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EDITORIAL COMMENT

Long-Term Outcomes of Acute Heart Failure

Where Are We Now?*

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The treatment of chronic heart failure (HF) has yielded significant improvements in outcomes for many patients over the last 30 years, although the majority of these advances have been in the therapy for heart failure with reduced ejection (HFrEF) (1,2). This momentum continues; the novel agent sacubitril/valsartan reduced cardiovascular mortality another 16% when compared with traditional optimal medical therapy for HFrEF in the landmark PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (3). However, HF is ultimately fatal; even in that contemporary clinical trial of optimally-managed *out*patients, 2-year mortality was 20% (2). The inpatient HF story is worse: in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial of tolvaptan for acute decompensated HF (ADHF), all-cause mortality was just over 25% at a median follow-up of 10 months (4). However, as remarkable as these data are, where do we stand in the world of routine practice across the spectrum of HF?

In this issue of the *Journal*, Shah et al. (5) explore longer-term outcomes among older patients hospitalized with HF in the GWTG-HF (Get With The Guidelines-Heart Failure) cohort who were linked to Medicare; these patients were stratified by ejection fraction (EF) into HFrEF, heart failure with borderline ejection fraction (HFbEF), or heart failure with preserved ejection fraction (HFpEF). There are 3 important messages in this study of a large, well-characterized HF registry: 1) regardless of EF, there is an alarming 75% mortality at 5 years (with the vast majority of events occurring in the first 2 years after index admission); 2) patients with *acute* heart failure that results in hospital admission are at particular high risk (in contrast to the "stable" outpatients who are generally the candidates enrolled in a clinical trial); and 3) despite longstanding, robust evidence for many medications in HFrEF to reduce mortality and HF hospitalizations, most rates of guideline-directed medical therapy *at discharge* were disappointing in this quality-improvement population.

There is surprisingly limited clinical trial data exploring long-term outcomes following acute HF hospitalization—most randomized trials examine 30-, 60-, or 90-day outcomes, in part due to the high early event rates and increased costs associated with longer trial follow-up. These new data are highly relevant, and it is enlightening to compare the outcomes of such trials to the current dataset (**Figure 1**).

One of the most striking findings is not only the relative risk of HFpEF mortality to HFrEF, but also the sobering 5-year survival among patients with HFpEF: 75% 5-year mortality, and an even higher readmission rate than those with HFrEF. Prior data from GWTG-HF demonstrated the rise in proportion of patients hospitalized with HFpEF relative to HFrEF, but noted that in-hospital mortality had improved over time for

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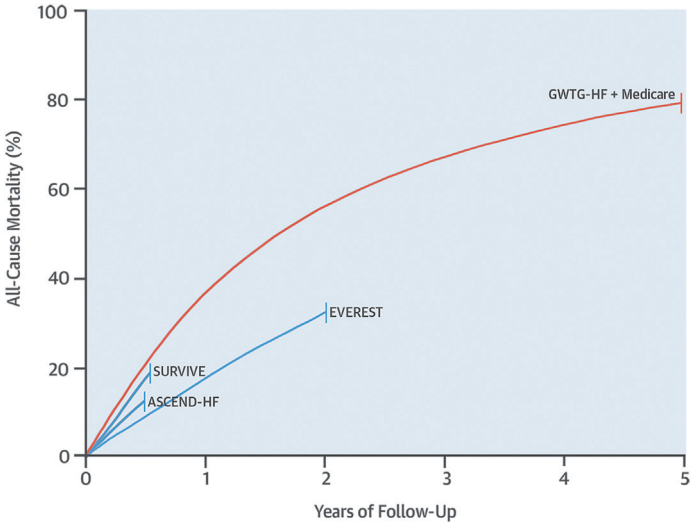
FIGURE 1 All-Cause Mortality in Acute Heart Failure



Rates of all-cause mortality among acute heart failure trials, compared with the present GWTG-HF (Get With The Guidelines-Heart Failure) linked with Medicare analysis (4,5,12,13). ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; EVEREST = Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan; SURVIVE = Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support.

patients with HFpEF (6). And, prior data from the CHARM (Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity) trial showed that the presence of HFrEF portended a worse prognosis compared with HFpEF (7). Yet, all historical data have not been consistent on this point, and the present analysis lays bare the significant long-term risk among patients hospitalized with HFpEF. There are likely a few reasons for this. First, despite significant advances in our understanding of the clinical entity of HFpEF, including unique clinical phenotypes and the role of the kidney in HFpEF pathophysiology (8,9), the pace of therapeutic development to effectively reduce morbidity and/or mortality in patients with HFpEF remains disappointing.

Second, we may be seeing the limitations inherent in classification of HF by EF, which is notoriously dynamic: almost one-half of patients with HFpEF will drop their EF <50% over 5 years, and conversely, close to one-half of patients with HFrEF will increase their EF to ≥50% over a similar period (10). Moreover, EF has long been recognized to be only a marginal predictor of sudden cardiac death and may be at best a modest biomarker (11). As we learn more about the neurohormonal and inflammatory mechanisms of HFrEF and the renocardiac interactions in HFpEF, new paradigms may emerge to classify HF patients using novel biomarkers that improve risk stratification, allow for more personalized treatments, and render EF a relic.

Alternatively, some might interpret this data as showing that outcomes of patients with HF and systolic dysfunction have "caught up" to those with preserved EF, potentially attributable to either the continued development of effective management strategies for HFrEF or at least their wider adoption in clinical practice. Perhaps a more conservative interpretation is that an HF hospitalization is a great "equalizer," and marks the transition point in the HF syndrome to an inexorable progression of the disease, regardless of EF. Moreover, debate continues on whether HF hospitalizations represent disease markers or disease factors. In light of the high mortality and high readmission rates, independent of EF, a case can be made that HF hospitalization is a sentinel event and represents disease progression of HF and/or the natural history of a compendium of comorbidities. It would appear that the presence of the decompensated HF *syndrome* conveys significant subsequent mortality risk, not the echocardiogram.

Equally disappointing is the suboptimal use of guideline-directed medical therapy at discharge for patients with HFrEF. Despite numerous guideline statements, educational efforts, and practice metrics, it is hard to understand why only 83% of patients with HFrEF were discharged on beta-blockers, 16%/56% on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 21% on aldosterone antagonists. As these therapies are well-known to reduce morbidity and mortality in HFrEF over the intermediate-term, this represents 1 opportunity to improve the sobering outcomes presented here.

