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

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Abstract

Limited data exists about the long-term prognosis of patients with acute decompensated heart failure (ADHF) further stratified according to ejection fraction (EF) findings. 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) (>50%), 37% had reduced EF HF (HF-REF) (≤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. 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.

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Keywords

acute heart failure; long-term prognosis; decade long trends

Introduction

Limited data are available, especially from the more generalizable perspective of a population-based investigation, describing the long-term prognosis of patients with acute heart failure according to their ejection fraction (EF) findings. Furthermore, few studies have used the 2013 American Heart Association recommended EF cutpoints to describe the long-term prognosis of patients with acute decompensated heart failure (ADHF)¹. The primary objective of this prospective 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 investigation²⁻⁶.

Methods

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. These years were selected due to the availability of federal funding support. The present population was restricted to individuals who had undergone a clinically indicated echocardiogram during their index ADHF-related hospitalization (n=3,604). Details of the Worcester Heart Failure Study (WHFS) have been described previously²⁻⁶.

In brief, the patient population included in this investigation was not contacted directly, but instead were identified through a systematic retrospective review of the computerized databases of all participating central Massachusetts hospitals which were searched for patients hospitalized with a possible diagnosis of ADHF. The inpatient 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 retrospectively reviewed by trained nurse and physician reviewers. Patients with a discharge diagnosis of HF (ICD-9 code 428) comprised the primary diagnostic rubric reviewed. 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 criteria⁷. 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 because we were interested in studying de novo cases of ADHF. Residents of the Worcester metropolitan area with a first hospitalization for ADHF (incident cases) as well as those in whom ADHF had been previously diagnosed were included in this study population.

Information was collected about patient's demographic characteristics, medical history, clinical characteristics, and laboratory test results through the review of information contained in the medical record. Each of the cardiovascular and non-cardiovascular comorbidities examined were identified through the review of medical history data provided

in hospital charts during the patient's index hospitalization for ADHF. Data on EF measurements 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 $\geq 40\%$, 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%⁷⁻¹¹. Ejection fraction measurements were not validated with other cardiac imaging techniques. In those cases in which a range for EF findings was reported, the average of the two values was recorded.

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 physician prescribing patterns 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 at hospital discharge. In addition, we examined medications shown to be effective in improving patient's symptomatic status (digoxin, diuretics) and selected cardiac medications (lipid-lowering agents, nitrates)³. 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 files and statewide death certificates.

We examined differences in the characteristics of patients with EF values ≥ 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 longterm mortality following discharge from all central Massachusetts hospitals. Postdischarge 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 hospital EF findings and 1 and 2-year postdischarge 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. 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 difficulty in the interpretation of resultant findings due to the nonrandomized nature of this descriptive observational investigation. The Committee for the Protection of Human Subjects in Research at the University of Massachusetts Medical School approved this study.

Results

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 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 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 1).

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 1A-C). Diuretics were more frequently prescribed to patients with HF-REF and to a similar extent in the other two categories in 2004 (Figure 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 1A and 1D).

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 2 and Figure 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 2).

At 1, 2, and 5 years after hospital discharge, patients with HF-BREF had the highest crude RR for 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).

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 4). However, lesser degrees of improvement in survival were

observed at 2 years after hospital discharge for patients discharged in 2004 compared with 1995.

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.

The baseline characteristics of our 3 ADHF groups were consistent with the results of a limited number of previous observational studies and clinical trials¹²⁻¹⁴. 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. 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.

To date, no studies of patients with ADHF have examined trends in longterm prognosis using current ACC/AHA cut points for EF values¹. 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.

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^{14,16}. The DIG¹⁷ and CHARM^{18,19} 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%¹⁷ to define patients with HF-PEF whereas the CHARM-Preserved trial used an EF cutpoint >40%¹⁸ 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 trials²⁰. 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 years¹¹. 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-PEF²¹. 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 registry²².

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 2009²³. 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.

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-REF⁸ 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. Further studies remain needed to better understand patient and provider level barriers to different treatment practices 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 status⁸. In addition, data from randomized clinical trials have demonstrated a lack of efficacy for the use of ARBs in HF patients with preserved EF^{18,24} and the results from a single randomized trial failed to show any efficacy for ACE-inhibitors²⁵. 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 verapamil²⁶. However, no data currently exists that suggest that calcium channel blockers improve mortality in patients with HF-PEF^{27,28}.

