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Hypertensive Acute Decompensated Heart Failure Presentations: On the Decline? : A Master's Thesis

Chad E. Darling
University of Massachusetts Medical School

Chad E. Darling, M.D
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Hypertensive Acute Decompensated Heart Failure Presentations:

On the Decline?

By

Chad Eric Darling

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Hypertensive Acute Decompensated Heart Failure Presentations: On the Decline?

A Masters Thesis Presented

By

Chad E. Darling, M.D.

The signatures of the Master's Thesis Committee signify completion and approval as to style and content of the Thesis

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Edwin Boudreaux, Ph.D., Chair of Committee

_____

Robert Goldberg, Ph.D., Member of Committee

_____

Steven Bird, M.D., Member of Committee

_____

Joel Gore, M.D., Member of Committee

The signature of the Dean of the Graduate School of Biomedical Sciences signifies that the student has met all master's degree graduation requirements of the school.

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Anthony Carruthers, Ph.D.,

Dean of the Graduate School of Biomedical Sciences Program

Master of Science in Clinical Investigation

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Dedication

I would like to dedicate this thesis to my wife Mollie and my children Gavin and Iain. Without the support of my family as I pursue my academic career this thesis would not have been possible.

Acknowledgements

I would also like to acknowledge the members of my Thesis Advisory Committee (Dr. Edwin Boudreaux, Dr. Joel Gore, Dr. Steven Bird, and Dr. Robert Goldberg) for the guidance they provided. In particular I would like to thank Dr. Goldberg who has also served as my K23 mentor and who has significantly helped me develop as a clinician researcher. I would like to acknowledge Darleen Lessard M.S. for analytic support. I would also like to express my gratitude to Dr. Greg Volturo Chair of Emergency Medicine who has supported my research career over the last several years.

Background: The initial systolic blood pressure (SBP) in patients with acute heart failure (AHF) can be used as a guide when choosing specific pharmacologic treatments by helping identify the underlying type of HF (e.g., HF with preserved ejection fraction). Clinical experience and research data from our medical center suggests that AHF with elevated SBP may be presenting less frequently than in the past. This may call into question the utility of initial SBP as a clinical guide. The goal of this Master's Thesis is to test the hypothesis that the frequency of AHF patients with a SBP>160mmhg has declined over time.

Methods: This observational study compares data from 4 cohorts of adult patients admitted with AHF in central MA. Data were obtained from a contemporary (2011-2013) study of patients with AHF as well as from the 1995, 2000, 2006 Worcester Heart Failure Study (WHFS) cohorts. The Framingham criteria the diagnostic criterion for AHF. The main outcome was the proportion of patients with AHF with a SBP > 160 mmHg who presented in each of the 4 study cohorts and was examined by multivariate logistic regression.

Results: 2,366 patients comprised the study population. The average age was 77 years, 55% were female, 94% white, and 75% had prior HF. In 1995 33.6% of AHF patients had a SBP >160 mmHg compared to 19.5% in 2011-2013 ($p<0.01$). Multivariate logistic regression demonstrated a reduced odds of patients presenting with a SBP>160 mmHg in 2006 (0.64, (0.42-0.96)) and 2011-13 (0.46, (0.28-0.74)).

Conclusion: The proportion of patients with AHF and an initial SBP >160 mmHg has significantly declined over time. This may warrant a reexamination of the utility of SBP to inform diagnosis and treatment in patients with AHF.

List of Tables:

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ED = Emergency Department; EM = Emergency Medicine; AHF = Acute Heart Failure; HF= Heart Failure; BP= Blood Pressure; SBP= Systolic blood pressure. ACE-I= Angiotensin Converting Enzyme-Inhibitor.

PREFACE

Data from the NHLBI funded training grant (K23HL101991, C. Darling PI) provided the contemporary data-set used in this study. Data from the Worcester Heart Failure Study (WHFS) (R37HL69874), R. Goldberg PI), a large multicenter study of patients hospitalized with acute heart failure (AHF) at all 11 central Massachusetts hospitals, provided additional historical data needed to perform the analyses presented.

I wrote and designed the study and analyses outlined in this thesis. Darleen Lessard MS provided assistance carrying out the analyses. Robert Goldberg, PhD, served as my primary mentor on this K23 award.

Dr. Goldberg, Edwin Boudreaux, PhD, Joel Gore, MD, and Steve Bird, MD, provided editorial assistance and served on my Thesis Committee.