It is important, however, to consider some limitations when interpreting these data. First, although the cohort is large, there are some selection biases, including: selection of hospitals participating in GWTG-HF, a voluntary quality-improvement program; and exclusion of both non-Medicare patients and Medicare patients who could not be could be linked to GWTG-HF. Notably, the 27% of patients who could not be linked were younger and were more likely to have risk factors for ischemic heart failure (diabetes, hypertension, and prior myocardial infarction). Furthermore, these data are primarily applicable to patients ≥65 years of age. Last, although detailed data are available from GWTG-HF at the time of index hospitalization, the use of Medicare for longer-term data limits those elements available over the 5-year follow-up—for example, longitudinal changes in EF are not typically available.

Nevertheless, the analysis by Shah et al. (5) serves as a dramatic reminder that when it comes to the syndrome of acute HF, with *or without* systolic dysfunction, there remains significant room for improvement in long-term outcomes as the absolute risk is large. The median survival of 2 years following HF hospitalization should be a particularly profound statistic to all who care for these patients. Moreover, EF does not appear to be an accurate biomarker for risk stratification after a patient has crossed the threshold to an HF admission. These data should serve as another wake-up call to all providers to recognize the risk associated with HF, and another call to arms for HF researchers to urgently find new targets and strategies to manage HF. For the time being, we are certainly not there yet, and we have a long way to go.

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Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction

5-Year Outcomes

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ABSTRACT

BACKGROUND Patients with heart failure (HF) have a poor prognosis and are categorized by ejection fraction (EF).

OBJECTIVES This study sought to characterize differences in outcomes in patients hospitalized with heart failure with preserved ejection fraction (HFpEF) (EF ≥50%), heart failure with borderline ejection fraction (HFbEF) (EF 41% to 49%), and heart failure with reduced ejection fraction (HFrEF) (EF ≤40%).

METHODS Data from GWTG-HF (Get With The Guidelines-Heart Failure) were linked to Medicare data for longitudinal follow-up. Multivariable models were constructed to examine 5-year outcomes and to compare survival to median survival of the U.S. population.

RESULTS A total of 39,982 patients from 254 hospitals who were admitted for HF between 2005 and 2009 were included: 18,299 (46%) had HFpEF, 3,285 (8.2%) had HFbEF, and 18,398 (46%) had HFrEF. Overall, median survival was 2.1 years. In risk-adjusted survival analysis, all 3 groups had similar 5-year mortality (HFrEF 75.3% vs. HFpEF 75.7%; hazard ratio: 0.99 [95% confidence interval: 0.958 to 1.022]; HFbEF 75.7% vs. HFpEF 75.7%; hazard ratio: 0.99 [95% confidence interval: 0.947 to 1.046]). In risk-adjusted analyses, the composite of mortality and rehospitalization was similar for all subgroups. Cardiovascular and HF readmission rates were higher in those with HFrEF and HFbEF compared with those with HFpEF. When compared with the U.S. population, HF patients across all age and EF groups had markedly lower median survival.

CONCLUSIONS Among patients hospitalized with HF, patients across the EF spectrum have a similarly poor 5-year survival with an elevated risk for cardiovascular and HF admission. These findings underscore the need to improve treatment of patients with HF. (J Am Coll Cardiol 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMS = Center for Medicaid and Medicare Services

CV = cardiovascular

EF = ejection fraction

HF = heart failure

HFbEF = heart failure with borderline ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

Heart failure (HF) is a global epidemic with >37.7 million individuals affected worldwide (1,2). This chronic, progressive condition is a frequent cause of hospitalization, especially in older adults (3). HF is categorized by left ventricular ejection fraction (EF), with the efficacy of evidence-based therapies varying by EF grouping. Heart failure with preserved ejection fraction (HFpEF) has been defined as having signs and symptoms of HF with preserved EF and diastolic abnormalities on echocardiography (4). Patients with HFpEF account for approximately 50% of all hospital admissions for HF. Although some studies have suggested that HFpEF patients have a substantially better prognosis compared with patients with heart failure with reduced ejection fraction (HFrEF), other studies have suggested that they have similar mortality and hospitalization rates (4–9). As the U.S. population continues to age, a thorough understanding of the characteristics and long-term outcomes of patients with HFpEF will be a crucial step in the investigation and development of strategies to reduce the burden of morbidity and mortality.

The European Society of Cardiology guidelines separate patients with HF to either reduced EF (<40%), mid-range EF (40% to 49%), and preserved EF (≥50%) (10). The American College of Cardiology and American Heart Association guidelines recommend subcategorizing HF into 1 of 3 categories: HFrEF (≤40%), HFpEF (≥50%), and heart failure with borderline ejection fraction (HFbEF) (41% to 49%) (6). Recently, in data from the GWTG-HF (Get With The Guidelines-HF) registry, patients hospitalized for HFpEF and HFbEF were shown to have a similar poor survival at 30 days and 1 year from admission compared with patients with HFrEF (11). In this study, we sought to analyze 5-year outcomes in patients with HF by EF group from the GWTG-HF registry. In addition, we sought to determine temporal trends in outcomes by EF group. Finally, we sought to compare median survival in patients with HF across EF groups by age group compared with the overall U.S. population in those same age groups.

METHODS

Data were obtained from the GWTG-HF registry, which has previously been described (12). The GWTG-HF program was launched by the American Heart Association for performance improvement; this national registry enrolls patients if they are admitted with worsening HF or develop HF symptoms during a hospitalization for which HF is the primary discharge diagnosis. Consecutive patients at each participating site are enrolled as previously described (12). All data are collected on a point-of-service web-based registry (Quintiles, Cambridge, Massachusetts).

The GWTG-HF registry was merged with claims from the U.S. Centers for Medicare and Medicaid Services (CMS) from January 1, 2005, through December 30, 2009, with 5 years of follow-up through the end of December 2014. Medicare files include all fee-for-service Medicare beneficiaries age ≥65 years hospitalized with a diagnosis of HF (International Classification of Disease-9th Revision-Clinical Modification [ICD-9-CM] 428.x, 402.x1, 404.x1, and 404.x3). Patients were merged with Medicare Part A inpatient claims by admission and discharge dates, hospital, date of birth, and sex using methods previously described (13). For patients with multiple hospitalizations in the registry, we selected the first hospitalization as the index hospitalization. We restricted the dataset to patients who did not leave against medical advice, were not transferred to another short-term hospital or to hospice, and had recorded EF information.

