor outcomes within the first year after hospital discharge for those older than 75 years included PVD and an admission eGFR between 30-59 (Table 4.3). COPD was an important prognostic factor for patients with REF and PEF, irrespective of age. Prognostic factors that were associated with dying during the first year after hospital discharge for younger patients with BREF were a history of diabetes, PVD, and a high admission systolic blood pressure. A low admission eGFR and previously diagnosed COPD were associated with an increased risk of dying for patients with PEF, irrespective of age. Older patients with PEF who had atrial fibrillation previously diagnosed were at increased risk for dying during this high risk first year period.

DISCUSSION

The results of this study in residents of central Massachusetts hospitalized at all 11 area medical centers suggest that patients with ADHF have high 1 and 2-year post discharge all-cause mortality rates, with patients with REF having the highest death rates at these time points. In addition, patients with PEF had the longest median

survival times as compared with patients in the other two EF strata. Several prognostic factors differed between the three EF groups including a prior history of COPD, CKD, atrial fibrillation, and diabetes. Advanced age was importantly associated with a poorer post-discharge prognosis among all patients discharged from central Massachusetts medical centers after hospitalization for ADHF, irrespective of EF findings. A low eGFR was associated with an increased risk for 1-year mortality after hospitalization for ADHF across the three EF strata. When the study population was further stratified according to age, different prognostic factors became important predictors of post discharge mortality.

Study population characteristics

Previously published observational studies and clinical trials have primarily examined differences in the demographic and clinical characteristics of patients with either PEF or REF, with few describing the characteristics of patients with BREF [12,20,21,53]. These studies found that HF patients with lower EF values had a higher burden of pre-existing diseases, including coronary heart disease and renal failure, and were primarily male. In contrast, patients presenting with preserved EF findings were typically older and mostly female. Our findings suggest that patients with BREF appear to represent an intermediate group with characteristics of patients with PEF and REF. These findings suggest that ADHF is a heterogeneous condition with distinct group characteristics whose prognosis may differ and whose long term management might need to be approached differently.

Post-hospital discharge mortality

There have been mixed published findings as to which EF strata has a better long-term survival after developing ADHF, with some groups suggesting that patients with PEF fare better and other groups suggesting that patients with PEF and REF have similar mortality rates after hospital discharge [17,62,63,64,65,66]. In the present study we observed that patients with PEF fared better over our period of long-term follow-up than patients with either REF or BREF. Our findings of higher death rates in patients with REF are consistent with the observation that patients with PEF typically have more non-cardiovascular comorbidities than patients with REF [87]. However, there are no clinical guidelines for the treatment of patients with PEF, suggesting that their lower discharge mortality might be less a factor of how these patients are managed and more a function of the underlying pathophysiology associated with PEF. This is supported by the observation that ACE/ARBs and beta-blockers are effective in patients with REF but not in those with PEF [16].

Characteristics of patients that died at 1-year post-hospital discharge

Patients in each of the three EF strata that died within the first year after hospital discharge compared to patients who survived this period exhibited significant differences in several baseline characteristics which were not the same between patients in the three EF strata examined.

Studies that have stratified patients with HF into groups based on EF findings and examined predictors of mortality have typically only assessed two strata, those with preserved and those with reduced EF findings [17,62,63,64,65,66]. A number of factors

that were associated with long-term mortality were common between the PEF and REF groups; however, several predictors were also unique to one group or the other. Obesity is a common finding in patients with PEF and a U-shaped relationship with adverse outcomes has been observed in which the greatest proportion of adverse outcomes occurs among patients in the lowest and highest BMI categories. In our study, lower rates of overweight patients were observed in patients with REF that died during the first year after hospitalization for ADHF.

