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## Impact of COPD on the Mortality and Treatment of Patients Hospitalized with Acute Decompensated Heart Failure (The Worcester Heart Failure Study): A Masters Thesis

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IMPACT OF COPD ON THE MORTALITY AND TREATMENT OF PATIENTS  
HOSPITALIZED WITH ACUTE DECOMPENSATED HEART FAILURE  
(THE WORCESTER HEART FAILURE STUDY)

A Masters Thesis Presented

By

Kimberly Ann Fisher

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

MASTER OF SCIENCE IN CLINICAL INVESTIGATION

JULY 30, 2014

## **Dedication**

This work is dedicated to my husband, Andrew Wilson, whose encouragement of me to enroll in the MSCI program, and unflagging optimism and support, made the completion of this work possible.

## **Acknowledgements**

I am deeply appreciative of my Thesis Advisor, Dr. Robert J. Goldberg, for lending his substantial expertise, guidance, and resources to the completion of this work. I would like to thank the members of my Thesis Advisory Committee (Dr. Joel Gore, Dr. J. Mark Madison, and Dr. Frederick Spencer) for the thoughtful review and feedback they provided. In particular, I would like to thank Dr. J. Mark Madison for providing me the flexibility in my clinical schedule for me to complete the MSCI program. I would also like to acknowledge and thank Ms. Darleen Lessard for the patience and expertise with which she provided statistical support. Finally, I appreciate the cooperation of the hospitals in the Worcester metropolitan area whose participation in the Worcester Heart Failure Study made this research possible. Funding for the Worcester Heart Failure Study was provided by the National Heart, Lung, and Blood Institute (R37 HL69874).

## **Abstract**

Objective: Chronic obstructive pulmonary disease (COPD) is a common co-morbidity in patients with heart failure, yet little is known about the impact of this condition in patients with acute decompensated heart failure (ADHF), especially from a more generalizable, community-based perspective. The primary objective of this study was to describe the in-hospital and post discharge mortality and treatment of patients hospitalized with ADHF according to COPD status.

Methods: The study population consisted of patients hospitalized with ADHF at all 11 medical centers in central Massachusetts during 4 study years: 1995, 2000, 2002, and 2004.

Results: Of the 9,748 patients hospitalized with ADHF during the years under study, 35.9% had a history of COPD. The average age of this population was 76.1 years, 43.9% were men, and 93.3% were white. At the time of hospital discharge, patients with COPD were less likely to have received evidence-based heart failure medications, including beta-blockers and ACE inhibitors/angiotensin receptor blockers, than patients without COPD. Multivariable adjusted in-hospital death rates were similar for patients with and without COPD. However, among patients who survived to hospital discharge, patients with COPD had a significantly higher risk of dying at 1 (adjusted RR 1.10; 95% CI 1.06, 1.14) and

5-years (adjusted RR 1.40; 95% CI 1.28, 1.42) after hospital discharge than patients who were not previously diagnosed with COPD.

Conclusions: COPD is a common co-morbidity in patients hospitalized with ADHF and is associated with a worse long-term prognosis. Further research is required to understand the complex interactions of these diseases and to ensure that patients with ADHF and COPD receive optimal treatment modalities.

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### **List of Symbols, Abbreviations or Nomenclature**

ACE – angiotensin-converting enzyme; ADHF – acute decompensated heart failure; COPD – chronic obstructive pulmonary disease; EF – ejection fraction; HF – heart failure; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; ICD - international classification of disease

## **PREFACE**

Data from the Worcester Heart Failure Study, a large community-based observational study of patients hospitalized with acute decompensated heart failure, was used to perform the analyses presented herein.

Kimberly A. Fisher, M.D. designed the analyses presented in this thesis, and wrote the manuscript. Darleen Lessard, MS provided assistance with Worcester Heart Failure Study data management and conducted the statistical analysis. Mihaela Stefan, M.D. co-authored the introduction and methods sections, and provided editorial assistance. Robert J. Goldberg, Ph.D. supervised all aspects of the design, analysis, and drafting the manuscript. Chad Darling, M.D. provided editorial assistance.



## CHAPTER I

### Introduction

Heart failure and chronic obstructive lung disease are leading causes of morbidity and mortality worldwide.<sup>1-3</sup> The two diseases often coexist,<sup>4,5</sup> owing to shared key predisposing factors, including the smoking of tobacco and advanced age. Chronic obstructive pulmonary disease (COPD) is one of the most common co-morbidities in patients with heart failure (HF) with a prevalence of 20-30%.<sup>6-10</sup>

There is increasing recognition of the prognostic and therapeutic importance of the co-morbid conditions associated with HF.<sup>10</sup> The presence of COPD in patients with HF has been associated with poor clinical outcomes<sup>7,11</sup> and the management of HF is complicated by the presence of COPD. The cornerstones of therapy for HF and COPD, beta-blockers and beta-agonists, have opposing pharmacologic actions, raising concerns that the treatment of one condition may worsen the other. Despite a growing evidence base demonstrating the safety of cardioselective beta-blockade in patients with COPD,<sup>12,13</sup> patients with COPD and HF are less likely to receive several guideline recommended therapies for HF.<sup>7,8,11,14</sup> For these and other reasons, COPD is expected to be an important co-morbidity in patients with HF, with the potential to negatively influence the treatment and mortality of patients hospitalized with acute decompensated heart failure (ADHF).