The patient population was stratified by EF into 1 of 3 groups: reduced EF (≤40%), borderline EF (41% to 49%), and preserved EF (≥50%). In the small proportion of patients (8.1%) where EF was qualified but not quantified, patients with normal or mildly

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impaired systolic function were classified as HFpEF and those with moderate or severe reduced systolic function were classified as HFrEF. Demographics, including prevalence of medication use at admission, were included regardless of contraindication or intolerance. Discharge medication use excluded patients who died or had specific contraindications. The outcomes of interest were mortality, all-cause readmission, cardiovascular (CV) readmission, HF readmission, and a composite of mortality/readmission. We determined all-cause mortality based on death dates in the Medicare denominator files, and we determined readmission based on Medicare inpatient claims, primary diagnosis diagnostic-related group codes, and ICD-9-CM codes.

Readmission was defined as any new nonelective inpatient claim, excluding the index hospitalization claim and transfers to or from another hospital and admissions for rehabilitation. CV readmission was defined as any new nonelective inpatient claim for CV reasons (including heart failure), excluding the index hospitalization claim and transfers to or from another hospital and admissions for rehabilitation. HF readmission was defined as any new nonelective inpatient claim for HF, excluding the index hospitalization claim and transfers to or from another hospital and admissions for rehabilitation. All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval.

Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Quintiles served as the registry coordinating center. The Duke Clinical Research Institute served as the data analysis center, and institutional review board approval was granted to analyze aggregate deidentified data for research purposes.

STATISTICAL ANALYSIS. Patient demographic characteristics, medical history, admission data, and hospital characteristics were described for all HF patients by EF groups. Proportions and median interquartile ranges were reported for categorical and continuous variables, respectively. The Pearson's chi-square test was used to compare binary or nominal categorical variables, and the Kruskal-Wallis tests were used to compare continuous variables or ordinal categorical variables. Percent standardized differences (standardized differences × 100) are also provided.

Cumulative incidences at 5 years are described for all follow-up outcomes in HF patients by EF groups. The log-rank test was used to assess difference in mortality; Gray's tests were used to assess differences in readmission outcomes. Unadjusted and adjusted associations between follow-up outcomes and EF groups were examined using Fine and Gray's models, which account for the competing risks of deaths. Robust sandwich variance estimators were used to account for patients clustered within the same hospital. Covariates used for adjustment in this analysis were: demographics (age, sex, and race/ethnicity), medical history (anemia, ischemic etiology, cerebrovascular accident/transient ischemic attack, diabetes [insulin and noninsulin treated], hyperlipidemia, hypertension, chronic obstructive pulmonary disease [COPD] or asthma, peripheral vascular disease, renal insufficiency, smoking), examination/laboratory results (heart rate, systolic blood pressure, body mass index, creatinine, sodium, blood urea nitrogen, and hemoglobin at admission), year and quarter of index admission, and hospital characteristics (geographic region, teaching status of hospital, number of beds, and rural location). In addition, we examined the risks of readmission or mortality outcomes in noncensored, event-free patients at 6 months and 1 year post-admission. Fine and Gray's models were used to follow-up patients from the landmark time of 6 months or 1 to 5 years post-admission.

Study dataset was linked to National Death Index (NDI) data based on encrypted patient identifiers to analyze causes of deaths. Causes of death were identified based on ICD-10 codes in NDI data. The risks of CV and HF mortalities at 1 year post-index admission were assessed using Fine and Gray's model. Mortalities due to other causes were treated as competing risks.

Variables with missing data were not imputed for univariate tables. Model covariates with <25% missing were imputed before entering into models, using multiple imputation methods with 25 datasets. Medical history missing was imputed to "No." All statistical analyses were performed at the Duke Clinical Research Institute using SAS software (version 9.4, SAS, Cary, North Carolina).

RESULTS

STUDY COHORT. The starting population included 115,220 HF hospitalizations from 276 hospitals in the GWTG-HF registry between January 1, 2005, and December 30, 2009. After excluding patients who were age <65 years at hospitalization (n = 33,378), were not linked to CMS inpatient claims (n = 22,297), had nonindex hospitalizations (n = 13,748), were not eligible for fee for service at discharge (n = 1,862), left

TABLE 1 Baseline Patient and Hospital Characteristics in HF Patients by EF Groups

	Overall (N = 39,982)	EF Groups			p Value	% Std. Diff.	
		HFrEF (EF ≤40%) (n = 18,398)	HFbEF (EF 41%-49%) (n = 3,285)	HFpEF (EF ≥50%) (n = 18,299)		HFrEF vs. HFpEF	HFbEF vs. HFpEF
Demographics							
Age, yrs	80 (74-86)	79 (73-85)	81 (74-86)	82 (75-87)	<0.0001	27.4	10.5
Female	54.02	40.99	51.51	67.58	<0.0001	55.4	33.2
Race/ethnicity					<0.0001		
White	80.94	79.58	81.71	82.17		5.9	0.9
Black	10.57	11.73	9.24	9.63		6.8	1.3
Hispanic (any race)	4.42	4.82	4.37	4.02		3.9	1.8
Asian	1.14	0.95	1.29	1.30		3.2	0.0
Other	2.94	2.92	3.39	2.88		0.3	2.9
LVEF source					<0.0001		
Quantitative LVEF	91.86	95.86	100	86.37		33.8	56.2
Qualitative LVEF	8.14	4.14	0	13.63		33.8	56.2
EF, quantitative, %	44 (30-56)	28 (20-35)	45 (45-45)	60 (55-65)	<0.0001	>99	>99
Medical history							
Atrial flutter/fibrillation	36.78	34.52	37.43	38.92	<0.0001	9.1	3.1
COPD or asthma	27.61	25.91	26.87	29.44	<0.0001	7.9	5.7
Diabetes	38.82	38.31	41.57	38.83	0.0029	1.1	5.6
Hyperlipidemia	42.05	43.52	44.02	40.23	<0.0001	6.7	7.7
Hypertension	73.98	69.86	75.29	77.88	<0.0001	18.3	6.1
Peripheral vascular disease	13.28	13.89	15.32	12.30	<0.0001	4.7	8.8
CAD	50.59	56.84	55.10	43.52	<0.0001	26.9	23.3
Prior MI	16.77	22.29	17.51	11.11	<0.0001	30.3	18.4
CVA/TIA	15.65	14.91	15.98	16.33	0.0013	3.9	1.0
Implantable cardioverter-defibrillator only	7.72	14.71	3.91	1.41	<0.0001	50.4	15.6
Heart failure	47.84	50.77	46.82	45.10	<0.0001	11.4	3.5
Anemia	17.55	14.73	19.40	20.03	<0.0001	14.0	1.6
Pacemaker	12.74	15.76	12.19	9.82	<0.0001	17.8	7.6
Dialysis, chronic	2.83	2.52	2.90	3.12	0.0035	3.6	1.3
Chronic renal insufficiency (SCr >2.0)	18.51	19.37	18.81	17.58	0.0001	4.6	3.2
Depression	9.34	7.78	9.59	10.87	<0.0001	10.6	4.2
Valvular heart disease	11.05	9.53	11.22	12.54	<0.0001	9.6	4.1
CRT-P (pacing only)	0.33	0.37	0.29	0.30	0.5460	1.1	0.1
CRT-D (with implantable cardioverter-defibrillator)	0.79	1.48	0.52	0.15	<0.0001	14.9	6.5
Ischemic etiology: medical history of CAD, MI, prior PCI, prior CABG, or prior PCI/CABG	57.78	65.94	62.70	48.72	<0.0001	35.4	28.4
Medical history panel missing	7.41	7.70	6.64	7.26	0.0581	1.7	2.4
Smoking	9.10	10.94	8.04	7.44	<0.0001	12.1	2.2