CHAPTER I

INTRODUCTION

There are more than 5 million Americans who have been diagnosed with heart failure (HF), and each year there are greater than 650,000 new cases of HF that occur among adult American men and women. [1] The majority of these episodes of acute HF (AHF) are cared for in the Emergency Department (ED) setting, resulting in nearly 1 million ED visits [2] and 1 million hospital admissions annually. [1, 3] Efficiently arriving at the diagnosis of AHF and starting appropriate treatment for these high risk patients can be challenging in the ED setting for a variety of reasons. These include the limited time available for patient evaluation and that there is often little known about the patient's previous medical history. However, several basic clinical parameters available at the time of hospital presentation provide information that is useful in diagnosing the presence of AHF and guiding treatment. [4-6] Therefore, it is recommended that the initial management of patient's with suspect AHF be based on the patient's clinical profile which is, in part , determined by their vital signs at the time of ED presentation. [6, 7]

The vast majority of patients with AHF present to the hospital with either elevated or normal blood pressure (BP) as few present in a hypotensive state. [6, 7] These initial BPs can be used to classify patients as having either "vascular failure", with systolic blood pressures (SBP's) ≥160 mmHg, or "cardiac failure", with SBP's in the normal range (110-159 mmHg). [6, 7] Both vascular and cardiac failure profiles are associated with unique clinical features that are useful in guiding the approach to therapy. These profiles are also related to the type of left ventricular dysfunction (systolic versus diastolic) that the patient may have, [4, 5] and may be used by ED providers to guide

clinical decision making as to the choice of pharmacologic and other therapies that should be employed to relieve patient's acute symptoms and pulmonary congestion.

Longitudinal studies have documented that many changes have occurred with regard to the clinical characteristics, management, and prognosis of patients with HF over the past several decades including advancing age, increasing comorbid disease burden, increased use of certain medications, and increased short and longer-term survival. [8, 9] There have also been several changes in the outpatient management of hypertension over time as definitions and targets of therapy have evolved. [10-12] In addition, clinical experience and recent unpublished research data from our medical center suggests that AHF patients with the vascular-failure profile may be presenting less frequently than in the past. If patient presentations of both AHF and elevated SBP are becoming less common than in the past, it may become more difficult to clinically distinguish between vascular and cardiac failure patients. Because of the importance that SBP plays in making the diagnosis and instituting appropriate management of AHF in the ED, the goal of this Master's Thesis is to test the hypothesis that the frequency of AHF presentations in the ED associated with hypertension (SBP>160mmhg) has declined over time.

CHAPTER 2

STUDY METHODS

This Master's Thesis compares data collected at the time of hospital presentation, specifically SBP, from patients seen in the EDs of 3 teaching hospital in central Massachusetts and ultimately admitted to the hospital with AHF. All data for this study were obtained from two separate NIH (NHLBI) sponsored research studies. The first study is a contemporary (2011-2013), observational investigation of the ED treatment of adult patients with AHF that has the overall goal of examining how ED-based treatment impacts short-term (inpatient) clinical outcomes. (K23HL101991, C. Darling PI). The second study is the Worcester Heart Failure Study (WHFS) which was a large, multicenter NHLBI funded investigation (R37 HL69874, R. Goldberg PI) based in central, MA that studied the clinical characteristics, treatments, and outcomes of adult patients admitted with AHF over multiple study years between 1995 and 2006. Each of these studies used the same diagnostic criteria for AHF, namely the Framingham criteria for HF.[13] The Framingham criteria was chosen because it has been used in several studies, including the WHFS [13-17], and it is relatively straightforward to apply. The presence, or absence, of the major and minor criteria used in the Framingham Study was ascertained in both studies by performing chart reviews of ED and inpatient clinical data. The Framingham criteria included the presence of 2 major criteria (e.g., orthopnea, increased jugular venous pressure, and radiological evidence of pulmonary edema) or 1 major and 2 minor (e.g., extremity edema, exertional dyspnea, and pleural effusion) criteria. [18] The specific approaches used in the identification of patients with AHF and collection of pertinent data in each of these studies were as follows:

2.1 Contemporary ED-based Study of AHF

This NHLBI supported investigation (K23HL101991) began in September, 2011, and enrolled patients over 2 years while they were in one of the ED's of a two campus tertiary care medical center (UMass Memorial University and Memorial campuses). In order to study ED-based clinical treatment of patients with AHF, patients were enrolled as soon as possible after arriving in the ED. Patients with possible AHF were identified by trained research staff by using the ED computerized tracking system. Adults ≥18 years were screened based on their chief complaint, medical history, and a brief consultation with the treating physician regarding clinical exam findings. Enrollment proceeded for patients with at least 1 sign (e.g., vascular congestion on chest xray, rales on lung exam, peripheral edema) and at least 1 symptom (e.g., dyspnea, orthopnea) consistent with the presence of AHF. For the present study we excluded AHF in the setting of acute myocardial infarction, in patients with cardiogenic shock, patients currently on hemodialysis, and those with a systolic BP <95mmHg. The latter BP cutoff restriction was put in place because it was an exclusion criteria for the main research aims of the grant that supported the original study. All data for patients subsequently discharged from the ED and who were not admitted to the inpatient setting were not used for this study.