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.

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, only 2 out of every 5 patients had their EF assessed acutely, and we could not account for the impact of potentially changing EF values on observed long-term mortality patterns.

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Figure 1. Trends in treatment practices according to ejection fraction findings

Figure 2. Trends in post-discharge survival rates according to ejection fraction findings

Table 1
Demographic and clinical characteristics of patients with acute decompensated heart failure according to ejection fraction findings

Variable	Ejection Fraction (%)			p-value
	40 (n=1,479)	41-49 (n=346)	50 (n=1,779)	
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	1,373 (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 (mean ± SD; kg/m ²)	27.5 ± 6.9	27.9 ± 6.8	28.7 ± 7.9	<0.01
Glomerular filtration rate (mean ± SD; mL/min/1.73 m ²)	51.1 ± 23.2	50.8 ± 23.2	53.7 ± 24.0	<0.01
Systolic BP (mean ± SD; mm Hg)	139.8 ± 30.9	150.6 ± 33.0	148.1 ± 32.5	<0.01
Diastolic BP (mean ± SD; mm Hg)	77.6 ± 19.5	78.0 ± 18.6	74.3 ± 19.7	<0.01
Glucose (mean ± SD; mg/dL)	160.0 ± 70.8	162.4 ± 76.7	155.0 ± 66.3	0.06
Total cholesterol (mean ± SD; mg/dL)	155.4 ± 42.6	154.9 ± 38.8	162.1 ± 44.2	0.11
Blood urea nitrogen (mean ± SD; mg/dL)	33.8 ± 22.6	31.1 ± 20.5	30.0 ± 19.7	<0.01
Serum sodium (mean ± SD; mEq/L)	137.2 ± 5.4	138.0 ± 4.3	137.5 ± 6.2	0.48
Hematocrit (mean ± SD; %)	37.2 ± 6.5	36.1 ± 6.6	35.9 ± 12.2	<0.01

Table 2
Changes over time in post-discharge case-fatality rates according to ejection fraction findings

Period	Ejection Fraction								
	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
Relative risk (RRs) for dying after hospital discharge according to ejection fraction findings

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

* Controlling for age, sex, history of atrial fibrillation, diabetes, coronary 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 4
Changes overtime in crude and multivariable adjusted relative risk (RRs) for dying at 1 and 2 years after hospital discharge according to ejection fraction findings

	EF 40%		EF=41-49%		EF 50%	
	Crude RR	Adjusted RR*	Crude RR	Adjusted RR	Crude RR	Adjusted RR
1-Year						
2000	0.74 (0.51-1.07) ⁰	0.69 (0.50-0.97)	1.30 (0.51-3.30)	0.91 (0.37-2.28)	0.73 (0.47-1.14)	0.69 (0.45-1.07)
2002	0.63 (0.36-1.10)	0.58 (0.35-0.96)	1.48 (0.37-5.99)	0.87 (0.22-3.46)	0.62 (0.32-1.22)	0.58 (0.30-1.11)
2004	0.55 (0.26-1.14)	0.48 (0.25-0.94)	1.69 (0.26-10.87)	0.84 (0.13-5.23)	0.53 (0.22-1.31)	0.48 (0.20-1.15)
2-Years						
2000	0.85 (0.64-1.11)	0.92 (0.77-1.09)	1.53 (0.78-3.02)	1.24 (0.67-2.32)	0.95 (0.67-1.35)	0.89 (0.64-1.24)
2002	0.78 (0.52-1.17)	0.88 (0.68-1.14)	1.90 (0.69-5.24)	1.38 (0.54-3.52)	0.93 (0.55-1.57)	0.84 (0.51-1.38)
2004	0.72 (0.42-1.24)	0.84 (0.60-1.19)	2.35 (0.61-9.11)	1.54 (0.44-5.36)	0.90 (0.45-1.83)	0.79 (0.40-1.54)

* Controlling for age, sex, history of atrial fibrillation, diabetes, coronary 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