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against medical advice (n = 846), and were missing EF data (n = 3,107), 39,982 patients remained in our cohort (Online Figure 1). Online Tables 1 and 2 provide characteristics of patients with missing EF and without CMS-linked claims, respectively.

BASELINE CHARACTERISTICS. Of the 39,982 patients, 18,398 (46.0%) had HFrEF, 3,285 (8.2%) had HFbEF, and 18,299 (45.8%) had HFpEF (**Table 1**). Missing rates of key variables are shown in Online Table 3. Patients with HFpEF were older and more likely to be female than those with HFrEF. Furthermore, patients with HFpEF were more likely to have comorbidities including atrial fibrillation/flutter, COPD or asthma, anemia, hypertension, depression, and valvular heart disease. Conversely, patients with HFrEF more often had a history of dyslipidemia, peripheral vascular disease, coronary artery disease, prior myocardial infarction, and smoking. Patients with HFbEF had characteristics more similar to those of HFpEF than HFrEF.

When compared with HFrEF, patients with HFpEF had higher systolic blood pressure, lower heart rate, higher body mass index, and higher admission weight. On laboratory findings, patients with HFpEF had higher cholesterol, lower hemoglobin, lower

TABLE 1 Continued

	Overall (N = 39,982)	EF Groups			p Value	% Std. Diff.	
		HFrEF (EF ≤40%) (n = 18,398)	HFbEF (EF 41%-49%) (n = 3,285)	HFpEF (EF ≥50%) (n = 18,299)		HFrEF vs. HFpEF	HFbEF vs. HFpEF
Vitals on admission							
Heart rate, beats/min	80 (69-95)	82 (70-97)	80 (70-96)	79 (68-92)	<0.0001	16.2	11.7
SBP, mm Hg	138 (120-158)	132 (115-151)	141 (123-161)	143 (124-164)	<0.0001	38.6	7.5
DBP, mm Hg	73 (63-84)	73 (63-85)	74 (63-87)	72 (62-84)	<0.0001	7.6	12.9
BMI, kg/m^2	26.43 (22.71-31.28)	25.64 (22.24-29.76)	26.82 (23.03-31.83)	27.34 (23.24-32.79)	<0.0001	28.9	9.1
Admission weight, kg	76 (63.49-90.70)	75.28 (63.95-88.89)	77 (64.00-92.52)	76 (63-92)	<0.0001	7.8	3.9
Discharge weight, kg	74 (61.22-88.44)	73.02 (61.68-86.17)	74.83 (62.00-90.25)	74 (61.00-90.25)	<0.0001	10.6	0.8
Change in weight, kg	−1.9 (−4.54 to 0.00)	−1.89 (−4.54 to 0.00)	−2 (−4.54 to 0.00)	−1.81 (−4.42 to 0.00)	0.1298	1.2	2.8
Lipids							
Total cholesterol, mg/dl	137 (113-166)	135 (110-164)	139 (116-167)	139 (115-168)	<0.0001	9.6	0.5
HDL, mg/dl	39 (31-49)	38 (30-48)	39 (31-49)	40 (32-50)	<0.0001	16.0	6.9
LDL, mg/dl	77 (59-100)	77 (59-101)	78 (60-102)	77 (59-99)	0.2947	0.4	5.7
Triglycerides, mg/dl	87 (65-121)	84 (64-115)	89 (65-130)	90 (66-126)	<0.0001	10.3	0.8
Laboratory measures							
Serum sodium, mEq/l	138 (135-141)	138 (135-141)	138 (136-141)	138 (135-141)	0.6710	1.5	0.8
Hemoglobin, g/dl	11.9 (10.5-13.3)	12.2 (10.9-13.5)	11.8 (10.5-13.2)	11.6 (10.3-12.9)	<0.0001	5.3	2.4
Albumin, g/dl	3.4 (3.0-3.7)	3.4 (3.1-3.7)	3.4 (3.0-3.7)	3.3 (3.0-3.7)	<0.0001	7.9	5.3
BNP, pg/ml	777 (388-1,541)	1,125.5 (568-2,093)	765 (404-1,392)	563 (301-1,058)	<0.0001	48.7	19.2
NBNP, pg/ml	5,956 (2,513-13,348)	8,845 (3,802-18,428)	5,054.8 (2,637-10,825)	4,104 (1,910-8,717)	<0.0001	47.1	9.6
Serum creatinine, mg/dl	1.3 (1.0-1.8)	1.4 (1.1-1.9)	1.3 (1.0-1.8)	1.3 (1.0-1.7)	<0.0001	0.3	0.3
BUN, mg/dl	26 (18-38)	26 (19-39)	26 (18-37)	25 (18-37)	<0.0001	10.0	2.9
Troponin, ng/dl	0.05 (0.03-0.11)	0.07 (0.04-0.14)	0.06 (0.03-0.11)	0.05 (0.03-0.10)	<0.0001	9.4	7.5
Potassium, mEq/l	4.2 (3.8-4.6)	4.2 (3.9-4.6)	4.2 (3.8-4.6)	4.2 (3.8-4.6)	0.0365	2.1	0.3
HbA1C, %	6.8 (6.0-7.6)	6.8 (6.0-7.7)	6.75 (6.0-7.6)	6.7 (6.0-7.6)	0.0197	12.6	3.9
Blood glucose, mg/dl	109 (93-136)	108 (93-135)	109 (94-142)	109 (92-137)	0.5658	1.8	3.3
ECG QRS duration, ms	108 (90-142)	126 (100-156)	108 (90-140)	96 (84-122)	<0.0001	72.5	35.8
Year of index admission					<0.0001		
2009	25.09	24.07	25.08	26.12		4.7	2.4
2008	20.92	20.89	21.22	20.90		0.0	0.8
2007	20.14	19.89	19.30	20.54		1.6	3.1
2006	20.86	21.31	21.00	20.38		2.3	1.5
2005	12.98	13.83	13.39	12.06		5.3	4.0

Values are median (interquartile range) or %. Standardized differences (Std. Diff.) of 10% or higher indicate relevant differences.