Despite the importance of co-morbid COPD on treatment and mortality of HF, data describing the clinical epidemiology of patients with HF and coexistent COPD from the more generalizable perspective of a population-based investigation are extremely limited.<sup>8,11</sup> Most prior studies examining the association between COPD and HF have utilized a registry-based design, or have been carried out as secondary analyses of data from randomized controlled trials, with more select patient populations.<sup>7,11,15</sup> The only community-based study examining the impact of COPD on mortality in patients with ADHF, conducted in the Somme region of France in 2000, studied a relatively small patient population (n = 799).<sup>8</sup>

The primary objective of this study was to describe the impact of COPD on the in-hospital and long-term mortality and treatment of patients hospitalized with acute decompensated heart failure (ADHF) from a community-wide perspective, utilizing a large observational dataset. A secondary aim was to examine decade long trends (1995-2004) in the survival and treatment patterns of patients with ADHF according to COPD status. Data from the population-based Worcester Heart Failure Study were utilized for purposes of this study.<sup>16,17</sup>

## CHAPTER II

### Study methods

#### Study population

The Worcester Heart Failure study is a population-based investigation that includes residents of the Worcester, MA, metropolitan area (2000 census estimate 478,000) hospitalized with ADHF at all 11 medical centers in Central Massachusetts during the 4 study years of 1995, 2000, 2002, and 2004.<sup>14-19</sup> These years were selected due to the availability of grant funding and for purposes of describing decade long trends in the descriptive epidemiology of ADHF. Details of this study have been previously provided.<sup>15-20</sup> This study was approved by the Institutional Review Board at the University of Massachusetts Medical School (IRB approval #10398 1).

In order to identify cases of possible ADHF, the medical records of patients discharged with a primary or secondary International Classification of Disease (ICD)-9 code consistent with HF were reviewed by trained study physicians and nurses. The presence of HF as the primary cause of hospitalization was confirmed using pre-established Framingham criteria<sup>18,19</sup> and determination was made whether the index hospitalization during the years under study was the first (incident) episode of HF or otherwise. 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 also

have had new onset ADHF.<sup>16</sup> Patients who developed HF during hospitalization for another acute illness (e.g., acute myocardial infarction) or after an interventional procedure (e.g., coronary artery bypass surgery) were not included in this study. COPD was considered to be present if a patient was described in his/her medical record as having clinical or radiographic evidence of COPD. Pulmonary function testing results were not available to confirm the diagnosis or to assess the severity of COPD.

#### Data collection

For each case of ADHF identified, abstracted data from hospital medical records included patient demographics (e.g., age, sex, race), medical history (e.g., coronary heart disease, diabetes, renal failure, stroke), clinical characteristics (e.g., presenting symptoms, physiologic findings), laboratory measurements including echocardiography results, length of hospital stay, and hospital discharge status. Use of selective cardiac medications (e.g., angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, diuretics, and hydralazine/nitrates) at the time of hospital discharge and hospital length of stay and vital status were determined through chart review. Long-term survival status through 2010 was assessed through the review of hospital medical records for subsequent health care encounters at all participating greater Worcester medical centers, as well as through the review of the Social Security Death Index and death certificates at the Massachusetts

State Health Department; follow-up information was obtained for greater than 99% of discharged patients.

### Data Analysis

Differences in the demographic and clinical characteristics, as well as in the receipt of HF-specific medications at hospital discharge, among patients with ADHF with and without a history of COPD were examined using chi-square-tests for discrete variables and Student's t-test for continuous variables.

A life table approach was utilized to include patients with varying duration of follow-up after being discharged from all metropolitan Worcester hospitals during the years under study. We calculated crude and multivariable adjusted relative risk (RR) estimates to examine the independent association between COPD status and in-hospital and post-discharge mortality at selected time points (30-days, 1 year, and 5 years) using Poisson regression with robust error variance. Multivariable logistic regression analyses were used to examine decade long trends in death rates at similar time points. We adjusted all regression models for a number of factors of prognostic importance that differed between our respective comparison groups including age, sex, race, hospital length of stay, previously diagnosed HF, prior vascular disease (history of stroke, peripheral vascular disease, angina, or coronary artery bypass surgery), prior comorbidities (diabetes, hypertension, renal disease, anemia, and atrial fibrillation), smoking status, and laboratory and physiologic variables at the time of hospital

presentation (blood pressure, sodium, creatinine). Variables with high rates of missing data, which occurred for ejection fraction findings and body mass index, were not included in our regression models. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, North Carolina).

## CHAPTER III

### Study findings

#### Study Population Characteristics

A total of 9,748 patients were hospitalized with ADHF at all metropolitan Worcester medical centers during the years under study of whom 3,500 (35.9%) had a history of COPD. Overall, the mean age of the study population was 76.1 years, 43.9% were men, and 93.3% were white. There were no significant changes in the prevalence of previously diagnosed COPD among patients with ADHF during the years under study (1995 = 35.5%; 2000 = 34.3%; 2002 = 37.9%; 2004 = 35.7%;  $p$  for trend = 0.37).

