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ORIGINAL RESEARCH

Clinical Profile, Health Care Costs, and Outcomes of Patients Hospitalized for Heart Failure With Severely Reduced Ejection Fraction

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BACKGROUND: Many patients with heart failure (HF) have severely reduced ejection fraction but do not meet threshold for consideration of advanced therapies (ie, stage D HF). The clinical profile and health care costs associated with these patients in US practice is not well described.

METHODS AND RESULTS: We examined patients hospitalized for worsening chronic heart failure with reduced ejection fraction ≤40% from 2014 to 2019 in the GWTG-HF (Get With The Guidelines-Heart Failure) registry, who did not receive advanced HF therapies or have end-stage kidney disease. Patients with severely reduced EF defined as EF ≤30% were compared with those with EF 31% to 40% in terms of clinical profile and guideline-directed medical therapy. Among Medicare beneficiaries, postdischarge outcomes and health care expenditure were compared. Among 113 348 patients with EF ≤40%, 69% (78 589) had an EF ≤30%. Patients with severely reduced EF ≤30% tended to be younger and were more likely to be Black. Patients with EF ≤30% also tended to have fewer comorbidities and were more likely to be prescribed guideline-directed medical therapy ("triple therapy" 28.3% versus 18.2%, $P<0.001$). At 12-months postdischarge, patients with EF ≤30% had significantly higher risk of death (HR, 1.13 [95% CI, 1.08–1.18]) and HF hospitalization (HR, 1.14 [95% CI, 1.09–1.19]), with similar risk of all-cause hospitalizations. Health care expenditures were numerically higher for patients with EF ≤30% (median US$22 648 versus $21 392, $P=0.11$).

CONCLUSIONS: Among patients hospitalized for worsening chronic heart failure with reduced ejection fraction in US clinical practice, most patients have severely reduced EF ≤30%. Despite younger age and modestly higher use of guideline-directed medical therapy at discharge, patients with severely reduced EF face heightened postdischarge risk of death and HF hospitalization.

Key Words: costs ■ ejection fraction ■ heart failure ■ outcomes

Existing guideline-directed medical therapies (GDMTs) for heart failure (HF) with reduced ejection fraction (HFrEF) are effective in substantially reducing rates of death and hospitalization, and improving patient-reported quality of life.[1–4] However, despite GDMT, HF remains a progressive clinical syndrome and patients remain at significant residual risk of death and HF hospitalization.[5] This risk is exaggerated several-fold once patients develop higher-risk features, such as experiencing a worsening HF event (eg, hospitalization, outpatient

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CLINICAL PERSPECTIVE

What Is New?

- More than 2 of 3 patients hospitalized for heart failure with reduced ejection fraction (EF) in US clinical practice have severely reduced EF ≤30%.
- Although patients with heart failure and EF ≤30% are generally younger with fewer comorbidities and modestly better use of guideline-directed medical therapy compared with patients with EF 31% to 40%, they remain at significantly higher risk of death and heart failure hospitalization.

What Are the Clinical Implications?

- Within the broad worsening chronic heart failure with reduced EF population, the majority of patients have EF ≤30% and remain at higher risk of death and heart failure hospitalization.
- Although background guideline-directed medical therapy was modestly better among patients with severely reduced EF ≤30%, absolute rates of guideline-directed medical therapy use at discharge were low and represent an urgent target for quality improvement.

Nonstandard Abbreviations and Acronyms

GDMT	guideline-directed medical therapy
HFrEF	heart failure with reduced ejection fraction
MRA	mineralocorticoid receptor antagonist

intravenous diuretic visit), or following progression to severe symptoms or severely reduced ejection fraction (EF).[6] Moreover, despite particularly high clinical risk, these patient subsets may be paradoxically less likely to receive appropriate therapy, or more likely to develop progressive intolerance to GDMT.[7,8] Thus, although such patients with worsening HF and severely reduced EF may not consistently meet threshold for consideration of advanced therapies such as heart transplantation or mechanical circulatory support, they have a clear unmet need for evidence-based strategies and therapies to reduce morbidity and mortality. Likewise, these patients may disproportionately contribute to excessive health care costs for HF.

Multiple recent clinical trials have studied the effect of novel medical therapies among patients with worsening HF, including those with severely reduced EF.[9–11] Severely reduced EF ≤30% is also a key component of the definition of severe HF (as defined by a position statement from the European Society of Cardiology), in addition to recurrent HF hospitalizations, and impaired functional capacity despite GDMT.[12] Yet, among the wealth of data characterizing outcomes among the broad population of patients with HFrEF with EF ≤40%, to our knowledge, there are no data from US clinical practice characterizing the subset of patients with both worsening HF and severely reduced EF. This population as recently been proposed as "stage C2" HF, to indicate their high-risk symptomatic HF status, but acknowledge that they are not to the point of stage D HF.[13] In this context, the aim of this analysis was to leverage the GWTG-HF (Get With The Guidelines-Heart Failure) registry to detail the relative frequency, clinical profile, outcomes, and costs of care for patients hospitalized with worsening chronic HF and EF ≤30%.

METHODS

Data Sources

The data used in this analysis cannot be made publically available by the authors. This study used data from the GWTG-HF registry, an ongoing national observational registry and quality improvement initiative started in 2005 and led by the American Heart Association.[14,15] Briefly, the registry includes data from patients hospitalized for HF at sites across the United States for whom HF was their primary diagnosis. Using an internet-based patient management tool (IQVIA, Parsippany, New Jersey), deidentified patient-level data such as demographics, medical history, in-hospital outcomes, and medications are abstracted. All sites participating in GWTG-HF obtain institutional review board approval. Since the primary role of the GWTG-HF registry is quality-improvement, sites are granted a waiver of patient informed consent. Data collection and coordination is managed by IQVIA, and the Duke Clinical Research Institute (Durham, North Carolina) serves as the data analysis center. To assess postdischarge outcomes and health care costs, patients ≥65 years of age with Medicare fee-for-service coverage were linked to Medicare beneficiary and claims data using a previously validated technique.[16] Medicare expenditures from discharge to 12-months postdischarge were extracted and considered continuously over the 12-month period.