BMI = body mass index; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; CVA = cerebrovascular accident; DBP = diastolic blood pressure; ECG = electrocardiogram; EF = ejection fraction; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HF = heart failure; HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NBNP = N-terminal pro B-type natriuretic peptide; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; SCr = serum creatinine; TIA = transient ischemic attack.

B-type natriuretic peptide, and lower creatinine. Patients with HFpEF (compared with HFrEF) were less likely to have the following home medications: angiotensin-converting enzyme inhibitor, beta-blocker, aldosterone antagonist, antiarrhythmic, aspirin, digoxin, nitrate, diuretic agent, or statin therapy (Table 2). Conversely, patients with HFpEF were more likely to have an angiotensin receptor blocker listed as a home medication.

DISCHARGE CHARACTERISTICS. At the time of discharge (Table 2), patients across all EF had similar changes in weight. Patients with HFrEF were more often prescribed an angiotensin-converting enzyme inhibitor, beta-blocker, aldosterone antagonist, anticoagulant agent, lipid-lowering therapy, and hydralazine/nitrate. GWTG-HF Quality Measures are presented in Online Table 4. Patients with HFpEF were less likely to receive anticoagulation for atrial fibrillation/flutter and less often received discharge instructions. More often, these patients received inpatient prophylaxis for deep vein thrombosis and vaccination for influenza and pneumococcus. Patients with HFrEF more often received a referral to an HF disease management program upon discharge.

MORTALITY AND READMISSION. The 5-year mortality rate for the entire cohort was 75.4% (Table 3). Mortality was similar across EF groups. Patients with

TABLE 2 Admission and Discharge Medications in HF Patients by EF Groups

		EF Groups				% Std. Diff.	
	Overall (n = 39,982)	HFrEF (EF ≤40%) (n = 18,398)	HFbEF (EF 41%-49%) (n = 3,285)	HFpEF (EF ≥50%) (n = 18,299)	p Value	HFrEF vs. HFpEF	HFbEF vs. HFpEF
Admission medications							
ACE inhibitor	35.87	40.42	33.19	31.85	<0.0001	17.9	2.9
Aldosterone antagonist	7.45	10.11	6.53	4.98	<0.0001	19.5	6.6
Angiotensin receptor blocker	15.88	14.55	16.90	17.01	<0.0001	6.7	0.3
Antiarrhythmic agent	8.29	9.91	7.87	6.77	<0.0001	11.4	4.2
Aspirin	44.51	48.05	45.43	40.83	<0.0001	14.6	9.3
Beta-blocker	37.00	37.95	36.54	36.15	0.0039	3.7	0.8
Digoxin	17.30	21.28	14.78	13.82	<0.0001	19.7	2.7
Nitrate	17.44	19.08	18.94	15.53	<0.0001	9.4	9.0
Anticoagulation therapy	26.32	26.73	26.53	25.87	0.2193	2.0	1.5
Diuretic agent	63.06	64.62	60.04	62.06	<0.0001	5.3	4.2
Hydralazine	4.99	4.88	4.97	5.10	0.6786	1.0	0.6
Statin	42.20	44.98	43.32	39.25	<0.0001	11.6	8.3
Discharge medications							
ACE inhibitor	48.09	56.12	46.71	40.37	<0.0001	31.9	12.8
ARB	17.49	16.41	18.00	18.47	<0.0001	5.4	1.2
Anticoagulation therapy	30.92	31.52	31.92	30.16	0.0288	2.9	3.8
Beta-blocker	77.05	83.89	78.50	70.02	<0.0001	33.4	19.5
Aldosterone antagonist	14.41	20.69	11.88	8.61	<0.0001	34.7	10.8
Diabetic treatment	47.20	47.12	48.54	47.06	0.7753	0.1	3.0
Lipid-lowering medications	52.89	56.66	55.41	48.73	<0.0001	15.9	13.4
Hydralazine nitrate	14.80	15.66	15.80	13.77	<0.0001	5.3	5.7
Diuretic agent	47.17	47.79	46.50	46.67	0.0805	2.2	0.3

Values are %. Medication treatment rates, irrespective of eligibility, contraindications, or intolerance.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; other abbreviations as in Table 1.

HFrEF had a similar 5-year mortality as patients with HFpEF (75.3% vs. 75.7%, respectively; hazard ratio [HR]: 1.011 [95% confidence interval (CI): 0.975 to 1.049]; p = 0.55). After adjusting for patient demographics, medical history, and examination and laboratory findings, the difference remained nonsignificant (adjusted HR: 0.989 [95% CI: 0.958 to 1.022]; p = 0.51). Kaplan-Meier analysis by EF group for mortality is shown in the **Central Illustration**. For the total cohort, readmission rate by 5 years was 80.4%. Patients with HFbEF had a slightly higher readmission rate than those with HFpEF (85.7% vs. 84.0%; adjusted hazard ratio [aHR]: 1.045 [95% CI: 1.005 to 1.087]; p = 0.029). Patients with HFrEF had a slightly lower readmission rate than those with HFpEF (82.2% vs. 84.0%; aHR: 0.971 [95% CI: 0.945 to 0.997]; p = 0.031) (**Figure 1A**). Patients with HFrEF and HFbEF had higher HF readmission rates than patients with HFpEF (48.5% vs. 40.5%, respectively; aHR: 1.335 [95% CI: 1.288 to 1.383]; p < 0.0001; 45.2% vs. 40.5%, respectively; aHR: 1.162 [95% CI: 1.098 to 1.229]; p < 0.0001) (**Figure 1C**). There were no significant differences across EF groups for the composite endpoint of mortality and readmission at 5 years (**Figure 1D**), and there were similar findings with imputed compared with nonimputed data and adjusting for medications (Online Tables 5 and 6, respectively). Similarly, mortality, all-cause readmission, and the composite endpoint of mortality and readmission were not found to be different across EF groups in noncensored, event-free patients who survived the first 6 months or 1 year post-admission (Online Table 7).