Compared to patients without COPD, patients with COPD were slightly younger, more likely to be obese, and to currently smoke. Patients with COPD had a significantly higher burden of co-morbidities, including a history of previously diagnosed renal disease, peripheral vascular disease, anemia, angina, and atrial fibrillation. On the other hand, these patients were less likely to have a history of cerebrovascular disease or to have previously undergone coronary artery bypass grafting. Patients with COPD were less likely to have presented with a first episode of ADHF, and were more likely to have a preserved ejection fraction among those in whom echocardiographic findings were available. A history of COPD was associated with a slightly longer hospital stay (**Table 3.1**).

## Hospital Discharge Treatment Practices

Patients with COPD were less likely to have been treated with most classes of HF specific medications at the time of hospital discharge than patients without COPD. These included ACE inhibitors/angiotensin receptor blockers (ACE-I/ARBs) and beta-blockers. Patients with COPD were slightly more likely to have been treated with diuretics on discharge than patients without COPD. There were no significant differences in the use of nitrates and hydralazine between patients with and without COPD; however, very few patients ( $\leq 1\%$ ) in either group were treated with this combination of medications (**Table 3.2**).

After restricting our sample to the subset of patients with ADHF and a documented ejection fraction (EF)  $< 40\%$ , patients with COPD ( $n = 333$ ) remained significantly less likely to have been prescribed beta-blockers at the time of hospital discharge than patients without COPD ( $n = 912$ ) (45.4% vs. 59.0%;  $p < 0.001$ ). Among patients with documented EF values  $< 40\%$ , there were no differences in the use of ACE-I/ARBs (71.2% vs. 73.5%;  $p = 0.42$ ), or diuretics (84.7% vs. 83.2%;  $p = 0.54$ ) at the time of hospital discharge between patients with and without COPD.

Use of beta-blockers increased between 1995 and 2004 at a relatively similar rate in patients with and without COPD. At the time of hospital discharge, beta-blockers were prescribed to 13.1% of patients with COPD as compared to 27.8% of patients without COPD in 1995; these percentages increased to 57.5% and 72.9%, respectively, in 2004. ACE-I/ARBs and diuretic use remained fairly



constant during the years under study in each of our primary comparison groups (**Figure 3.1**).

### In-Hospital Death Rates

Patients with previously diagnosed COPD had higher in-hospital death rates compared to patients without COPD (7.9% vs. 6.8%,  $p = 0.05$ ). After adjusting for differences in several baseline demographic and clinical characteristics, differences in hospital death rates were no longer statistically significant (RR 0.99, 95% C.I. 0.98, 1.00) (**Table 3.3**). In multivariable adjusted logistic regression models examining decade long trends in in-hospital survival, we observed a significant improvement among patients without COPD between 1995 and 2004 (OR 1.70; 95% CI 1.23, 2.36), but not in patients with COPD (OR 1.34; 95% CI 0.92, 1.97) (**Figure 3.2**), in in-hospital survival.

### Post Discharge Death Rates

Among patients who survived to hospital discharge, patients with COPD were more likely to have died over the course of our extended follow-up (**Figure 3.3**). While there were no differences in our multivariable adjusted death rates at 30 days after hospital discharge (RR 1.01, 95% C.I. 1.00, 1.03), patients with COPD were significantly more likely to have died at 1 year (adjusted RR 1.10, 95% C.I. 1.06, 1.14) and 5 years (adjusted RR 1.40, 95% C.I. 1.28, 1.52) following hospital discharge for ADHF (**Table 3.3**). These findings did not

materially change when the use of HF medications (ACE-I/ARBs and beta-blockers) at the time of hospital discharge were included in the regression model (data not shown).

When we examined decade long trends in post-discharge survival between 1995 and 2004, we observed an improvement in survival at 30 days post-discharge among patients with COPD (OR 1.67; 95% CI 1.13, 2.49), but not in patients without COPD (OR 1.23; 95% CI 0.89, 1.70). Overall, long-term survival improved significantly between 1995 and 2004 among all patients hospitalized for ADHF. However, patients without COPD had a more marked improvement than patients with COPD in 1-year (OR 1.69; 95% CI 1.41, 2.02 vs. OR 1.42; 95% CI 1.13, 1.80) and 5-year (OR 2.08; 95% CI 1.70, 2.56 vs. OR 1.65; 95% CI 1.23, 2.23) multivariable adjusted post-discharge survival rates between 1995 and 2004 (**Figure 3.2**).