Study Population

This current analysis included patients who were hospitalized for worsening chronic HFrEF ≤40% across 423 sites in the GWTG-HF registry between January 1, 2014 and December 31, 2019 and discharged alive. Patients who were discharged on hospice, to another acute care facility, or left against medical advice were excluded. Other notable exclusion criteria included

patients with heart transplantation or durable mechanical circulatory support, severe kidney disease (estimated glomerular filtration rate <20 mL/min per 1.73 m^2 or dialysis), new diagnosis of HF, or missing data for blood pressure or kidney function (Figure 1, Table S1).

In the current analysis, patients were grouped by EF into 2 comparator groups of EF ≤30% versus 31% to 40%. EF was recorded quantitatively in the GWTG-HF case report form, and represented the most recent value (ie, during index admission or before admission).

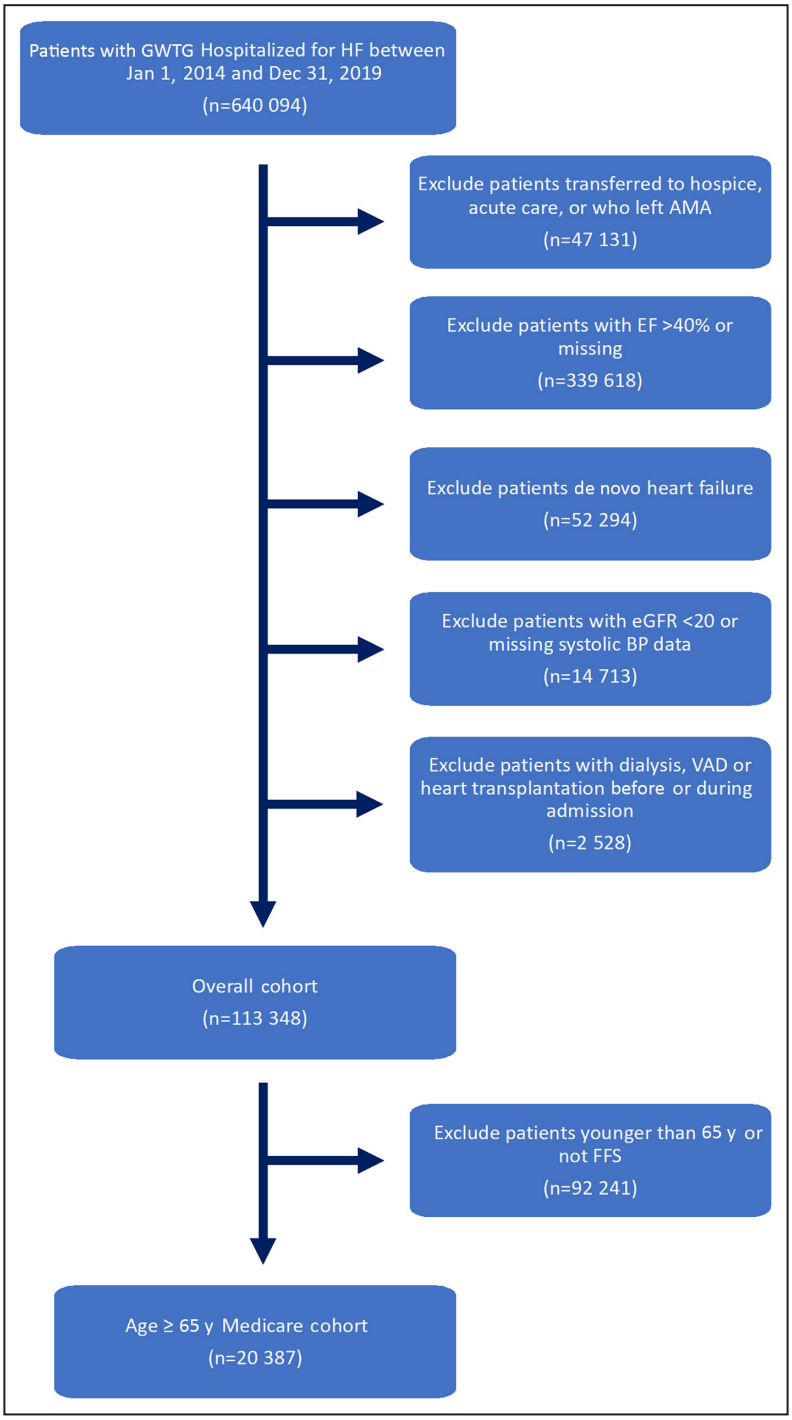

Figure 1. Selection of study populations included in overall and Medicare cohorts.
AMA indicates against medical advice; BP, blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FFS, fee-for-service; GWTG, Get With The Guidelines; HF, heart failure; and VAD, ventricular assist device.

The choice of EF ≤30% was prespecified to be consistent with a component of the definition of severe HF, as defined by a position statement from the European Society of Cardiology.[12]

Study End Points

Clinical outcomes were assessed at 3- and 12-months postdischarge and included the following: all-cause death, HF hospitalization, all-cause hospitalization, and total number of HF hospitalizations (including first and recurrent). Per-patient Medicare expenditure (total Part A and Part B costs) was evaluated over these same postdischarge timeframes.

Statistical Analysis

Continuous variables were presented as median (25%, 75%) and compared using the Wilcoxon rank-sum test. Categorical variables were presented as frequencies with percentages and were compared using the Pearson Chi-square test. Patient characteristics (eg, demographics, past medical history, vital signs, laboratory values, and medications) were compared using absolute standardized mean differences (SMDs), with differences ≥10 indicating a meaningful difference. These analyses were also performed within the population of patients aged ≥65 years with available data in the Center for Medicare and Medicaid Services claims database.

Among patients aged ≥65 years linked to Medicare hospitalized between January 1, 2014 and December 30, 2018, time-to-death, HF hospitalization, and all-cause hospitalization were compared at 3- and 12-months postdischarge for patients with EF ≤30% versus EF 31% to 40%. Kaplan–Meier event rates and cumulative incidence curves were compared by EF group. Using Cox regression models, unadjusted cause-specific hazard ratios for EF group were calculated for each event, using a sandwich variance estimator to account for the correlation of outcomes for patients at a common site. The proportional hazards assumption was checked with Schoenfeld residuals and was met.