MEDIAN SURVIVAL COMPARED WITH THE GENERAL POPULATION. We examined the median survival (14) for the population of patients hospitalized with HF by age and EF group as shown in **Figure 2**. The median survival for patients with HF (age 80.0 years) was similar by EF group, but declined with advancing age. Even among patients age 65 to 69 years, median survival was ≤4.0 years. Based on the National Vital Statistics Report for the general U.S. population, individuals age 65 to 69 years have an expected median survival of 18.7 years. Across all age groups, patients with HF (regardless of EF) had a markedly lower median survival than the life expectancy of individuals in the United States (**Figure 2**).

TEMPORAL TRENDS. We assessed the relationship of EF group with time for the risk of 5-year mortality,

TABLE 3 Mortality, Readmission, and Composite Outcomes at 5 Years Post-Admission in HF Patients by EF Groups

		Unadjusted Analysis		Adjusted Analysis	
	Cumulative Incidence*	HR (95% CI)	p Value	HR (95% CI)	p Value
5-yr mortality					
p value	0.6492		0.8288		0.8047
HFrEF (EF ≤40%)	13,847 (75.26)	1.011 (0.975-1.049)	0.5527	0.989 (0.958-1.022)	0.5127
HFbEF (EF 41%-49%)	2,487 (75.71)	1.007 (0.962-1.054)	0.7695	0.995 (0.947-1.046)	0.8552
HFpEF (EF ≥50%)	13,843 (75.65)	Reference		Reference	
5-yr all-cause readmission					
p value	<0.0001		<0.0001		0.0010
HFrEF (EF ≤40%)	14,576 (82.21)	0.967 (0.945-0.989)	0.0031	0.971 (0.945-0.997)	0.0310
HFbEF (EF 41%-49%)	2,716 (85.73)	1.055 (1.016-1.097)	0.0056	1.045 (1.005-1.087)	0.0288
HFpEF (EF ≥50%)	14,892 (83.98)	Reference		Reference	
5-yr CV readmission					
p value	<0.0001		<0.0001		<.0001
HFrEF (EF ≤40%)	11,238 (63.85)	1.176 (1.145-1.208)	<0.0001	1.180 (1.148-1.213)	<.0001
HFbEF (EF 41%-49%)	1,991 (63.25)	1.137 (1.086-1.191)	<0.0001	1.117 (1.067-1.169)	<.0001
HFpEF (EF ≥50%)	10,336 (58.93)	Reference		Reference	
5-yr HF readmission					
p value	<0.0001		<0.0001		<.0001
HFrEF (EF ≤40%)	8,505 (48.45)	1.305 (1.262-1.350)	<0.0001	1.335 (1.288-1.383)	<.0001
HFbEF (EF 41%-49%)	1,416 (45.23)	1.164 (1.098-1.234)	<0.0001	1.162 (1.098-1.229)	<.0001
HFpEF (EF ≥50%)	7,072 (40.49)	Reference		Reference	
5-yr composite of mortality/readmission					
p value	0.8174		0.8803		0.4899
HFrEF (EF ≤40%)	17,131 (96.40)	0.995 (0.965-1.026)	0.7481	0.984 (0.957-1.011)	0.2337
HFbEF (EF 41%-49%)	3,083 (97.16)	1.005 (0.970-1.043)	0.7692	0.995 (0.960-1.032)	0.8007
HFpEF (EF ≥50%)	17,282 (97.32)	Reference		Reference	

*For cumulative incidence, the log-rank p value is shown for 5-year mortality and Gray's p value is shown for other 5-year cumulative incidences. For unadjusted and adjusted analysis, the first p value is the global p value with degree of freedom of 2; the other p values test whether the hazards ratio of given outcome equals 1.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; other abbreviations as in Table 1.

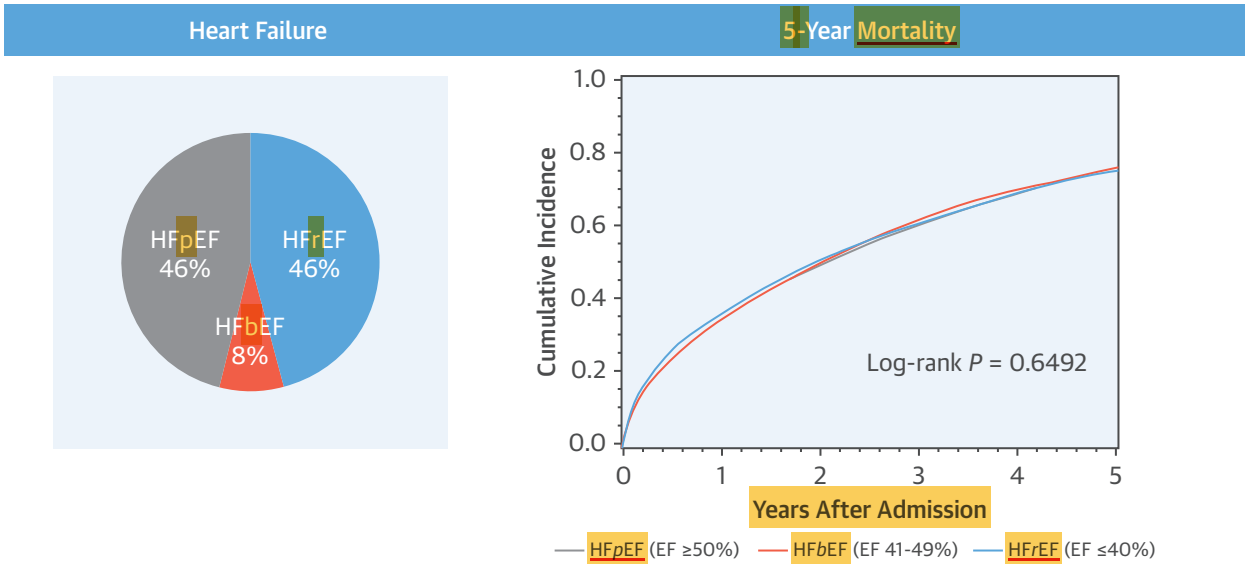
readmission, CV readmission, HF readmission, and the composite endpoint. There was no significant interaction between time and EF groups for any outcome (Online Table 8). When evaluating the relationship between calendar year of admission and outcomes, there was a small yearly increase in 5-year mortality (HR: 1.020 [95% CI: 1.008 to 1.032]; p = 0.0012). There was no other significant temporal relationship with any readmission or the composite endpoint (Online Table 9).