**Table 3.1 Characteristics of patients hospitalized with acute  
decompensated heart failure according to history of chronic obstructive  
pulmonary disease (COPD)**

<b>Patient characteristic</b>	<b>COPD (+) (n = 3,500)</b>	<b>COPD (-) (n = 6,248)</b>	<b>p-value</b>
<b>Demographics</b>			
Age, mean (years)	75.6	76.5	<.001
Age, n (%)			
< 65	548 (15.7)	976 (15.6)	<.001
65-74	910 (26.0)	1,187 (19.0)	
75-84	1,317 (37.6)	2,298 (36.8)	
≥ 85	724 (20.7)	1,783 (28.6)	
Male, n (%)	1,562 (44.6)	2,722 (43.6)	.31
White race, n (%)	3,319 (94.8)	5,772 (92.4)	<.001
Current smoker, n (%)	514 (14.7)	429 (6.9)	<.001
Former smoker, n (%)	2,025 (57.9)	2,360 (37.8)	<.001
BMI*, mean (kg/m <sup>2</sup> )	28.2	27.5	<.001
BMI*, n (%)			
< 25 kg/m <sup>2</sup>	1,177 (41.2)	2,091 (41.9)	<.001
25 – 30 kg/m <sup>2</sup>	712 (25.0)	1,537 (30.8)	
≥ 30 kg/m <sup>2</sup>	965 (33.8)	1,358 (27.2)	
<b>Medical History, n (%)</b>			
Diabetes	1,370 (39.1)	2,437 (39.0)	.89
Hypertension	2,371 (67.7)	4,322 (69.2)	.14
Stroke	412 (11.8)	886 (14.2)	<.001
Renal disease	959 (27.4)	1,571 (25.1)	.015
Peripheral vascular disease	729 (20.8)	1,188 (19.0)	.032
Angina	643 (18.4)	1,018 (16.3)	.009
Coronary artery bypass grafting	661 (18.9)	1,403 (22.5)	<.001
Anemia	904 (25.8)	1,495 (23.9)	.037
Atrial fibrillation	1,408 (40.2)	2,337 (37.4)	.006
<b>Vital signs, on presentation (means)</b>			
Systolic blood pressure (mm Hg)	140.6	143.8	<.001
Diastolic blood pressure (mm Hg)	73.0	75.7	<.001

Hg)			
Pulse (beats/min)	91.5	87.8	<.001
Respiratory rate (breaths/min)	24.8	23.1	<.001
<b>Laboratory findings, on admission</b> (means)			
Creatinine (mg/dl)	1.58	1.68	<.001
eGFR (ml/min/1.73 m <sup>2</sup> )	52.1	50.2	<.001
B-type natriuretic peptide (ng/L)**	988	1078	.15
Serum sodium, mmol/L	137.6	137.3	.002
<b>Heart failure characteristics</b>			
Incident heart failure, n (%)	773 (22.1)	2,061 (33.0)	<.001
Baseline ejection fraction (mean,%)***	47	45	<.001
Baseline ejection fraction, n (%)***			<.001
>50%	555 (51.5)	1,058 (44.9)	
41-50%	160 (14.8)	335 (14.2)	
≤40%	363 (33.7)	963 (40.9)	
Length of stay (mean, days)	6.5	6.0	.007

**Table 3.1 Legend.**

\* BMI data available on 7,840 patients

\*\* BNP data available on 1,502 patients, of which 96.9% were in the 2004 cohort

\*\*\* Echocardiographic data available on 3,434 patients, n = 1078 COPD (+); n = 2356 COPD (-).

**Table 3.2 Heart failure specific discharge medications in patients hospitalized with acute decompensated heart failure according to history of chronic obstructive pulmonary disease (COPD)**

<b><u>Medication</u></b>	<b><u>COPD (+)</u></b> <b><u>(n = 3,223)</u></b>	<b><u>COPD (-)</u></b> <b><u>(n = 5,821)</u></b>	<b><u>p value</u></b>
ACE-I/ARB	1,596 (49.5)	3,157 (54.2)	<.001
Beta-blockers	1,271 (39.4)	3,251 (55.9)	<.001
Diuretics	2,701 (83.8)	4,676 (80.3)	<.001
Nitrates and hydralazine	36 (1.1)	48 (0.82)	.17

**Table 3.2 Legend**

ACE – Angiotensin converting enzyme; ARB – Angiotensin receptor blocker

**Table 3.3 In-hospital and post discharge death rates of patients hospitalized with acute decompensated heart failure according to history of chronic obstructive pulmonary disease (COPD)**

<u>Outcome</u>	<u>COPD (+)</u>	<u>COPD (-)</u>	<u>Unadjusted RR<sup>o</sup></u>	<u>Multivariable adjusted RR*</u>
<u>Mortality</u>				
In-hospital	277 (7.9)	427 (6.8)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
30-Days	309 (9.6)	443 (7.6)	1.02 (1.01, 1.04)	1.01 (1.00, 1.03)
1-year	1,348 (41.8)	2,031 (34.9)	1.12 (1.08, 1.16)	1.10 (1.06, 1.14)
5-year	2,626 (81.5)	4,190 (72.0)	1.51 (1.39, 1.64)	1.40 (1.28, 1.52)