To assess health care costs within the cohort of Medicare Beneficiaries, total unadjusted payments made by Medicare (total Part A plus Part B) were evaluated at 3- and 12-months postdischarge. Unadjusted payments were calculated as the sum from discharge to the selected time point of the inpatient cost, skilled nursing facility cost, outpatient cost, and carrier cost, which were standardized according to 2019 US dollars using the Market Basket Update and Productivity Adjustment published on the Center for Medicare and Medicaid Services website.[17] When assessing health care expenditures, mean total cost from discharge with SDs was calculated at 3- and 12-months postdischarge. Daily mean per-patient Medicare expenditures were plotted from discharge to 12-months postdischarge by EF group. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Cohort

From an initial population of 640 094 patients hospitalized for HF between January 1, 2014 and December 31, 2019, patients were excluded if they had an EF of >40% or if information on EF was missing (339 618 patients), were presenting with de novo HF (52 294 patients), were transferred to hospice or acute care, or left against medical advice, or discharge status not documented (47 131 patients), were missing data on systolic blood pressure or had estimated glomerular filtration rate <20 mL/min per 1.73 m^2 (14 713 patients), or if they required a ventricular assist device, heart transplant, or dialysis during their hospitalization (2528 patients). This yielded 113 348 patients in the final analytic cohort, of which 20 387 (18.0%) were aged ≥65 years and linked to Medicare claims (Figure 1).

Patient Characteristics by EF Group

Among 113 348 study patients hospitalized with worsening chronic HFrEF ≤40%, 78 589 (69%) had an EF ≤30%. Compared with patients with an EF of 31% to 40%, patients with an EF ≤30% tended to be younger with fewer comorbidities and higher natriuretic peptide concentration and were more likely to be men and Black (Table 1). Patients with an EF ≤30% tended to have lower systolic blood pressure and a higher HR at both admission and discharge, and were more likely to have a systolic blood pressure <100 mm Hg at discharge (17.1% versus 9.2%; Figure S1). Patients with an EF ≤30% had a modestly higher median estimated glomerular filtration rate than those with an EF 31% to 40% (56 versus 53 mL/min per 1.73 m^2).

Patients with an EF ≤30% were significantly more likely to be prescribed an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/angiotensin receptor-neprilysin inhibitor (ACEI/ARB/ARNI) (66.2% versus 61.2%) or mineralocorticoid receptor antagonist (MRA) at discharge (38.8% versus 26.1%) but had similar rates of beta-blocker prescription (87.6% versus 88.2%; Table 1). Patients with an EF of ≤30% were also significantly more likely like to be prescribed triple therapy at discharge with ACEI/ARB/ARNI, beta-blocker, and MRA (28.3 versus 18.2%), and were more likely to have an implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator (39.6% versus 20.2%). Patterns of patient characteristics and GDMT use by EF group were generally similar among the subset of Medicare beneficiaries, though there was a smaller difference in age (78 versus 80 years), and patients overall had more similar burdens of comorbidities (Table S2).

Table 1. Patient Characteristics by Left Ventricular Ejection Fraction

	EF ≤30% (n=78 589)	EF 31%–40% (n=34 759)	Standardized difference (%)
Age, y	68.0 (57.0–79.0)	74.0 (63.0–83.0)	36.8
Female sex	24 451 (31.1%)	13 664 (39.3%)	17.2
Race			24.0
White	45 409 (57.8%)	23 910 (68.8%)	
Black	23 228 (29.6%)	7020 (20.2%)	
Other	9943 (12.7%)	3824 (11.0%)	
Ejection fraction	22 (18–25)	35 (33–39)	320.6
Admission vitals and laboratory exams			
Heart rate, beats/min	88 (75–102)	84 (72–98)	15.8
Systolic blood pressure, mm Hg	127 (112–146)	138 (120–158)	38.4
Systolic blood pressure <100 mm Hg	6920 (8.8%)	1642 (4.7%)	16.3
BMI, kg/m^2	28.3 (24.2–33.9)	29.3 (24.8–35.3)	13.5
NT-proBNP, pg/mL	7572 (3565–15 245)	6021 (2897–12 801)	15.7
BNP, pg/mL	1441 (782.0–2604)	993.4 (509.0–1858)	28.8
eGFR, mL/min per 1.73 m^2	56 (40–75)	53 (37–72)	11.3
eGFR <45 mL/min per 1.73 m^2	26 290 (33.5%)	13 182 (37.9%)	9.34
Discharge vitals and laboratory exams			
Heart rate, beats/min	78 (70–89)	75 (67–86)	19.0
Systolic blood pressure, mm Hg	114 (103–127)	121 (109–136)	40.0
Systolic blood pressure <100 mm Hg	13 435 (17.1%)	3195 (9.2%)	23.6
BMI, kg/m^2	27.5 (23.5–33.0)	28.5 (24.1–34.5)	14
NT-proBNP, pg/mL	7095 (3269–14 517)	5715 (2696–12 165)	15.0
BNP, pg/mL	1334 (703.0–2469)	913.0 (456.0–1734)	29.0
eGFR, mL/min per 1.73 m^2	56.2 (40.1–75.9)	52.5 (37.3–71.9)	13.8
eGFR <45 mL/min per 1.73 m^2	25 510 (32.5%)	13 177 (37.9%)	11.4
Medical history			
Atrial fibrillation	28 833 (36.7%)	15 476 (44.5%)	16.0
Diabetes	34 378 (43.7%)	16 959 (48.8%)	10.1
Hypertension	64 787 (82.4%)	30 160 (86.8%)	12.0
Dyslipidemia	9261 (11.8%)	3507 (10.1%)	14.5
Prior MI	22 534 (28.7%)	10 094 (29.0%)	0.81
Stroke/transient ischemic attack	12 716 (16.2%)	6283 (18.1%)	5.03
COPD/asthma	26 659 (33.9%)	13 170 (37.9%)	8.28
Smoker, past 12 mo	18 949 (24.1%)	6140 (17.7%)	24.0
Device therapy			
Cardiac resynchronization therapy	13 564 (17.3%)	3324 (9.6%)	22.7
Implantable cardioverter-defibrillator	31 116 (39.6%)	7020 (20.2%)	43.4
Discharge medications			
ACEI/ARB/ARNI	52 018 (66.2%)	21 279 (61.2%)	17
ARNI	6666 (8.5%)	1824 (5.2%)	17.5
Beta-blocker	68 878 (87.6%)	30 667 (88.2%)	12.1
MRA	30 486 (38.8%)	9063 (26.1%)	36.2
ACEI/ARB/ARNI + beta-blocker + MRA	22 235 (28.3%)	6327 (18.2%)	35.6