CAUSE OF DEATH BY EF GROUP. Cause of death analysis by examining CMS death and linking to NDI records with the Center for Disease Control was performed. There were 12,708 deaths between 2005 and 2008 matched between CMS and NDI data. Patients with HFrEF had the greatest percentage of deaths caused by CVD (n = 3,992; 65.89%), whereas patients with HFpEF had 2,995 (52.55%) deaths attributed to CVD. CVD causes of death included deaths linked to all ICD-10 codes starting with "I" (circulatory system cause) or related to nonspecified chest pain. Patients with HFrEF had 670 deaths caused by HF (n = 670; 11.06%) and HFpEF had 584 (10.39%) deaths attributed to HF (Online Table 10). From competing risks analysis, HFrEF patients were more likely to see CV-caused deaths within 1-year post-admission compared with HFpEF patients (aHR: 1.262; p < 0.0001) (Online Table 11).

DISCUSSION

From this analysis of a large national registry-based cohort, amongst patients hospitalized for HF, patients with HFpEF and HFbEF make up >50% of patients. This study includes one of the largest cohorts with long-term follow-up of patients hospitalized for HF classified using the most contemporary guideline specifications for classification by EF groups. Notably, patients with HFrEF, HFbEF, and HFpEF have very high rates of 5-year mortality and rehospitalization that are similar with and without risk adjustment (**Central Illustration**). There were higher rates of CV- and HF-specific rehospitalizations for patients with HFrEF and HFbEF compared with HFpEF. The median survival for patients hospitalized

CENTRAL ILLUSTRATION **5-Year Outcomes in Patients Hospitalized With HF With Preserved, Borderline, and Reduced EF**



Outcomes – 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

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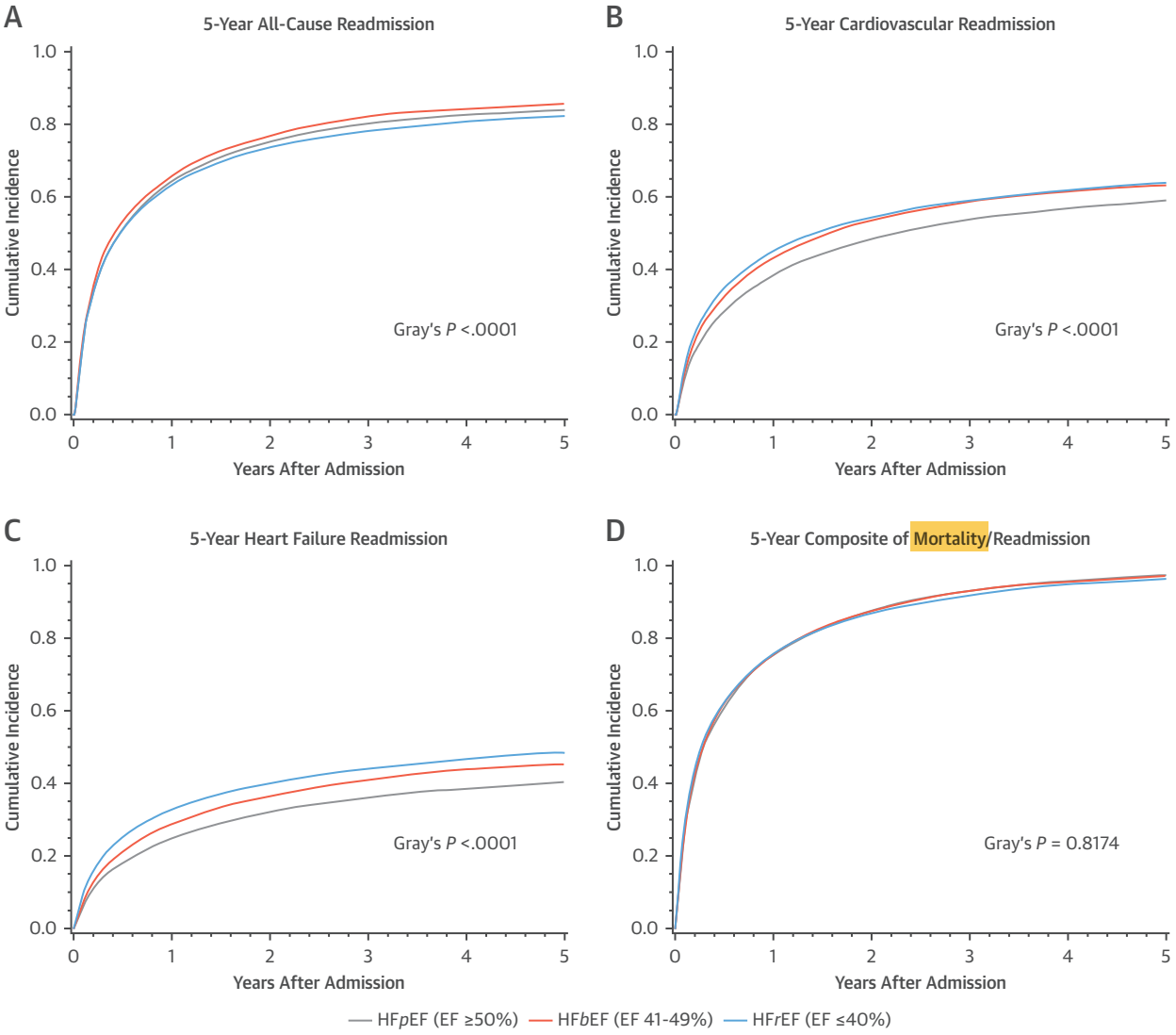
Patients ≥65 years of age hospitalized for decompensated heart failure (HF) in the GWTG-HF (Get With The Guidelines Heart Failure) registry had a similar percentage of preserved and reduced ejection fraction (EF), with 8% having borderline EF. The 5-year survival outcomes were poor across these subgroups, and rates of HF and cardiovascular (CV) admission were slightly greater in patients with reduced and borderline EF. The event rates for each outcome and HF subgroup are listed in the table. HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

with HF is markedly shortened compared with those of similar age in the general U.S. population, with between 4 and 15 years of life lost. These findings quantify the substantial burden that HF places on patients and the health care systems, irrespective of EF group, and highlight the critical need to identify new therapies that can improve outcomes for patients with HFrEF, HFbEF, and HFpEF. As has been shown in many other studies, patients with HFpEF were more often female with a higher prevalence of comorbidities including COPD, hypertension, and anemia. Comorbidities are frequently seen in HFpEF and likely contribute to the development of CV abnormalities and signs/symptoms of HFpEF (15). As expected, patients with a history of HFrEF are more often prescribed goal-directed medical therapies than patients with HFbEF and HFpEF. These findings underscore the contrast between proven evidence-based therapies for patients with HFrEF and HFpEF (4). Interestingly, patients with HFpEF had a lower rate of prescription upon discharge for anticoagulation for atrial fibrillation/flutter than patients with HFrEF. The rate of stroke and HF hospitalization is similar in patients with HFpEF and HFrEF (16). This represents at least 1 area for improvement in the overall management to reduce morbidity.