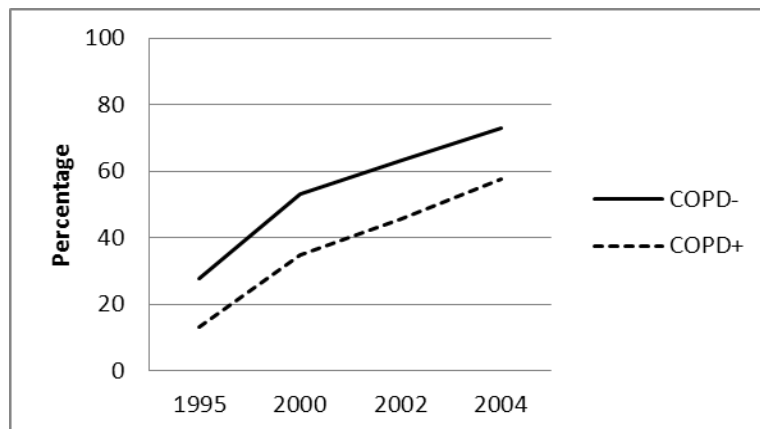
**Table 3.3 Legend.**

\* Adjusted for age, sex, white race, incident vs. previously diagnosed HF, length of hospital stay, prior vascular disease (history of stroke, peripheral vascular disease, angina, or coronary artery bypass surgery), prior other co-morbidities (diabetes, hypertension, renal disease, anemia, and atrial fibrillation), smoking status, and physiologic variables on presentation (blood pressure, sodium, creatinine).

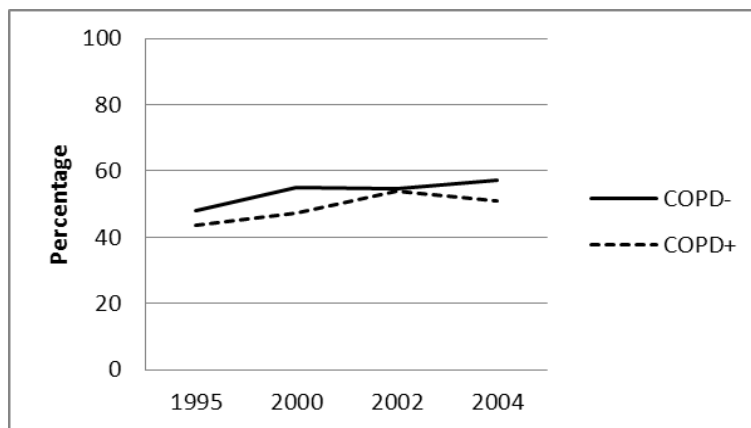
<sup>o</sup>Relative risk (RR) of selected endpoints in patients with, as compared to those without, COPD. Patients without COPD comprised the referent group

**Figure 3.1. Changes in discharge medical therapy by study year, according to history of chronic obstructive pulmonary disease (COPD).**

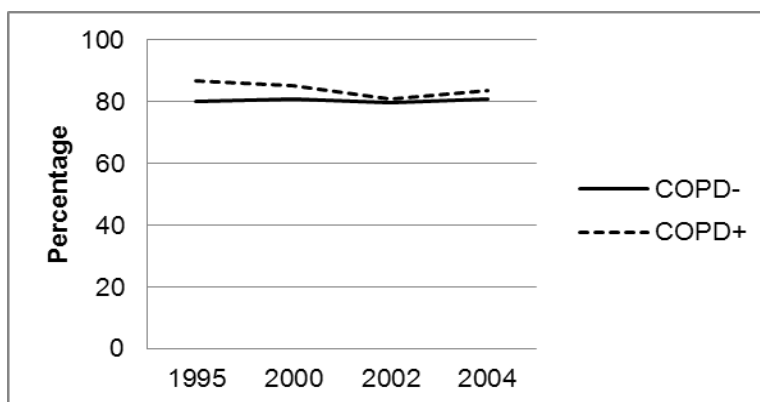
A.



B.



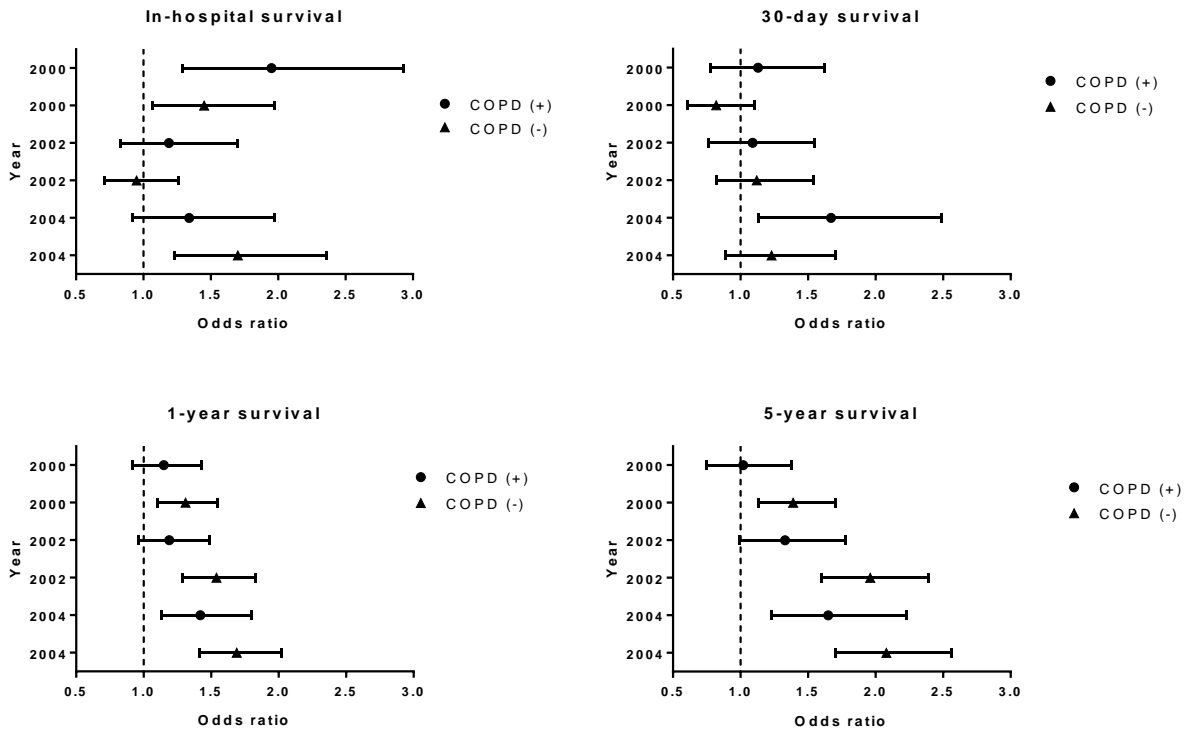
C.