Data presented as median (interquartile range) or n (%). Standardized difference represents the absolute differences in rank-based means or proportions divided by the standard error and multiplied by 100. Standardized differences >10 indicate imbalance between groups. The other race category includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, and unknown race. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Postdischarge Outcomes by EF Group

Among patients hospitalized for worsening chronic HFrEF age ≥65 years linked to Center for Medicare and Medicaid Services, overall absolute rates of postdischarge adverse events were high. Over 12-month follow-up, 38.4% of patients died, 36.0% of patients experienced an HF hospitalization, and 65.6% of patients experienced an all-cause hospitalization.

Compared with EF 31% to 40%, patients with EF ≤30% carried significantly greater risk of death at 3-months (event rate 16.9 versus 15.3; HR, 1.12 [95% CI, 1.05–1.20] *P*<0.001) and 12-months postdischarge (event rate 39.7 versus 36.1; HR, 1.13 [95% CI, 1.08–1.18] *P*<0.001; Table 2; Figure 2). Patients with an EF ≤30% also had a significantly higher hazard of HF hospitalization at both 3-months (event rate 22.9 versus 19.5; HR, 1.20 [95% CI, 1.13–1.29]) and 12-months postdischarge (event rate 43.4 versus 40.0; HR, 1.14 [95% CI, 1.09–1.19]). Risk of all-cause readmission was similarly high among patients in both EF groups with no significant between group difference (at 12 months: event rate 71.4 versus 71.3, HR, 1.01 [95% CI, 0.98–1.05] *P*=0.54).

For both EF groups, the mean (SD) number of HF hospitalizations over 12-months follow-up was 1.6 (1.1). Among patients with ≥1 HF hospitalization, the distribution of number of HF hospitalizations was similar between groups (*P*=0.106; Figure 3).

Medicare Expenditures by EF Group

Compared with patients with EF 31% to 40%, mean unadjusted Medicare Part A and Part B payments were nominally higher for patients with EF ≤30% at both 3-months (mean $16 632 [SD 32 327] versus $14 878 [SD 23 994], *P*=0.15) and 12-months postdischarge ($39 157 [SD 53 843] versus $36 721 [SD 46 629], *P*=0.11), but this was not statistically significant (Figure 4).

DISCUSSION

In this analysis of patients hospitalized for worsening chronic HFrEF in US clinical practice, more than 2 of every 3 patients had a severely reduced EF ≤30%. Compared with patients with EF 31% to 40%, patients with a severely reduced EF tended to be younger with fewer comorbidities, and were modestly more likely to be prescribed GDMT, including triple therapy (ACEI/ARB/ARNI+beta-blocker+MRA) at hospital discharge. Despite marginally better medical therapy, patients with worsening HF and severely reduced EF were significantly more likely to experience postdischarge death or HF rehospitalization. This higher relative risk was coupled with exceptionally high absolute risk, as within 12 months of discharge, ≈4 in 10 such patients died and nearly 4 in 10 experienced HF rehospitalization. Compared with patients with EF 31% to 40%, the higher clinical event rate among patients with worsening HF and severely reduced EF was coupled with nominally higher per-patient health care costs.

As defined by a position statement from the European Society of Cardiology, severe HF is characterized by severely reduced EF ≤30%, recurrent HF hospitalizations, and impaired functional capacity despite GDMT.[12] Severe HF has been associated with both high morbidity and mortality, as well as a high burden of symptoms.[12] Despite these risks, we observed that at time of discharge from an index HF hospitalization, less than one third of patients with severe HF in clinical practice were prescribed "triple therapy" with ACEI/ARB/ARNI, beta-blocker, and MRA. Though

Table 2. Absolute and Relative Risks of Death, Heart Failure Hospitalization, and All-Cause Hospitalization by Ejection Fraction; Data Taken From Medicare Cohort, N=20 387

Outcomes	EF group	No.	No. with event	Event rate (95% CI)	Hazard ratio (95% CI)	Hazard *P* value
3-mo postdischarge						
Death	EF 31%–40%	7618	1163	15.3 (14.5–16.1)	*Reference*	
	EF ≤30%	12 769	2161	16.9 (16.3–17.6)	1.12 (1.05–1.20)	<0.001
HF hospitalization	EF 31%–40%	7618	1394	19.5 (18.6–20.5)	*Reference*	
	EF ≤30%	12 769	2730	22.9 (22.2–23.7)	1.20 (1.13–1.29)	<0.001
All-cause hospitalization	EF 31%–40%	7618	3134	42.8 (41.6–43.9)	*Reference*	
	EF ≤30%	12 769	5275	43.2 (42.3–44.1)	1.02 (0.98–1.07)	0.40
12-mo postdischarge						
Death	EF 31%–40%	7618	2747	36.1 (35.0–37.1)	*Reference*	
	EF ≤30%	12 769	5075	39.7 (38.9–40.6)	1.13 (1.08–1.18)	<0.001
HF hospitalization	EF 31%–40%	7618	2597	40.0 (38.8–41.2)	*Reference*	
	EF ≤30%	12 769	4741	43.4 (42.5–44.4)	1.14 (1.09–1.19)	<0.001
All-cause hospitalization	EF 31%–40%	7618	5020	71.3 (70.2–72.3)	*Reference*	
	EF ≤30%	12 769	8349	71.4 (70.5–72.2)	1.01 (0.98–1.05)	0.54

EF indicates ejection fraction; and HF, heart failure.