2.1a Data Collection Activities for the ED-based AHF Study

Clinical data gathered on these patients was first recorded by trained RA's on individual patient data entry forms and then transcribed into a customized Redcap database. Initial clinical data (e.g., vital signs) was obtained in real-time while RA's were present in the ED and subsequent data were gathered by a structured chart review at a later time. Demographic data included patient's age, sex, and race. Historical data

included patient's medical history, current medications, and social history. Clinical data regarding ED care included vital signs on arrival (blood pressure, heart rate, respiratory rate, pulse oximetry) and at ED discharge (admission), time of ED arrival and departure to the inpatient setting, prehospital use of HF specific medications, respiratory treatments, urine output, entry laboratory values (e.g., creatinine, B- type natriuretic peptide), and type and timing of ED initiated HF-specific medication treatment. For the main variable of interest, SBP, we recorded the first available reading after the patient arrived at the hospital. This BP reading was obtained via direct observation of vital signs obtained on ED arrival. Specific medications of interest included diuretics and afterload reducers (nesiritide, nitroglycerin, ACE-inhibitors). The results of diagnostic tests in the ED and hospital including chest x–rays, echocardiography (when done), were also recorded. Other in-hospital data included trends in lab values (e.g, serum creatinine) over the initial 24 hours, and inpatient complications (e.g., arrhythmias or myocardial infarction (MI). Within 2 months of hospital discharge, a structured chart review was undertaken by trained research staff to obtain information on short-term clinical outcomes including inpatient length of stay (LOS), need for ICU admission, endotracheal intubation and inpatient mortality.

2.2 The Worcester Heart Failure Study (WHFS)

Whereas the contemporary AHF study was conducted at a single medical center in Worcester, MA, the WHFS studied adult patients admitted to multiple (n=11) hospitals in central Massachusetts with the diagnosis of AHF over multiple study years including 1995, 2000, 2002, 2004, and 2006. For the present study, we restricted this patient population to patients admitted to one of 3 teaching hospitals in Worcester, MA (UMass-Memorial University campus and Memorial campus, and St. Vincent Hospital). We

restricted our population to these medical centers for several reasons. First all 3 are in Worcester, are teaching hospitals, and see similar patient populations. Secondly, including St. Vincent hospital specifically allowed us to increase the size of our study sample to enhance the comparisons between study cohorts. The details of the WHFS study methods have been published elsewhere [8, 9, 19-21] but will be briefly reviewed below.

2.2a Data Collection Activities in the WHFS

Patients with potential AHF were first identified by trained WHFS study staff by performing a standardized review of the medical records of patients with primary or secondary International Classification of Diseases (ninth Revision) (ICD-(9)) consistent with a possible admission for AHF. Patients who were discharged with the HF code of (428.X) were used as the primary means of identifying cases of AHF occurring in residents of central MA. In order not to miss other potential cases of AHF, the medical records of patients with other ICD-9 codes where HF may have occurred were reviewed by trained study staff.. These records were identified by the following ICD-9 codes: rheumatic HF (398.9) acute cor pulmonale (415), diseases of the endocardium (424), cardiomyopathy (425.4), hypertensive heart and renal disease (402 and 404), pulmonary heart disease and congestion (416.9 and 514), lung edema (518.4), dyspnea and respiratory abnormalities (786), and edema (782.3). All available data in the medical records were then used to determine if AHF was present based on the Framingham Study criteria. [18] Patients who developed AHF following admission for a different acute illness (e.g., myocardial infarction) or after a medical procedure were excluded since the WHFS was seeking to study patients admitted primarily for AHF. For comparison with the contemporary AHF study, we included only adult (>18 years old) patients evaluated

in one or our 3 study ED's and excluded those on hemodialysis, who developed an acute MI, cardiogenic shock, or who presented with a systolic BP less than 95 mmHg.

Key data elements for both the contemporary AHF and WHFS studies were defined based on whether an abstractor could locate the element in question in the medical record. For instance, an incident (first) case of AHF was identified when there were no prior hospitalizations for AHF or diagnosis of HF, and no prior treatment of HF. The WHFS collected a wide range of detailed data relevant to this Master's Thesis study. Briefly, data were collected about each patient's demographic, past medical history (e.g., coronary heart disease, hypertension, diabetes), physical exam findings, home medications, clinical characteristics (e.g., vital signs on arrival, HF symptoms) admission status (e.g., ICU versus floor), and laboratory results (e.g., creatinine, beta-natriuretic peptide). Initial SBP was defined as the first available SBP in the medical record and was collected from the medical records. Ejection fraction findings were obtained if echocardiography was carried out during the index admission.