**Figure 3.1 Legend.**

A, Beta-blockers. B, ACE-inhibitor or angiotensin receptor blocker. C, Diuretic therapy

**Figure 3.2 Trends in multivariable adjusted\* odds of survival among patients hospitalized with acute decompensated heart failure according to history of chronic obstructive pulmonary disease (COPD).**

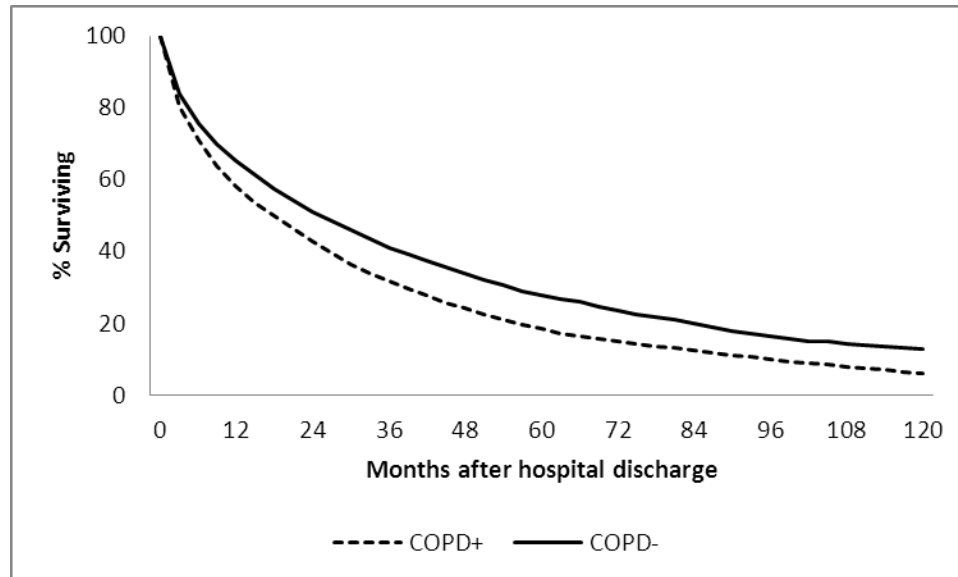


**Figure 3.2. Legend.**

\* Adjusted for age, sex, white race, incident HF, length of hospital stay, prior vascular disease (history of stroke, peripheral vascular disease, angina, or coronary artery bypass surgery), prior other co-morbidities (diabetes, hypertension, renal disease, anemia, and atrial fibrillation), smoking status, and laboratory and physiologic variables on presentation (blood pressure, sodium, creatinine). Study year 1995 comprised the referent group.



**Figure 3.3 Survival following hospital discharge for acute decompensated heart failure according to history of chronic obstructive pulmonary disease (COPD).**



## CHAPTER IV

### Discussion

In this large, community-based, study of residents of central Massachusetts hospitalized with ADHF, we found COPD to be a common co-morbidity, affecting approximately one in every three patients with ADHF. We observed significant differences between patients with and without COPD with regards to co-morbidity burden, presenting clinical characteristics, medications prescribed at hospital discharge, and all-cause mortality. COPD was associated with an increased risk of dying over the long-term in the setting of ADHF. While long-term survival following hospital discharge improved in patients with and without a history of COPD during the decade long period under study (1995-2004), patients with ADHF and co-existent COPD continued to fare worse than those without COPD. We found a marked increase in the use of beta-blockers at the time of discharge in all patients during the years under study; however, a gap in the use of these medications persisted between patients with and without prior COPD, independent of HF classification based on echocardiographic findings.

#### Prevalence of COPD in ADHF and Clinical Characteristics

Approximately one-third of patients hospitalized for ADHF in our study had a prior history of COPD. This proportion is slightly higher than the findings from other observational studies which found prevalence estimates to have ranged from 10% to upwards of 25%.<sup>6-8,10,11,20,21</sup> In one of the only other community-

based studies of COPD in patients with HF, 20% of 799 patients hospitalized with HF at any of the 11 healthcare establishments responsible for managing patients with HF in the Somme region of France during 2000 had co-existing COPD. This study was, however, limited to patients with a first episode of HF which likely accounted for the lower observed prevalence of COPD than was observed in our study.<sup>8</sup> Although the prevalence of COPD in patients with HF has been noted to be higher in more recent studies,<sup>20</sup> we were encouraged that the prevalence of COPD in residents of central Massachusetts hospitalized at all metropolitan Worcester medical centers remained stable during the decade long period under study.

Patients with COPD had a higher burden of vascular co-morbidities, likely related to increased rates of smoking which is a common risk factor for these conditions; COPD itself may also be an independent risk factor for cardiovascular morbidity, although our study was not designed to address this.<sup>22</sup> In contrast to prior studies,<sup>7,8</sup> patients with COPD in the present investigation were slightly more likely to have a preserved ejection fraction (HFpEF). Interpretation of this finding is limited, however, by the substantial rate of missing echocardiographic data in our study population, rates of which differed according to COPD status. However, emphysema and airflow obstruction have been shown to impair left ventricular filling without association with EF, suggesting a potential mechanism by which COPD may predispose patients to HFpEF.<sup>26</sup> It is also possible that the presence of COPD or emphysema may affect echocardiographic acoustic

windows and therefore make estimation of EF impossible or inaccurate. Finally, as COPD and HF present with similar symptoms, it is possible that patients with COPD may have been misclassified as having ADHF and these patients are therefore more likely to have a preserved EF. The present results confirm that COPD is a common co-morbidity in patients hospitalized with ADHF. Since the two diseases present with relatively similar symptoms, further research is needed to accurately identify and optimally manage these frequently overlapping conditions.

#### Hospital Treatment practices

Given long-standing concerns about the safety of beta-blocker use in patients with obstructive lung disease, it was not surprising that patients with COPD were significantly less likely to have been prescribed beta-blockers at the time of hospital discharge than patients without COPD. Reflecting the results of clinical trials demonstrating benefits on survival through the use of beta-blockers in patients with HF, beta-blocker use increased in both groups over time. However, even during the most recent year under study (2004), almost half of patients with ADHF and COPD were not prescribed a beta-blocker on discharge, as compared with only 25% of patients without COPD. The observed gap in the use of beta-blockers in patients with COPD and ADHF may have diminished in more recent years as evidence demonstrating the safety of cardioselective beta-

blockers in patients with COPD has strengthened<sup>12,13</sup> since 2004, the most recent year under study.

It is possible that the observed differences in beta-blocker use at the time of hospital discharge were related to patients with COPD being less likely to have heart failure with reduced EF (HFrEF) (EF < 40%) and, therefore, not having a definite indication for treatment with beta-blockers. However, the observed differences in beta-blocker use persisted even after restricting our analysis to patients with documented HFrEF, suggesting that even among the subset of patients proven to benefit from beta-blocker treatment, patients with COPD were less likely to have received this evidence based therapy. Because echocardiographic data were only available on a subset of patients, and the use of echocardiography differed according to COPD status, this subgroup analysis should be interpreted with appropriate caution, however. Nonetheless, in light of data demonstrating the safety of cardioselective beta-blockers in patients with COPD,<sup>12,13</sup> sustained educational efforts of health care professionals are needed to ensure that potential gaps in treatment are eliminated.

We also observed a significant difference in hospital prescribing practices in the use of ACE-I/ARB medications between patients with and without COPD. This finding may be accounted for by the increased prevalence of renal disease among patients with COPD, lower presenting blood pressure, or more frequently preserved ejection fraction. Our finding that ACE-I/ARB treatment did not differ between patients with and without COPD when restricted to those with HFrEF

supports the notion that differences in heart failure classification (HFpEF vs. HFrEF), and, therefore, indications for ACE-I/ARB use, account at least in part for the observed differences in use of this class of medications between patients with and without COPD.

Consistent with the findings from several other studies, we found a slightly higher rate of use of diuretics in patients with ADHF and concomitant COPD.<sup>6-8,11,23</sup> This may reflect increased volume overload in these patients related to concomitant steroid use, or the presence of pulmonary hypertension and right heart failure. The present results suggest that the use of several classes of HF specific medications differs between patients with and without COPD. These differences may reflect the complex physiologic interactions between COPD and ADHF,<sup>24</sup> resulting in differing requirements for, and responses to, HF specific medications.

#### In-Hospital and Post Discharge Death Rates

We found that patients with a history of COPD had similar short-term (in-hospital and 30-days post-discharge) mortality as patients without COPD. However, COPD was associated with a substantially worse long-term prognosis. This is in keeping with the results from other observational studies which have found increased long-term death rates in patients hospitalized with HF and concomitant COPD.<sup>7,8,10,21</sup> Because we did not have spirometric data available to confirm the diagnosis of COPD, our findings are subject to potential

misclassification bias; however, this is expected to reduce the magnitude of the association between COPD and the observed increased risk of dying over the long-term period of follow-up. Thus, it is possible that COPD confers an even greater risk of dying following hospitalization for ADHF than we have observed. In addition, measures of the severity of COPD (FEV1 and GOLD stage) have been shown to be independent predictors of mortality and event-free survival, respectively, in patients with COPD and concomitant HF.<sup>9,25</sup> Therefore, the degree of increased mortality associated with COPD in ADHF is dependent on the severity of COPD. Our study is limited in not being able to quantify the severity of COPD; however, the community-based nature of this investigation is expected to have included individuals with varying degrees of COPD severity and, therefore, may provide a more reliable estimate of the short and long-term impact of COPD on prognosis in patients with HF than studies with more highly selected patient populations.

The impact of COPD on mortality in patients with ADHF appears to have been more pronounced over the long term. For example, while there were no differences in short-term death rates during the first 30-days after hospital discharge, there was a 10% increased risk of dying at 1 year, and 40% at 5 years post-discharge, in patients with, as compared to those without, COPD. This finding is consistent with the results from other observational studies. In the OPTIMIZE-HF registry of patients hospitalized with ADHF at over 200 medical centers across the United States between 2003 and 2004, there were no

differences in the risk adjusted all-cause in-hospital or 60-day mortality rates between patients with and without COPD.<sup>6</sup> Similarly, in a community-wide study of patients hospitalized with newly diagnosed HF in the Somme region of France in 2000, there was no significant impact of COPD on short-term survival.

Consistent with our findings, this study demonstrated a significant association between COPD and long-term mortality with an approximately 50% lower 5-year survival rate observed among patients with, as compared to those without, previously diagnosed COPD.<sup>8</sup>

Prior studies have suggested that the severity of ADHF at the time of hospital presentation is strongly associated with early mortality.<sup>16</sup> Thus, one possible explanation for these findings is that short-term mortality is predominantly influenced by ADHF presenting characteristics, whereas co-morbidities such as COPD may be stronger determinants of long-term outcomes. Although our study did not assess the cause of death, this supposition is supported by the findings from other studies in which the excess mortality associated with COPD in patients with ADHF was mainly non-cardiac in etiology.<sup>15</sup> Further studies are needed to determine and address the factors leading to increased long-term mortality in patients with COPD and ADHF.

The present study is unique in examining changing trends in a variety of descriptive patient characteristics, treatment practices, and outcomes over a decade long period (1995-2004). We observed improvements in survival over time in all patients with ADHF, but there was a larger improvement in survival



among patients without, as compared to those with, COPD. Although our study was not designed to explain which factors influenced the observed decreases in mortality, these results suggest that the overall quality of care of patients with ADHF may be either more consistently applied to, or more effective in, patients without COPD. For example, patients with COPD were less likely to have received evidence-based HF medications on discharge. In addition, these patients were more likely to have a preserved ejection fraction, and there have been fewer advances in the treatment of patients with preserved ejection fraction during this time period than for those with reduced ejection fraction findings.<sup>26,27</sup>

#### Study strengths and limitations

The primary strength of this study was the large sample of patients with independently validated hospitalizations for ADHF from the perspective of a large community-based investigation, with collection of detailed clinical characteristics and excellent rates of long-term follow up. Limitations include the lack of spirometric data to confirm the diagnosis of COPD. However, numerous prior studies of COPD and HF have defined COPD in a similar manner.<sup>6-8,11</sup> We did not collect data on the specific causes of mortality and were, therefore, unable to determine if the increased mortality observed in patients with COPD was cardiac or non-cardiac in etiology. We did not include patients who developed HF during hospitalization for another illness and are, therefore, unable to comment on how COPD status might differentially impact patients who develop HF in this context.

Because our most recent hospitalized cohort included patients admitted to all central MA medical centers with ADHF in 2004, our results may not reflect more recent advances in the care of patients with ADHF and/or COPD. It is unknown whether these advances have differentially affected patients based on their COPD status. In addition, we did not collect information on use of COPD medications. Our predominantly white population limits the generalizability of our findings to other racial and ethnic groups. Finally, we did not have information on medication use following hospital discharge; however, prior studies have demonstrated that prescription of cardiac medications at hospital discharge significantly increases the likelihood of long-term use.<sup>28</sup>

## **CHAPTER V**

### **Conclusions**

In summary, COPD is a common co-morbidity in patients hospitalized for ADHF. Patients with COPD are less likely to receive HF-guideline recommended medications at the time of hospital discharge, including beta-blockers and ACE-I/ARBs, than patients without COPD. Use of beta-blockers increased during the period of study in all hospitalized patients, but the gap in the use of beta-blockers between patients with and without COPD persisted during each of the years examined. COPD was associated with significantly increased long-term death rates in patients with ADHF. Long-term survival improved for all patients discharged from central Massachusetts hospitals with ADHF between 1995 and 2004; however, these improvements were greater for patients without COPD than for those with co-existent COPD. Further studies are needed to better understand how to optimize the long-term outpatient treatment for patients with COPD and ADHF and address the causes of increased mortality in these patients.

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