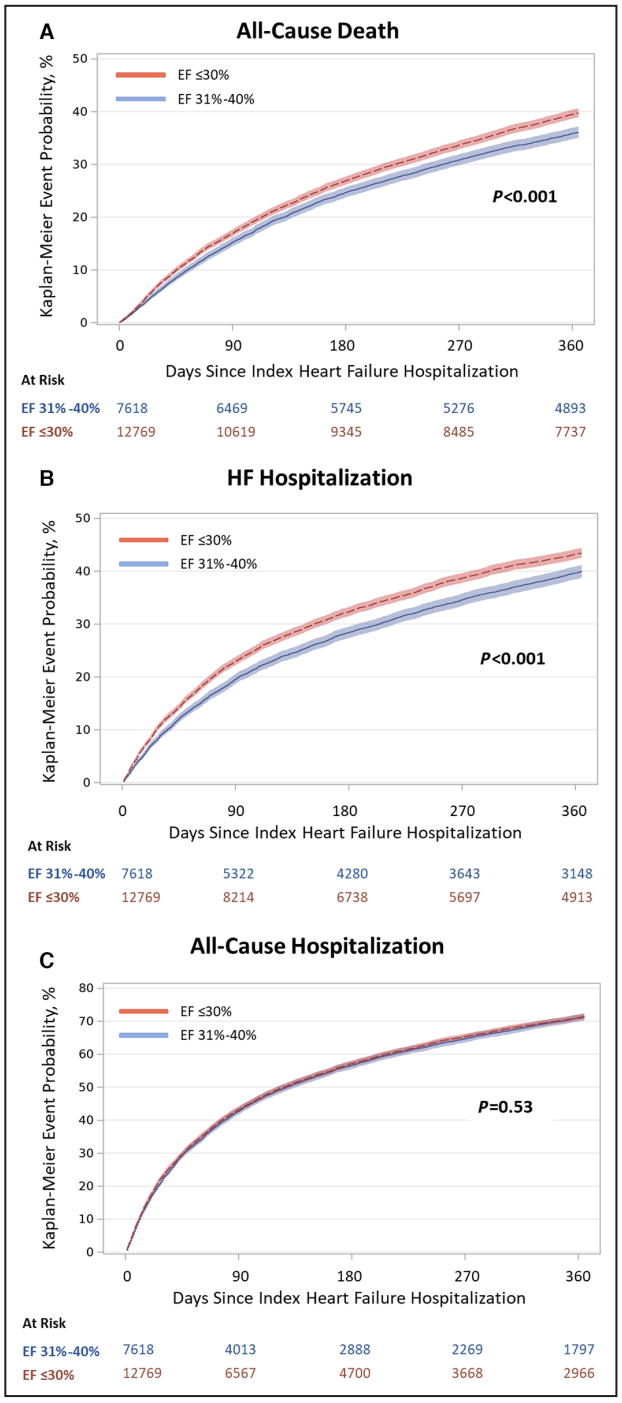

Figure 2. Cumulative incidence death, heart failure hospitalization, and all-cause hospitalization over 12-month follow-up by ejection fraction.
Cumulative incidence shown by ejection fraction group following index hospitalization. **A**, All-cause mortality. **B**, Heart failure hospitalization. **C**, All-cause hospitalization. Data taken from Medicare cohort, N=20387. EF indicates ejection fraction; and HF, heart failure.

data about sodium-glucose co-transporter-2 inhibitor use were not available during the study period, based on experiences with other novel therapies for HF, early adoption of sodium-glucose co-transporter-2 inhibitor for HFrEF may likewise be anticipated to be slow.[18] Prior data have consistently supported the importance of in-hospital initiation of medical therapy as a highly effective means of improving postdischarge use and outcomes.[19,20] The current data reinforce this message, highlighting the HF hospitalization as a critical opportunity to close gaps in medical therapy as tolerated, particularly among patients with severely reduced EF where risks of death and HF hospitalization are heightened. This imperative is especially strong given the high absolute events rates within 90 days of discharge in the current study, and the rapid reductions in relative and absolute risk that appear soon after initiation of each pillar of quadruple medical therapy for HFrEF.[19,21]

Although prior analyses have highlighted multiple examples of a risk-treatment paradox among patients with HF, this relationship was not seen in the current analysis.[22,23] Patients with severely reduced EF had worse clinical outcomes, and had modestly higher use of GDMT use, including higher rates of MRA, ACE/ARB/ARNI, and triple therapy with beta-blocker, MRA and ACE/ARB/ARNI. There are several potential reasons for this finding. Patients with severely reduced EF may be more likely to be managed by an advanced HF specialist, who may be more aggressive about escalation of GDMT and have a higher threshold to reduce or stop these therapies. These patients are also younger and have fewer comorbidities, and as such may be perceived to have a higher potential tolerance to GDMT. We additionally found that patients with EF ≤30% tended to have modestly better kidney function, which prior work has associated with improved rates of GDMT.[22]

Although continued prioritization of quadruple medical therapy as tolerated is critical, patients with severe HFrEF continue to face a high residual risk of morbidity and mortality, even after GDMT optimization.[12] Moreover, as HF progresses, potential challenges with GDMT ineligibility and intolerance may increase, potentially because of low blood pressure, worsening kidney function and/or hyperkalemia. Patients with severely reduced EF were almost twice as likely to have a systolic blood pressure <100 mm Hg as compared with other patients with HFrEF. Indeed, among patients with severely reduced EF ≤30% in the current study, nearly 1 in 5 patients had a systolic blood pressure <100 mm Hg at time of hospital discharge. In this context, there exists a continued need for additional novel therapies for patients with worsening HF and/or severely reduced EF that are both effective and well-tolerated.[12] Beyond proven benefits on morbidity and mortality, the safety and tolerability of sodium-glucose co-transporter-2 inhibitor therapy is particularly well-suited for such patients, including minimal to no effect on blood pressure, kidney protective effects, and