2.3 Comparing blood pressures on patients with AHF over time

The main goal of this Master's Thesis is to compare SBP findings at the time of ED presentation in patients admitted with AHF over time in order to gain an understanding as to whether AHF presentations accompanied by hypertension have declined over the past 15-20 years. We, therefore, obtained initial SBP readings for the WHFS study years of 1995, 2000, and 2006, and from the ED-based AHF study (2011-2013). Hypertension was defined as a systolic BP >160mmHg based on the upper cut point of AHF BP categories as defined by the OPTIMIZE-HF registry study, [4] and also because this high BP group would be most likely to fall into the "vascular failure" phenotype and be treated with afterload reduction agents in the ED setting.

2.4 Data Analysis

Study Population: A total of 338 patients were available from the contemporary AHF study for analysis. To obtain a comparison sample of historical WHFS subjects from our 3 study years (1995, 2000, 2006), we took a 2:1 random sample of all available subjects in the WHFS database which resulted in a total of 676 patients from each WHFS study cohort. Differences in the demographic and clinical characteristics of patients in each of the 4 study groups were compared by chi-square tests for categorical variables and ANOVA for continuous factors.

Our primary study endpoint was the percentage of patients presenting to the ED with AHF who had a SBP > 160mmHg during each of the years under study. Our hypothesis was that the frequency of AHF presentations accompanied by hypertension (SBP > 160 mmHg) has declined over time. For the univariate analyses, differences in the mean arrival SBP according to study year were compared by chi square tests of statistical significance. In addition, a multivariate logistic regression analysis was performed to examine whether study year was associated with a decrease in hypertensive AHF presentations over time at a SBP cut point of 160 mmHg. We set 1995 as the referent year and created a multiple logistic regression model by adding potential confounders to the analysis which were based on clinical relevance and a $P<0.20$ on univariate examination. We made sure to consider several other additional confounders that have been shown to predict mortality and other clinical outcomes in patients with AHF [6, 22-25] including patient's age, sex, history of HF, renal function, diabetes, and coronary heart disease, and the need for mechanical ventilation during their ED stay. Ejection fraction findings were missing in 58% of the study sample and was not controlled for in the regression model. Similarly BNP level was not collected in

the 1995 and 2000 study cohorts and was not incorporated into the regression analyses. The Committee for the Protection of Human Subjects in Research at the University of Massachusetts Medical School approved both the WHFS as well as the contemporary ED-based study.

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CHAPTER III

STUDY RESULTS

Characteristics of the entire study population

A total of 2,366 individuals admitted with AHF were analyzed in this study. This included 3 cohorts of 676 randomly selected patients from the WHFS that were admitted each year in 1995, 2000, and 2006, and 338 patients admitted between 2011-2013 in the ED-based study of AHF. The average age of this study population was 77 years, 55% were female, 92 % were white, and 75% had been previously diagnosed with HF. Between 1995 and 2011-13 there were several notable changes in the clinical characteristics of patients with AHF. Compared to patients admitted for AHF in 1995, those admitted with AHF in the more recent study years of 2011-13 were significantly more likely to have a number of co-morbid cardiovascular conditions previously diagnosed including hypertension, atrial fibrillation, chronic kidney disease, and hyperlipidemia. These patients were also more likely to be taking ACE-Inhibitors and beta-blockers but less likely to be taking digoxin at the time of presentation than more recently hospitalized patients. They also had a shorter length of hospital stay (LOS). **(Table 3.1)**

Trends in the Characteristics of Patients with SBP>160 mmHg

Among patients with AHF and an SBP>160 mmHg, the average age was 76 years, 61% were female, and 91% were white. Consistent with the findings in the entire study sample, between 1995 and 2011-13 the characteristics of patients with AHF and a presenting SBP>160mmHg also evolved over time. In more recent study years this group of patients had a smaller proportion of women, a shorter LOS, a lower mean SBP, and fewer were on digoxin as outpatients. In contrast, these patients had higher

ejection fractions, more preexisting hypertension, kidney disease, and hyperlipidemia, and a greater percentage were taking ACE-Inhibitors and beta-blockers as outpatients. **(Table 3.2)**

Mean SBP and the Frequency of Elevated SBP Over Time

The SBP at presentation averaged 151 mmHg in 1995 and decreased over time to 140 mmHg by 2011-2013 ($p<0.01$). In 1995, 33.6% of all AHF patients had a SBP >160 mmHg which decreased to 19.5% by 2011-2013 ($p<0.01$). **(Figure 3.1)** The distribution of SBP across four BP strata has also changed over time with more recent years (after 2006) demonstrating a more balanced distribution of SBP than earlier years where a greater percentage of patients fell into the higher (>140 and $\geq$160) SBP strata. **(Figure 3.2)**

When compared to patients hospitalized in 1995 (referent year), the crude odds ratios demonstrated that there was a significantly lower odds of patients with AHF presenting with SBP>160 in 2000, 2006, and 2011-2013. After adjustment for several demographic, medical history, and clinical factors only the 2006 and 2011-13 cohorts were found to have significantly reduced odds of presenting with a SBP >160 mmHg. **(Table 3.3)** These findings are consistent with our hypothesis that SBP at the time of presentation in patients with AHF has declined over time.