All patients in this cohort, regardless of EF, had a remarkably high mortality rate at 5 years from index admission (75.4%). This is among the first large, long-term outcomes analysis of patients using the contemporary EF subgroups (including borderline EF). The novelty of this analysis is a demonstration of high mortality and the composite of mortality and readmission in this cohort across the EF spectrum.

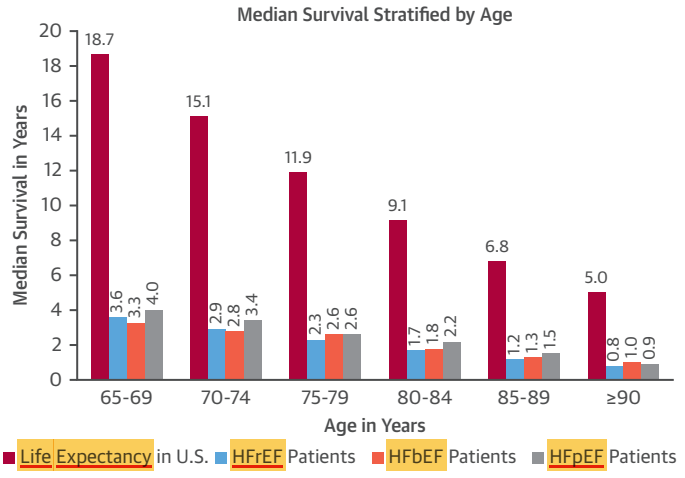
FIGURE 1 Cumulative Incidence Plots for Mortality and Readmission Outcomes by EF Groups



Kaplan-Meier curves of patients hospitalized with heart failure separated by ejection fraction (EF) group for 5-year rates of **(A)** all-cause readmission, **(B)** cardiovascular readmission, **(C)** heart failure readmission, and **(D)** composite of mortality/readmission. There were no significant differences in mortality or the composite of mortality and readmission. HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

The median survival for HF patients across all EF groups was significantly lower than the average life expectancy in United States. Previous studies have shown conflicting data with respect to survival in patients with HFpEF compared with HFrEF (4,5,7,9,11,17). Studies based on select patients enrolled in randomized clinical trials have suggested a substantially better prognosis for patients with HFpEF. The findings from this analysis of a large national cohort demonstrate that regardless of EF, once hospitalized, patients with HF have a poor long-term survival and high CV admission and HF readmission risk. The use of EF to categorize HF inherently has limitations, as the assessment of EF is subject to a degree of variability. These endorsed cutoffs are mostly based on inclusion criteria for patients in HF trials. These findings underscore the importance to further characterize and phenotype HF beyond EF. Among those who die from CV causes, patients with HFrEF make up a higher percentage than those with borderline or preserved EF. HF as a cause of death has as similar prevalence across EF groups, although

FIGURE 2 Median Survival in Years by Age Group in HF Patients Compared With the Life Expectancy in the United States



Across various age groups, median survival is greater in the U.S. population compared with patients with HF across the EF spectrum. Data from National Vital Statistics Report 2004 (14). HF = heart failure; other abbreviations as in Figure 1.

patients with borderline EF have the lowest percentage. Determination of the specific CV causes of death (i.e., rhythm monitoring, autopsy) that patients with HFpEF die from may be important to map natural history and determine cause-specific mortality.

HF hospitalization and readmission is a continued burden on the economic system worldwide (5,18,19). In the present study, patients with a history of HFrEF had a similar rate of all-cause rehospitalization, but a lower rate of CV and HF admission than patients with HFbEF and HFpEF. There does not seem to be a relationship between EF over time and hospitalization over 5 years. This is an area of continued effort for improvement in chronic HF management (20-22). Given the paucity of randomized controlled data demonstrating mortality benefit in patients with HFpEF, it is imperative to aggressively manage underlying risk factors (including hypertension, dyslipidemia, and anemia) as well as identify novel therapies. The benefit of the renin-angiotensin-aldosterone system antagonism is likely related to the degree of up-regulation of the sympathetic nervous system, more commonly seen in HFrEF (23,24). Other areas for improvement of HF outcomes may be in therapies for diabetes including empagliflozin, which has shown a marked benefit in reducing HF hospitalizations (25). Future studies are needed to further evaluate the potential effect of this therapy across EF groups and in patients with and without type 2 diabetes mellitus.

STUDY LIMITATIONS. This study has limitations that are inherent to most observational studies. There are potential selection biases inherent to the GWTG-HF registry, because it is dependent on voluntary participation. However, prior studies have suggested that Medicare beneficiaries enrolled in this registry are representative of the U.S. Medicare population (26). Furthermore, the generalizability of this data is limited given the patient population, including those in the GWTG-HF registry receiving Medicare. Patients with HF with unmeasured or missing EF were excluded, although the fraction of missing EF was relatively low in this study: 2.7% (Online Table 1). Previous studies have shown that EF is not consistently captured in the Medicare HF population, with >40% missing measurements, making this study particularly informative. Only fee-for-service Medicare patients could be linked, and these findings may not apply to patients age <65 years or in Medicare Advantage plans. Some patients may have navigated between categories of HF during the time of the study, and we do not have data to assess these patients separately. Post-discharge data were not directly tracked or recorded. Cause-specific readmissions and cause of death are dependent on diagnosis-related group and ICD-9-CM coding, which are subject to misclassification. We attempted to adjust for potential confounders, but we cannot exclude residual confounding.

CONCLUSIONS

Heart failure is a clinical syndrome for which EF is a commonly used discriminator. There are continued differences in the clinical characteristics and medications prescribed to patients with HFpEF, HFbEF, and HFrEF. Hospitalization for HF is associated with a poor long-term prognosis and an elevated risk of CV and HF admission, irrespective of EF. Furthermore, the causes of death due to CVD are highest in patients with a history of HFrEF, whereas death attributed to HF is similar across EF groups. These findings demonstrate the need for a continued effort to identify novel strategies to phenotype HF, to develop innovative therapies to reduce the burden of morbidity and mortality associated with HF, and to measure their integration into clinical practice.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients age ≥65 years hospitalized with HF, 5-year risk of all-cause mortality is high regardless of EF, and the median survival is substantially lower than the general population of similar age.

TRANSLATIONAL OUTLOOK: More work is needed to develop and implement therapies that reduce the morbidity and mortality associated with HF across the spectrum of left ventricular ejection fractions.

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APPENDIX For a supplemental figure and tables, please see the online version of this article.