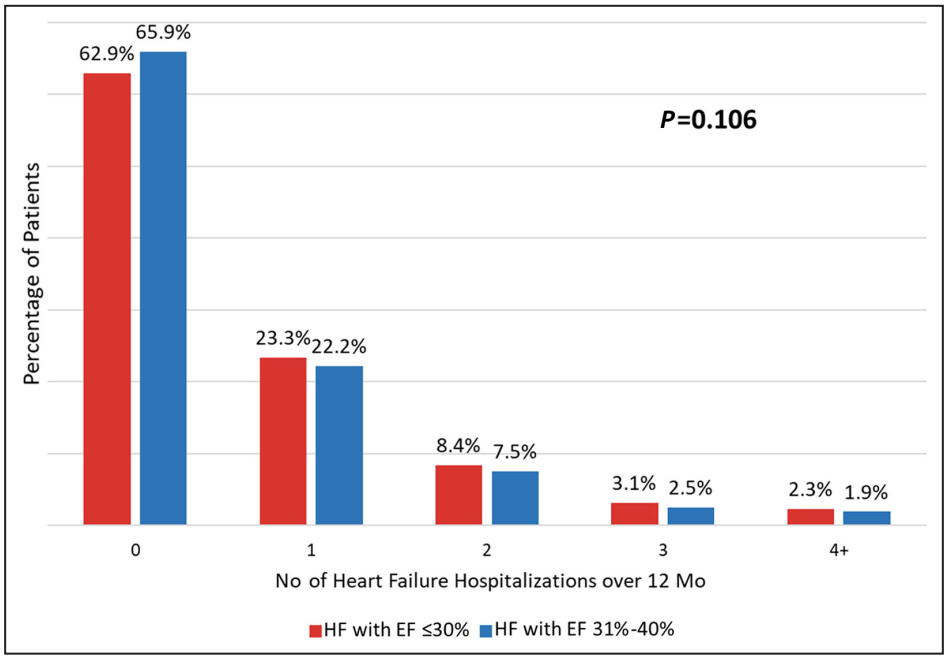

Figure 3. Number of heart failure hospitalizations >365 days by ejection fraction group.
Percentage of patients with 0, 1, 2, 3, or 4+ hospitalizations for heart failure. Data taken from Medicare cohort, N=20 387. EF indicates ejection fraction; HF, heart failure; Mo, month; and No, number.

prevention of hyperkalemia.[24] In addition, vericiguat has been shown to further reduce the relative risk of cardiovascular death or hospitalization for HF by 10% among patients with HFrEF already optimized on GDMT.[9,10] Although not currently commercially available, omecamtiv mecarbil demonstrated similar results in the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in

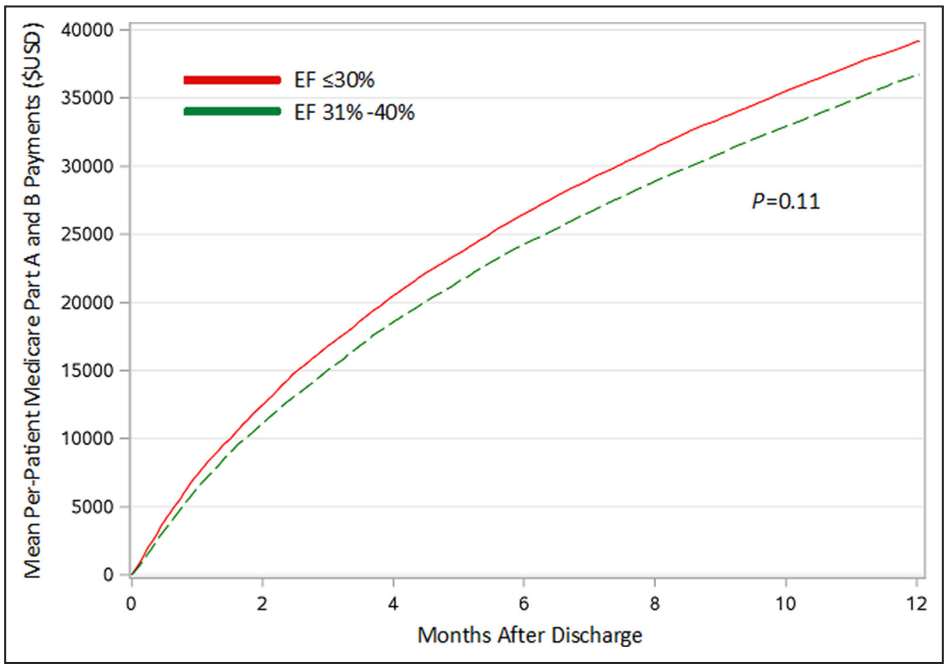

Figure 4. Mean per-patient Medicare expenditure through 12-months postdischarge by ejection fraction group.
Graph depicts cumulative costs in each patient group divided by number of patients at risk at that timepoint, accounting for competing risk of death. EF indicates ejection fraction. Data taken from Medicare cohort, N=20 387.

Heart Failure) trial.[6] However, with each of these novel therapies, certain subsets may derive larger benefits. For example, post hoc analyses of the GALACTIC-HF trial demonstrated a significant treatment interaction such that patients with severe HFrEF (defined similarly to the current GWTG-HF population by including EF ≤30% and recent HF hospitalization) experienced a larger 20% relative risk reduction for cardiovascular death or worsening HF with omecamtiv mecarbil, compared with placebo.[25] Omecamtiv mecarbil was also well-tolerated, without an observed impact on kidney function, serum potassium, or blood pressure.