Table 3.1 Demographic and Clinical Characteristics of Entire Study Sample

	Study Year				
	1995	2000	2006	2011-13	p-value
Demographics	(n=676)	(n=676)	(n=676)	(n=338)	
Age (mean, yrs)	76.7	76.9	77.6	74.8	<0.01
Female (%)	57.9	56.7	56.4	41.2	<0.01
White (%)	95.9	91.4	90.1	89.6	<0.01
Clinical Characteristics					
Body mass index (kg/m^2)	26.9	27.7	28.0	31.7	<0.01
Triage Systolic BP (mean, mm Hg)	151.4	146.7	141.3	140.0	<0.01
Diastolic BP (mean, mm Hg)	81.8	76.3	72.1	75.1	<0.01
Heart Rate (bpm)	94.4	90.4	87.1	88.1	<0.01
Respiratory Rate (breaths/min)	26.0	23.9	22.6	22.0	<0.01
Length of stay (days) (mean, SD)	7.24	5.66	5.47	5.50	<0.01
Chest XRay with pulmonary edema (%)	61.0	51.3	48.8	66.0	0.57
Mechanical Ventilation (%)	11.1	6.5	4.1	2.7	<0.01
Inpatient Death (%)	8.0	5.6	5.8	3.2	<0.01
Mean EF (%)	40.7	43.2	47.3	44.4	0.51[#]
Past Medical and Surgical History (%)					
Hypertension	64.4	68.1	82.7	89.4	<0.01

Atrial fibrillation	36.7	36.7	45.9	53.9	<0.01
Diabetes mellitus	39.5	38.2	37.9	52.7	<0.01
Coronary heart disease	56.7	58.4	58.1	58.3	0.63
Chronic obstructive pulmonary disease	38.0	34.6	40.1	35.8	0.62
Stroke	15.8	16.4	14.1	18.6	0.89
Chronic kidney disease	20.6	22.0	36.5	46.5	<0.01
Heart failure	24.7	26.6	20.7	28.1	0.57
Hypercholesterolemia	14.4	24.9	53.3	73.7	<0.01
HomeMedications (%)					
ACE-Inhibitors	39.1	36.1	39.6	55.9	<0.01
Beta Blockers	21.3	40.4	64.4	74.9	<0.01
ACE-I + Beta Blockers	7.0	17.5	28.7	44.4	<0.01
Calcium Channel Blockers	33.6	24.0	23.8	26.3	<0.01
Diuretics (any)	70.4	66.7	72.0	77.5	<0.01
Digoxin	39.9	33.1	18.1	18.3	<0.01
Laboratory					
Creatinine	1.46	1.50	1.50	1.55	0.52
Hematocrit (%)	37.2	36.2	35.3	35.1	<0.01

Table 3.1 Legend: Selected demographic and clinical characteristics of the entire study sample. # - missing data in over 50% of patients, ACE-I= angiotensin converting enzyme-inhibitor.

Table 3.2 Demographic and clinical characteristics of patients of patients with a SBP>160 mmHg on presentation

	Study Year				
	1995	2000	2006	2011-13	p-value
Demographics	(n=227)	(n=189)	(n=143)	(n=66)	
Age (mean, yrs)	76.8	76.4	76.7	73.5	0.25
Female (%)	66.5	61.4	53.9	54.6	<0.01
White (%)	96.0	87.3	89.5	90.0	0.09
Clinical Characteristics					
Body mass index (kg/m^2)	27.9	28.6	28.3	33.4	<0.01
Triage Systolic BP (mean, mm Hg)	188.8	184.7	182.1	182.8	<0.01
Diastolic BP (mean, mm Hg)	94.9	90.7	85.7	91.5	<0.01
Heart Rate	95.7	92.8	88.7	89.2	0.02
Respiratory Rate	26.9	24.6	23.3	22.2	<0.01
Length of stay (days) (mean, SD)	6.90	5.0	4.9	5.1	<0.01
% Ejection Fraction (mean)	43.0	46.9	49.0	49.1	0.04**
Chest XRay with pulmonary edema (%)	66.5	54.0	54.6	71.2	0.59
Past Medical and Surgical History (%)					
Hypertension	75.3	77.8	88.1	93.9	<0.01
Atrial fibrillation	32.6	29.6	30.8	45.5	0.23
Diabetes mellitus	44.9	42.3	39.9	50	0.96
Coronary heart disease	55.1	57.1	49.0	54.6	0.36
Chronic obstructive pulmonary disease	35.2	31.2	34.3	25.8	0.36