Our findings suggest that patients with REF who died after hospital discharge were more likely to have a prior history of COPD, CKD, and diabetes whereas patients with PEF who died were more likely to have a history of COPD, CKD, and atrial fibrillation than those who survived. Previous reports have identified renal failure and PVD as important predictors of poorer long-term survival in patients with REF or PEF (15,17); diabetes and COPD have been associated with higher post hospital discharge death rates in patients with PEF (15,17,20). None of the previous reports described, however, included patients with BREF. Our investigation found that diabetes and CKD (eGFR <60 mL/min/1.73m^2) were significantly associated with an increased risk of dying for patients with REF. Often present as comorbidities, diabetes and chronic kidney disease are common causes of heart failure, and the risk of death in HF may be more strongly associated with a decline in the GFR than with a reduction in EF [88]. The discrepancies between the current findings and the previous literature could be due to a number of factors including comparatively small numbers of women, use of clinical trial data, different HF diagnostic criteria [61], exclusion of patients with BREF [17], and the EF strata that were used. Future studies should employ the same EF strata as were

proposed in the 2013 AHA/ACC guidelines [4] to ensure that studies can be adequately compared. Further work remains needed to understand the impact of various chronic conditions and socio-demographic, psychosocial, and clinical factors on the overall mortality of patients with ADHF further divided according to currently recommended EF strata.

Impact of age on prognostic factors affecting long-term mortality

Age had a significant impact on the factors associated with long-term prognosis for patients in each of the EF strata examined in the present study. Additionally, the two age groups we analyzed had different prognostic factors within the same EF group. Diabetes and atrial fibrillation, which have been reported to be important prognostic factors in patients with ADHF [12,53,67], appeared to have a differential impact based on EF strata and age. In addition, COPD was an important prognostic factor for patients with REF and PEF, but not for those with BREF. One possibility for this observation is that the pathophysiological processes that result in BREF might be different than either PEF or REF or that these patients are being incorrectly diagnosed and treated. Taken collectively, these findings suggest that age and EF findings should be considered when designing appropriate treatment plans for patients with ADHF. Future clinical trials should include older patients with different comorbidities to better understand the effects of age and selected comorbidities on ADHF, its various EF strata, and the management of this clinical syndrome and its various subtypes.

Study Strengths and limitations

Our study has several strengths including its population-based design and inclusion of only validated cases of ADHF which occurred among adult patients of all ages from a well-defined and characterized large metropolitan area. On the other hand, since this New England community is predominantly white, the generalizability of our findings to other race/ethnicities may be limited. In addition, more contemporary data are needed to extend the present findings. We also did not collect information on patient's socioeconomic or cognitive status, serum biomarkers, or other factors that have been shown to affect long-term prognosis after ADHF. Finally, we only had a single EF measurement from the index hospitalization for each patient. Since EF findings may change over time [81], we cannot account for the impact of potentially changing EF values over time, and how these changes may affect the mortality profile of at risk patients.

CONCLUSIONS

Patients with ADHF experience high death rates after discharge from the hospital, with approximately one half dying by two years, irrespective of EF strata. The highest post discharge mortality rates were observed for patients with REF. The results of our study suggest that prognostic factors that are associated with mortality within one year after hospital discharge differ between patients in the various EF strata with advanced age having a large impact on which prognostic factors are important determinants of mortality. This study reinforces ongoing discussions that different treatment guidelines may be needed for patients with PEF, REF, and BREF in order to design more personalized treatment plans for each of these high risk groups.

Table 4.1

Characteristics of patients with acute decompensated heart failure according to ejection fraction (EF) findings and 1 year survival status

	REF (EF<=40%)		BREF (EF=41-49%)		PEF (EF>=50%)	
	Alive	Dead	Alive	Dead	Alive	Dead
Demographics	(n=1,109)	(n=571)	(n=276)	(n=101)	(n=1,623)	(n=613)
Age (mean yrs, +/- SD)	72.0(13.3)	77.0(11.7)**	75.3(11.4)	79.3(10.3)	76.2(12.2)	78.4(12.2)*
<65, n(%)	274(78.1)	77(21.9)**	43(89.6)	5(10.4)*	270(79.7)	69(20.4)*
65-74	283(73.3)	103(26.7)**	65(73.9)	23(26.1)*	308(74.2)	107(25.8)*
75-84	385(61.3)	243(38.7)**	111(71.6)	44(28.4)*	611(71.4)	245(28.6)*
>85	142(53.0)	126(47.0)**	41(60.3)	27(39.7)*	361(68.9)	163(31.1)*
Male, n (%)	652(58.8)	324(56.7)	125(45.3)	44(43.6)	533(32.8)	213(34.7)
White, n (%)	999(90.1)	547(95.8)* *	254(92.0)	96(95.1)	1,503(92.6)	588(95.8)*
Body mass index (mean kg/m^2)	28.2(7.0)	26.1(6.2)*	28.5(6.9)	26.1(7.3)	29.3(8.0)	27.4(7.7)
Length of hospital stay, days (mean)	6.3	8.2*	6.2	9.7**	6.1	10.6**
Co-morbidities, n (%) Atrial fibrillation	377(34.0)	220(38.5)	82(29.7)	47(46.5)*	566(34.9)	260(42.4)*
Chronic obstructive pulmonary disease	296(26.7)	181(31.7)*	87(31.5)	41(40.6)	555(34.2)	229(37.3)
Chronic kidney disease	282(25.4)	204(35.7)**	65(23.6)	31(30.7)	361(22.2)	177(28.8)**
Coronary heart disease	598(53.9)	349(61.3)*	147(53.3)	60(59.4)	730(45.0)	272(44.3)
Diabetes	423(38.1)	240(42.0)	104(37.7)	37(36.6)	573(35.3)	210(34.2)

Heart failure	687(62.0)	415(72.7)**	156(56.5)	67(66.3)	921(56.8)	361(58.8)
Hypertension	757(68.3)	373(65.3)	211(76.5)	65(64.4)*	1,225(75.5)	412(67.1)**
Peripheral vascular disease	204(18.4)	140(24.5)*	69(25.0)	18(17.8)	323(19.9)	125(20.4)
Stroke	138(12.4)	75(13.1)	41(14.9)	18(17.8)	195(12.0)	81(13.2)
<u>Laboratory variables (mean +/- SD)</u>						
Estimated glomerular filtration rate (mL/min/1.73 m^2)	54.9(22.8)	44.0(22.0)	51.2(22.3)	48.4(24.8)	53.9(23.0)	49.6(24.8)*
Systolic blood pressure (mm Hg)	143.6(30.5)	131.1(28.9)	151.2(33.2)	144.6(30.4)	149.2(31.8)	140.6(32.3)
Diastolic blood pressure (mm Hg)	80.5(19.5)	71.7(18.1)*	77.3(18.7)	76.5(18.4)	74.4(19.3)	71.0(19.5)
Serum glucose (mg/dL)	157.0(67.8)	160.2(72.7)	165.8(77.0)	151.2(68.8)	153.0(65.1)	154.0(65.9)
Serum total cholesterol (mg/dL)	157.3(42.2)	148.0(41.2)	154.6(39.8)	146.1(34.4)	156.3(42.5)	160.0(45.1)
Serum sodium (mEq/L)	137.8(5.4)	136.6(5.3)	138.2(4.1)	138.1(4.8)	137.9(5.0)	137.0(7.9)**
Hematocrit (%)	37.8(6.5)	36.2(6.4)	36.3(6.6)	35.7(6.6)	36.3(12.7)	34.6(6.3)**

* $p<0.05$
**$p<0.001$

Table 4.2

Factors associated with 1 year mortality according to ejection fraction (EF) strata

	REF(EF<=40%) (n=1,384)		BREF(EF=41-49%) (n=334)		PEF(EF>=50%) (n=1,646)	
Demographics						
	HR	95% CI	HR	95% CI	HR	95% CI
Age (yrs)						
75-84	1.25(1.06,1.46)		1.55(1.07,2.24)		1.30(1.10,1.53)	
>85	2.19(1.90,2.52)		2.82(2.00,3.97)		1.84(1.60,2.11)	
Comorbidities						
Chronic obstructive pulmonary disease	1.23(1.09,1.38)		1.21(0.95,1.53)		1.28(1.15;1.42)	
Chronic kidney disease	1.61(1.42,1.82)		1.29(1.00,1.67)		1.31(1.16,1.48)	
Diabetes	1.14(1.02,1.27)		1.20(0.95,1.51)		1.03(0.93,1.14)	
Atrial Fibrillation	1.21(1.07,1.36)		1.31(1.04,1.65)		1.41(1.27,1.57)	
Laboratory variables						
Estimated glomerular filtration rate						
<30	2.39 (1.91,2.99)		1.67(1.22,1.80)		1.59 (1.32,1.91)	
30-59	1.42(1.23,1.65)		1.22(0.96,1.55)		1.11 (.98,1.26)	

Table 4.3

Factors associated with 1-year mortality after hospital discharge further stratified according to ejection fraction and age

	REF (EF<=40%)		BREF (EF=41-49%)		PEF (EF>=50%)	
	<75 years (n=614)	>75 years (n=681)	<75 years (n=129)	>75 years (n=205)	<75 years (n=566)	>75 years (n=1,076)
Comorbidities	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI
Chronic obstructive pulmonary disease	1.25(1.03,1.50)	1.44(1.22,1.70)	1.35(0.87,2.10)	1.21(0.83,1.75)	1.45(1.20,1.75)	1.29(1.13,1.48)
Chronic kidney disease	1.34(1.06,1.71)	1.14(0.94,1.38)	1.64(0.98,2.75)	0.75(0.46,1.24)	1.12(0.88,1.43)	1.08(0.91,1.29)
Hypertension	0.86(0.72,1.02)	0.93(0.79,1.08)	0.71(0.44,1.14)	1.01(0.68,1.49)	0.94(0.78,1.15)	0.94(0.81,1.08)
Diabetes	1.22(1.00,1.48)	1.02(0.86,1.21)	1.47(0.90,2.41)	1.44(0.98,2.11)	1.21 (0.99,1.49)	1.03(0.88,1.19)
Peripheral vascular disease	1.18(0.95,1.46)	1.33(1.10,1.59)	1.61(1.00,2.60)	0.91(0.61,1.35)	1.01(0.80,1.28)	1.06(0.90,1.25)
Stroke	1.41(1.08,1.83)	0.94(0.76,1.16)	1.32(0.74,2.33)	1.33(0.83,2.11)	1.48(1.12,1.95)	1.04(0.86,1.25)
Atrial fibrillation	1.01(0.83,1.23)	1.07(0.91,1.25)	1.25(0.78,2.02)	1.20(0.88,1.64)	1.31(1.07,1.62)	1.39(1.22,1.58)
Coronary heart disease	1.10(0.92,1.31)	1.02(0.86,1.20)	1.33(0.84,2.09)	1.03(0.73,1.44)	1.00(0.83,1.21)	0.88(0.77,0.99)
Laboratory variables						
Estimated GFR (L/min/1.73m^2)						
<30	2.33(1.72,3.16)	1.63(1.28,2.08)	1.67(0.93,3.02)	1.24(0.67,2.27)	1.45(1.09,1.94)	1.54(1.24,1.92)
30-59	1.24(1.03,1.50)	1.27(1.07,1.52)	1.05(0.66,1.67)	0.88(0.62,1.24)	0.96(0.78,1.17)	0.98(0.85,1.12)
Systolic blood pressure (mmHg)						

60

150-159	0.52(0.36,0.75)	0.71(0.53,0.94)	2.99(1.06,8.43)	1.05(0.53,2.10)	0.81(0.54,1.23)	0.81(0.58,1.12)
>160	0.44(0.29,0.64)	0.58(0.42,0.79)	2.63(0.93,7.40)	0.92(0.46,1.84)	0.70(0.46,1.06)	0.75(0.53,1.05)
Serum sodium (mEq/L)						
>135	0.63(0.51,0.77)	0.91(0.76,1.08)	0.66(0.38,1.12)	1.01(0.64,1.59)	0.89(0.71,1.11)	0.98(0.84,1.13)

** Referent groups for laboratory variables were GFR $\geq$60 mL/min/1.73 m^2, systolic blood pressure <100 mmHg, and serum sodium <135 mEq/L.

CHAPTER 5

DISCUSSION AND CONCLUSIONS

Acute heart failure (ADHF) is a significant public health and clinical problem in the US and worldwide [3]. This clinical syndrome is the leading cause of hospitalizations in the elderly, accounting for approximately one million hospital admissions annually [4,6,7], and is an important cause of morbidity, mortality, and functional disability. Recent efforts have attempted to identify better methods for the enhanced prevention and prognosis of patients with ADHF. One noninvasive diagnostic test that is used to stratify patients into different prognostic categories is EF findings, which quantitatively differentiates patients into various groups, including those with reduced, borderline, and preserved EF. Limited data exists, however, as to the long-term prognosis of patients with HF further subdivided into these three EF strata, which this thesis has attempted to address.

The three main objectives of this thesis were to: 1) describe the characteristics of the three EF subtypes of patients hospitalized with ADHF; 2) examine the long-term prognosis of patients after hospital discharge for ADHF stratified according to three EF strata; and 3) determine if there were any prognostic factors associated with an increased risk of dying within the first year after hospital discharge for patients with reduced, borderline, and preserved EF findings. Data from the WHFS were used to address these three primary objectives.

Objective #1: Characteristics of patients with reduced, borderline, and preserved EF

We observed that patients in the three EF strata had different demographic and clinical characteristics. Patients with HF-REF were slightly younger, predominantly male, presented with lower systolic blood pressure findings at the time of hospital admission, and had higher BUN and serum hematocrit levels at the time of hospital admission than did patients with either HF-BREF or HF-PEF (Chapter 3). They were also less likely to have a history of chronic lung disease, but were more likely to have a history of previously diagnosed coronary heart disease, chronic kidney disease, and HF. Patients with HF-PEF were older, mostly female, and presented with higher eGFR findings at the time of hospital admission than patients in the other EF strata. In addition, these patients were more likely to present with a first episode of ADHF and to have a history of chronic lung disease and hypertension.

We are one of only a few groups to describe the characteristics of patients with HF-BREF, who had characteristics relatively similar to the other two groups but were slightly older than patients with HF-REF and included a higher percentage of women. In addition, they included a greater percentage of patients with previously diagnosed diabetes and PVD compared to patients with either HF-REF or HF-PEF. The different demographic and clinical characteristics we observed in this study should be taken into account when treating these patients. Further characterization of patients in these three EF strata should be conducted in more contemporary cohorts of patients with ADHF in

order to provide a more in depth understanding of these groups and to provide current insights into their management and natural history.

Objective #2: Long-term outcomes of patients discharged from the hospital after ADHF according to EF strata

Results from this investigation provide insights into whether patients with HF-PEF fare better over the long-term than patients with HF-REF or those with HF-BEF. The long-term death rates in patients with ADHF were extremely high, with half of discharged patients dying by two years, irrespective of EF strata. However, patients with HF-PEF experienced slightly better prognosis during the first 5-years after discharge compared to patients with HF-REF or HF-BREF. Overall, the case-fatality rates at 1, 2, and 5 years after hospital discharge were approximately 35%, 48%, and 71% for patients with HF-REF; 30%, 46%, and 71% for those with HF-BREF; and 30%, 43%, and 69% for patients with HF-PEF, respectively (Chapter 3). After multivariable adjustment, patients with HF-BREF had the highest risk of dying compared with patients in the other two groups. In addition, although the average survival times for all patient groups was approximately 2 years, the longest mean survival times were observed in patients with preserved EF findings (Chapter 3 and 4). We also observed an increase in mean survival times when the 2006 cohort was included in our analyses of between 3 to 4 months for each of the three groups, with patients with HF-PEF having the longest mean survival time of 2.7 years.