In addition to findings on clinical events, the current report found patients with severely reduced EF to be associated with numerically greater postdischarge health care expenditure, though this difference was not statistically significant. This lack of significant difference may have been driven in part by similar rates of all-cause hospitalization and baseline comorbidities between EF groups in the Medicare cohort. Nonetheless, irrespective of between-group differences, the absolute magnitude of Medicare payments in excess of mean $35 000 per-patient over the first 12 months following HF hospitalization are notable. These findings are consistent with other data outlining costs associated with an HF diagnosis, costs that may be on average >5 times that of a patient without HF.[26] The cost of HF is primarily driven by hospitalizations for HF.[27] Acknowledging that the pattern of recurrent HF hospitalizations was not significantly different in the current study, the overall higher rate of HF hospitalization among those with severely reduced EF suggests that implementation of existing and novel therapies proven to prevent HF hospitalization in this population may be a particularly impactful and efficient means of curtailing health care costs. The impact of this cost-saving measure may be amplified in patients with severely reduced EF, a group where HF hospitalizations tend to comprise a higher proportion of total hospitalizations.[28] In addition to reducing HF-associated costs, there are important clinical implications to reducing HF hospitalizations, given the relationship between HF hospitalization and disease progression and worsening patient-reported health status.[29,30]

Limitations

Limitations of this analysis should be noted. First, this retrospective observational analysis cannot definitively determine cause-effect relationships. Second, serial EF data were not available and EF measurements reflected assessments during the index hospitalization or most recent assessment before hospitalization. Thus, we were unable to examine the interplay between EF trajectory (eg, increasing versus decreasing) and the clinical profile and outcomes associated with each EF group. Third, hospital participation in GWTG-HF is voluntary and despite prior analysis suggesting strong national representativeness, the registry may not entirely represent all patients receiving care across all hospitals in the United States.[31] Fourth, based on the nature of data in GWTG-HF, the definition of severe HF in this analysis was less encompassing than the ESC's definition of severe HF, which also included echocardiographic and functional markers of severe HF as alternatives to severely reduced EF.[12] Fifth, given the goal of this analysis to characterize patients with severe HF but who may be still be responsive to medical therapy, the current data should be interpreted in the context of excluding patients with history of advanced HF therapies including left ventricular assist device or heart transplant. Lastly, the clinical outcomes and expenditure analyses were limited to Medicare beneficiaries aged ≥65 year, and the extent to which such results may generalize to younger patients with worsening chronic HFrEF is unclear.

CONCLUSIONS

More than 2 of every 3 patients hospitalized for worsening chronic HFrEF have severely reduced EF ≤30%. Despite being younger with fewer comorbidities and modestly higher rates of GDMT, patients with severely reduced EF continue to face excessive absolute and relative risks of death and HF hospitalization beyond those seen in the general HFrEF population, as well as high health care expenditure. To improve outcomes for this patient subset, further efforts are urgently needed to maximize use of quadruple medical therapy for HFrEF as tolerated, as well as consideration of additional novel therapies in select patients that may further reduce residual risks of death and hospitalization.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figure S1

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Supplemental Material

Table S1. Selection of the Study Population Stratified by Ejection Fraction Group.

	EF ≤30%			*EF >30%*		
Inclusion / Exclusion Criteria	**N excluded**	**N remaining**	**Excluded %**	**N excluded**	**N remaining**	**Excluded %**
Starting Population: age >18 years hospitalized for HF between Jan 1,2014-Dec 31,2019	-	191,050	-	-	86,575	-
Include patients not to hospice, not to acute care facility, did not leave AMA, or ND	(18,354)	172,696	9.61	(5,926)	80,649	6.84
Include patients not transferred out	(0)	172,696	0.00	(0)	80,649	0.00
Exclude Patients with LVEF >40% or missing	(0)	172,696	0.00	(0)	80,649	0.00
Exclude Patients with no prior history of HF	(34,196)	138,500	19.80	(18,098)	62,551	22.44
Exclude patients with missing eGFR data at baseline and discharge	(48,859)	89,641	35.28	(21,613)	40,938	34.55
Exclude patients with eGFR <20	(7,438)	82,203	8.30	(4,973)	35,965	12.15
Exclude patients with missing SBP data at baseline and discharge	(1,671)	80,532	2.03	(621)	35,344	1.73
Exclude patients with left ventricular assist device as in-hosp procedure	(445)	80,087	0.55	(27)	35,317	0.08
Exclude patients with dialysis as an in-hospital procedure	(385)	79,702	0.48	(205)	35,112	0.58
Exclude patients with dialysis or ultrafiltration unspecified as an in-hosp proc	(142)	79,560	0.18	(74)	35,038	0.21
Exclude patients with heart transplant as in-hospital procedure or listed for transplant in HF history	(254)	79,306	0.32	(42)	34,996	0.12
Exclude patients with history of chronic dialysis	(336)	78,970	0.42	(176)	34,820	0.50
Exclude patients with history of ventricular assist device	(381)	78,589	0.48	(61)	34,759	0.18