Stroke	18.1	12.1	16.8	25.8	0.27
Chronic kidney disease	19.8	22.8	37.8	42.4	<0.01
Heart failure	72.3	66.1	72.0	60.6	0.35
Hyperlipidemia	19.4	25.4	48.3	74.2	<0.01
Home Medications (%)					
ACE-Inhibitors	36.1	34.4	39.9	62.1	<0.01
Beta Blockers	26.9	48.2	62.9	77.3	<0.01
ACE-I + Beta Blockers	7.5	21.1	29.4	50.0	<0.01
Digoxin	36.6	26.5	14.0	7.6	<0.01
Diuretics (any)	64.8	56.6	60.1	69.7	0.81
Laboratory					
Creatinine, mean (mg/dl)	1.46	1.50	1.50	1.55	0.80
Hematocrit mean (%)	38.1	36.9	36.2	35.9	0.03

Table 3.2 Legend: Selected demographic and clinical characteristics of patients of patients with a SBP>160 mmHg on presentation.
** data missing in 55% of cases

Table 3.3 Crude and multivariable adjusted odds ratios for patients with AHF presenting with a SBP> 160 mmHg

	Crude OR	Adjusted OR*
1995[0]	1.0	1.0
2000	0.70	0.94
	(0.54-0.90)[$]	(0.67-1.31)
2006	0.41	0.64
	(0.30-0.55)	(0.42-0.96)
2011-13	0.35	0.46
	(0.23-0.52)	(0.28-0.74)

Table 3.3 Legend: Crude and adjusted odds ratios for patients to present with a SBP >160mmHg over all study years.
* Controlling for all variables with a P<0.20
[0]1995 is the referent year for all regression analyses
[$] 95% confidence intervals

Figure 3.1 Proportion of Patients Presenting with SBP>160 mmHg Over Time

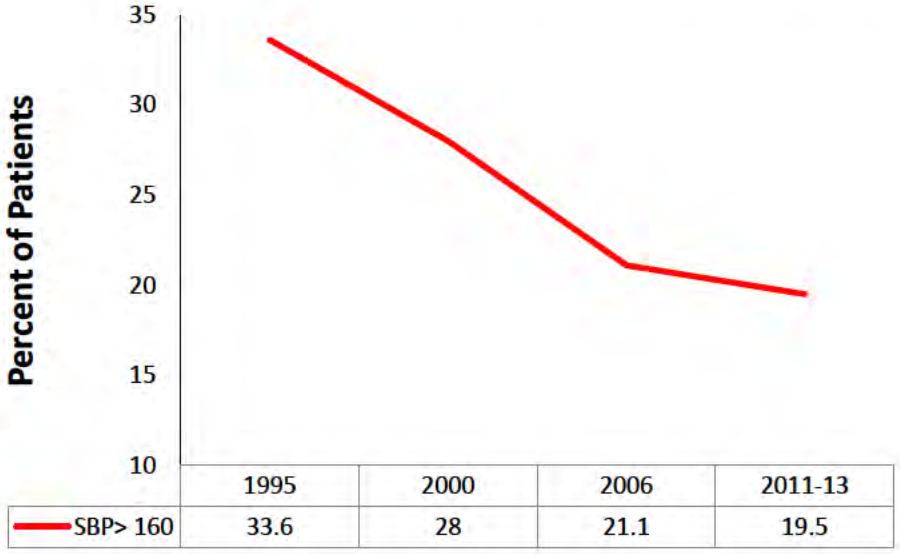

Figure 3.1 Legend: Proportion of patients with a presenting SBP>160mmHg by study year

Figure 3.2 Distribution of SBP by Study Year

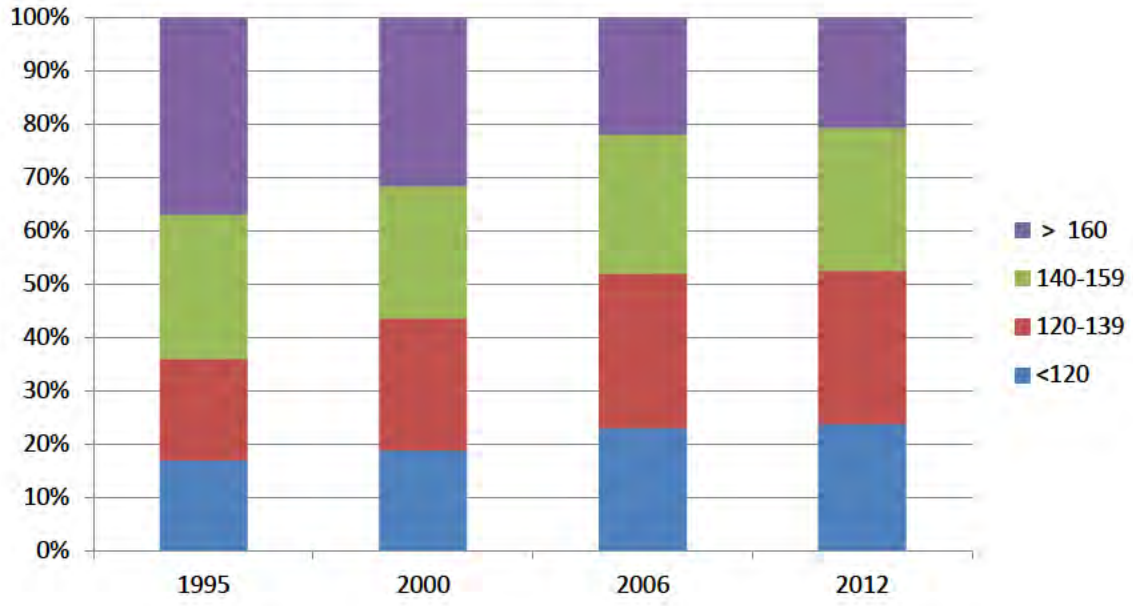

Figure 3.2 Legend: Distribution of SBP in each study year across 4 BP strata

CHAPTER IV

DISCUSSION

In the present study we compared the frequency with which patients with AHF presented to the hospital with SBP's greater than 160 mmHg in four separate cohorts studied between 1995 and 2011-13. The rationale for studying how often these patients present is based on the fact that presenting SBP has been demonstrated to be clinically useful as a guide to help clinicians make decisions regarding the early diagnostic and treatment approach they will pursue in patients presenting with suspected AHF. Clinical experience and recent unpublished data suggested that there may be fewer of these hypertensive patients with AHF than in the past. Our results demonstrate that there has been a significant decrease in the percentage of AHF patients with SBP > 160 mmHg over time at the time of hospital presentation as well as a similar decrease in the mean SBP at presentation.

Despite a decrease the proportion of patients with an SBP> 160 mmHg over time, the overall mean SBP results we observed in the study cohorts are consistent with other large observational studies of patients admitted with AHF. The Acute Decompensated Heart Failure National Registry (ADHERE) collected data on patients with AHF who were admitted to 263 medical centers from all regions of the United States. An early study from ADHERE of patients admitted between 2001 and 2003 found that mean SBP on presentation was 144 mmHg which falls between our mean SBP's for 2000 and 2006 which were 147 mmHg and 141 mmHg respectively.[26] Similarly the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) national registry study found that the mean

SBP of patient admitted with AHF in 2003 and 2004 was 143 mmHg. This suggests that despite the redistribution of SBP into lower SBP strata there remains a large group of patients with normal to elevated SBP at the time of presentation.

The importance of SBP in providing a framework for clinicians to approach patients with AHF has been discussed in several prior studies. [5-7] The Optimize-HF registry contained nearly 50,000 patients and found that those patients with higher SBP's were more likely to be female, African American, and to have HF with a preserved ejection fraction. [4] It is because of this relationship between SBP and the characteristics of patients with AHF that SBP is felt to be useful in the ED or acute care setting. The Optimize-HF registry also documented the relationship between initial or triage SBP and short-term (inpatient) and post-discharge prognosis, where patients having higher SBPs (> 140mmHg) were found to have a decreased mortality compared with patients in lower SBP strata. [4] It is currently unknown what the effect on short and longer-term prognosis might be, if any, if the proportion of patients with AHF who have elevated SBP is declining. Lastly, an AHA working group focused specifically on AHF in the ED has advocated an approach whereby SBP is central to early risk stratification with patients having an SBP>160 falling into the lowest risk group and having the best inhospital and post-discharge prognosis. [27] However, if the distribution of SBPs is evolving over time this approach may need to be refined as it may be more difficult presently to distinguish between which patients will have a better or worse prognosis.

Prior literature has described patients with AHF and significantly elevated SBP as having "vascular failure" rather than "cardiac failure". This distinction may be helpful to clinicians as they attempt to distinguish between patients with different treatment needs. [6, 7, 28] The vascular failure patient typically does not have significant total body fluid

overload and, as a result, early treatment needs to focus on afterload reduction rather than intensive diuresis. [6, 28] However, if elevated SBP is becoming less common than in the past, it may become more difficult to clinically distinguish between vascular and cardiac failure patients.

It is unclear why presenting SBP, and the frequency of AHF accompanied by SBP> 160mmHg, has decreased over time, but it is known, and our data demonstrates, that many demographic and clinical features of patients with AHF have changed during the last few decades. For instance, a large study of more than 55 million Medicare patients admitted and subsequently discharged with a principle diagnosis of AHF found that admission rates for AHF declined significantly between 1998 and 2008 perhaps reflecting improved management of these patients. [3] Findings from the WHFS have demonstrated that, since 1995, patients admitted with AHF have become older, have a greater comorbid disease burden, but have an improved post-discharge prognosis.[8, 29] Similarly, other studies have documented improvement in the long-term survival of AHF patients over the last several years.[30, 31] With increased survival, particularly of HF patients with reduced EF, the overall mix of patients presenting with AHF (incident and recurrent) would be expected to change as well, which would in turn be expected to lower the mean SBP's at the time of acute presentation if more patients with recurrent AHF are present.

Other factors may explain why there may be fewer patients with elevated BP and AHF presenting for treatment than in the past. First, the outpatient management of HF has changed significantly since 1995, [32-35] and there has been an enhanced recognition that the outpatient treatment of hypertension in patients with HF can decrease the incidence of AHF presentations. [36-38] Indeed in our sample there was a

steady increase in the use of ACE-inhibitors and beta-blockers in isolation and in combination in the outpatient management of these patients over time. Others have documented similar increases in beta blocker and ACE-inhibitor use between 1995 and 2000. [39] It is unclear how the outpatient pharmacologic management of patients with HF influences the SBP when a patient presents with AHF, but it may, in part ,explain the trends we have observed.

Furthermore, the management of hypertension has changed significantly over time with new definitions of hypertension and targets for therapy being put forth with each Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC) update since 1977 (most recent update is JNC-8). [10-12, 40] Of note, in the present study we observed a significant increase in the proportion of patients with preexisting hypertension over time which likely reflects the increased comorbid disease burden in these patients as well as the changing definitions of what constitutes hypertension and the heightened focus on this disease. Since hypertension is an important cause of HF, and blood pressure control has improved somewhat over time, these changing trends may have also influenced our results. [41, 42]

D. Study Strengths and Limitations

The major strength of this study lies in its' ability to combine detailed current and historical data in order to better understand how patients with AHF may have changed their presentation, specifically with regards to SBP, over time. . However, there are also several limitations that need to be acknowledged in the interpretation of these study findings. First there was no standard way in which initial SBP was measured clinically. Next, ejection fraction (EF) is an important variable that is related to presenting SBP insofar as patients with hypertensive AHF presentations often have

preserved EF. However, data on EF was missing in a large proportion of the patients in our study sample and was not included in our regression models. Similarly, BNP was not obtained in the first 2 patient cohorts due to it not being used at all the study medical centers. Another potential limitation is that WHFS data were compared to an ED-based AHF study and there were some differences in how the patients were identified (chart identification versus warm pursuit surveillance). Such heterogeneity could introduce a potential selection bias. However, the significant trend in reduction of hypertensive presentations in patients with AHF was also observed in the most recent WHFS cohort (2006), reinforcing the likelihood of our observed trends being real. Changes in prehospital (EMS) treatment may also have influenced the initial SBP's, but the proportion of patients transported by EMS has not significantly changed over time (data not shown). This study was also based on data collected from hospitals in central MA which may narrow the generalizability of the present findings. This limitation is tempered by the fact that the sociodemographic characteristics of the greater Worcester population are similar to those observed in the general U.S. population.

CHAPTER V

CONCLUSIONS

Our study demonstrates that the proportion of patients with AHF with SBP >160 mmHg at the time of presentation to the hospital has significantly declined over time. In addition, the mean SBP at presentation has also declined during the more than decade long period covered under this study. One clinical consequence of these declines is that it may make it more difficult to distinguish between vascular and cardiac failure patients in the ED. Why these changes have occurred is unknown but is likely a result of the changes that have occurred in the outpatient management of both HF and hypertension over the last 15-20 years. The improved management of these patients has resulted in patients with HF living longer and having less frequent hospitalizations. [3, 8, 30] As a result, the overall mix of patients presenting with AHF has evolved since our earliest study sample was selected. These findings may help inform clinical trials as to what the contemporary clinical profiles of patients presenting with signs and symptoms of AHF are. It also highlights a need to study the short and long-term prognosis of these patients in surveillance studies as they continue to increase in prevalence with the aging of the population. Multicenter data on the clinical characteristics, treatment, and prognosis of patients with AHF from racially diverse population over time would help to more systematically determine the generalizability of the trends described in this study.

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