Stratification of patients into clinically meaningful subgroups to more accurately identify those patients requiring more aggressive monitoring and treatment from those

that might not remain of considerable importance to practicing clinicians. In addition to the lives saved and improvements in quality of life for patients with ADHF, these efforts would hopefully translate into health care savings with reduced hospitalizations and decreased prescription drug costs.

Objective #3: Prognostic factors associated with an increased risk of dying during the first year after hospital discharge for ADHF

The prognostic factors that were associated with mortality within one year after hospital discharge differed between the three EF strata with advanced age having a large impact on which prognostic factors were important determinants of mortality in all patient groups. In addition to the major prognostic impact of advanced age, patients with a prior history of diabetes and high BUN levels at admission were also associated with an increased risk of dying, irrespective of EF findings. The prognostic factor associated with mortality for patients with either PEF or REF was a prior history of chronic lung disease/COPD whereas a history of renal failure was a predictor of decreased mortality for patients with REF. Only atrial fibrillation was associated with increased discharge mortality for patients with PEF (Chapter 4).

When age (the cut-off being 75 years old) was used as a stratifying variable, the prognostic factors associated with lower post discharge survival changed significantly. Diabetes, a low glomerular filtration rate (GFR), high systolic BP findings , and high serum sodium levels at the time of hospital admission were associated with a poorer post discharge survival for patients with REF who were younger than 75 years old.. Patients with REF who were older than 75 years had a poor 1-year discharge survival if

they also had a history of PVD and an admission GFR between 30-59 L/min/1.73m^2

(Chapter 4). Chronic lung disease/COPD remained an important prognostic factor for

patients with REF and PEF, irrespective of age. Diabetes and stroke were associated

with an increased risk of dying for patients with BREF that were younger than 75 years

old. A low admission GFR was associated with death within the first year after

discharge for patients with PEF, irrespective of age. Finally, atrial fibrillation was

associated with increased one-year death rates for older patients with PEF. A better

understanding of the prognostic factors associated with a poor discharge survival would

hopefully lead to more tailored therapies that will improve the long-term outcomes for

patients with ADHF. Further work should also investigate the factors associated with

hospital readmissions, overall and during select high risk periods, since this should

result in decreased utilization of healthcare services and decreased costs. Finally,

using EF as the sole variable to stratify patients with ADHF might not be able to fully

differentiate high versus low risk patients. Several additional clinical variables, in

addition to EF findings, should be identified and incorporated into future predictive

models.

Future Directions

The results of this large observational study indicate that patients with ADHF

have a very poor long-term prognosis. On the other hand, patients with a preserved EF

fared slightly better than patients in the other two EF strata. Further clinical and

epidemiologic research utilizing contemporary EF criteria in more recently hospitalized

patient cohorts remains needed to improve the long-term prognosis of patients who

develop ADHF. In addition, studies exploring preventive methods and novel therapeutics are urgently needed. Better life style interventions after the patient is discharged from the hospital to prevent decompensation and readmission are also needed. These interventions could include methods to increase adherence to effective cardiac medications and dietary restrictions including smartphone applications and reducing the intake of sodium. Another avenue with the potential to improve the quality and length of life for patients, but is currently speculative, is the use of RNAi-based therapeutics, which might be able to prevent the development of ADHF or treat ADHF and prevent it from worsening. RNAi-based therapeutics have the potential to selectively reduce the amount of proteins that cause the pathology associated with ADHF, but with fewer side effects than current medications, which remains needed at present for patients with ADHF.

In conclusion, EF measurements differentiate patients with ADHF into three groups with different patient characteristics, outcomes, and prognostic factors associated with increased mortality. Further work is needed in the areas of prevention, diagnosis, and treatment to improve the lives and associated meaningful health outcomes of patients with ADHF.

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