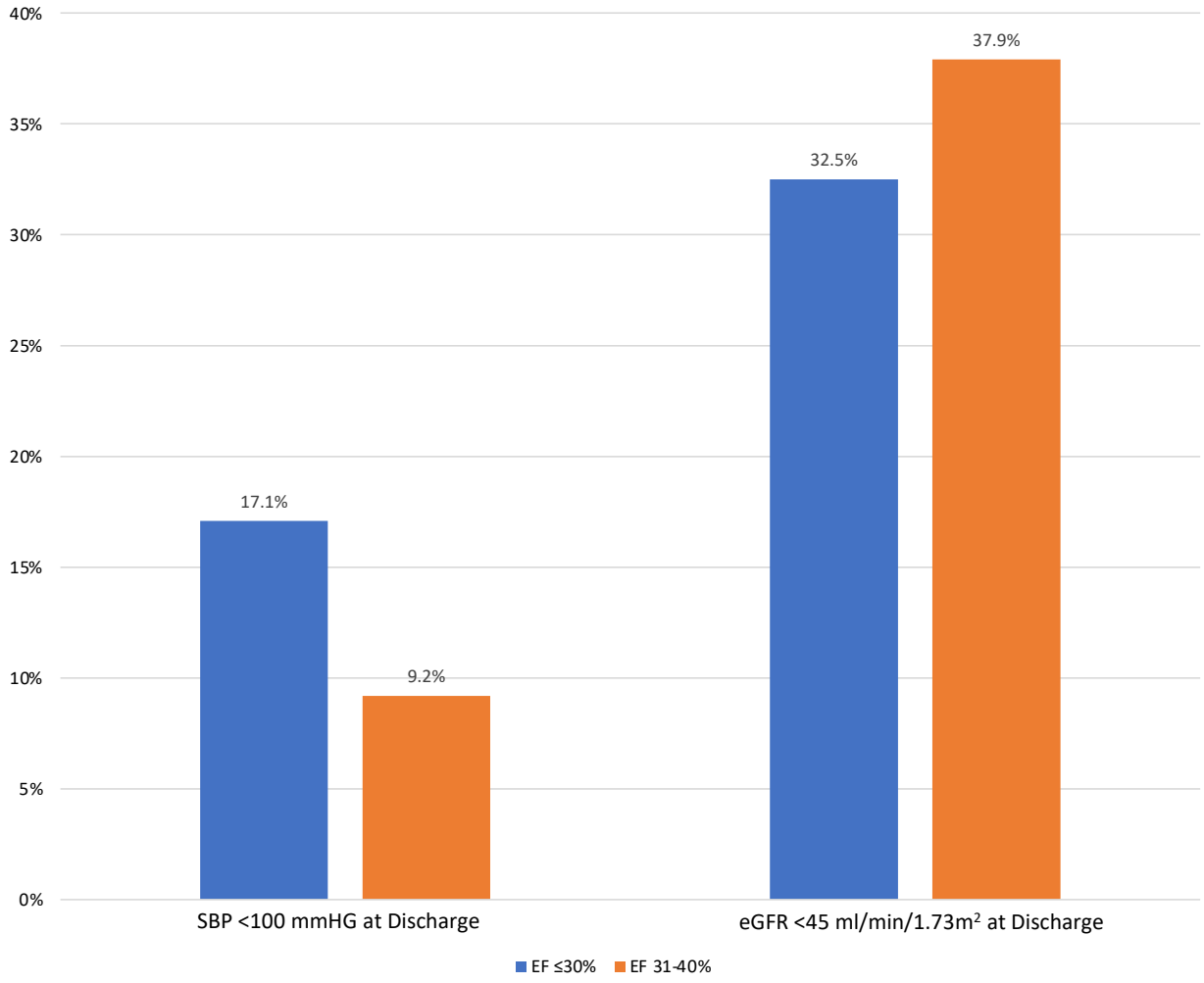
Table S2. Patient Characteristics by Left Ventricular Ejection Fraction (CMS Linked Cohort).

	EF ≤30% (N=12,769)	EF 31-40% (N=7,618)	Standardized Difference (%)
Age, years	78.0 (71.0-85.0)	80.0 (73.0-87.0)	19.7
Female Sex	4,329 (33.9%)	3,156 (41.4%)	15.6
Race			12.2
White	10,118 (79.2%)	6,361 (83.5%)	
Black	1,652 (12.9%)	708 (9.3%)	
Other	997 (7.8%)	546 (7.2%)	
Ejection Fraction	23 (19-27)	35 (34-40)	313.8
Admission Vitals & Labs			
Heart rate, beats/min	84.0 (72-98)	82 (70-96)	8.6
Systolic blood pressure, mmHg	128 (113-145)	137 (120-155)	33.5
Systolic blood pressure <100 mmHg	995 (7.8%)	327 (4.3%)	14.7
BMI, kg/m²	26.9 (23.5-31.2)	27.7 (24.0-32.6)	14.1
NT-proBNP, pg/mL	9343 (4582-18504)	6850 (3347-13708)	26.6
BNP, pg/mL	1424 (784.0-2560)	979.0 (525.0-1782)	28.6
eGFR, ml/min/1.73m^2	50 (37-67)	51 (37-68)	1.7
eGFR <45 ml/min/1.73m^2	5,153 (40.4%)	3,111 (40.8%)	1.0
Discharge Vitals & Labs			
Heart rate, beats/min	76 (68-86)	74 (66.0-84)	9.0
Systolic blood pressure, mmHg	114 (103-128)	121 (109-135)	33.2
Systolic blood pressure <100 mmHg	2,091 (16.4%)	743 (9.8%)	19.8
BMI, kg/m²	26.0 (22.7-30.3)	26.9 (23.3-31.7)	15.0
NT-proBNP, pg/mL	8779 (4170-17559)	6560 (3204-13061)	23.3
BNP, pg/mL	1306 (709.0-2391)	874.0 (461.0-1623)	30.7
eGFR, ml/min/1.73m^2	51 (38-68)	51 (37-68)	1.0
eGFR <45 ml/min/1.73m^2	4,953 (38.8%)	3,078 (40.4%)	3.3
Medical History			
Atrial fibrillation	5,827 (45.6%)	3,832 (50.3%)	9.4
Diabetes	5,345 (41.9%)	3,272 (43.0%)	2.2
Hypertension	10,342 (81.0%)	6,447 (84.6%)	9.6

Dyslipidemia	1,480 (11.6%)	765 (10.0%)	12.7
Prior MI	3,912 (30.6%)	2,189 (28.7%)	4.2
Stroke/ Transient ischemic attack	2,181 (17.1%)	1,440 (18.9%)	4.7
COPD / asthma	3,796 (29.7%)	2,601 (34.1%)	9.5
Smoker (past 12 months)	1,403 (11.0%)	740 (9.7%)	4.2
Discharge Medications			
ACEI/ARB/ARNI	8,088 (63.3%)	4,570 (60.0%)	16.6
Beta-blocker	11,428 (89.5%)	6,777 (89.0%)	12.7
MRA	4,295 (33.6%)	1,739 (22.8%)	31.3
ACEI/ARB/ARNI + beta-blocker +MRA	2,933 (23.0%)	1,161 (15.2%)	31.6

Data are presented as median (interquartile range) or n (%). eGFR calculated using CKD-EPI formula. ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA/TIA: cerebrovascular accident/transient ischemic event; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; SBP: systolic blood pressure

Figure S1. Differences in Discharge Systolic Blood Pressure and Kidney Function at Discharge in Patients with EF ≤30% vs 41-40%.



Differences were statistically significant with standardized mean difference of >10 for both categories. eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure.