


Heart failure ejection fraction class conversions: impact of biomarkers, co-morbidities, and pharmacotherapy

Christian J. Lorenzo^{1*} , Jorge I. Conte¹, Ricardo J. Villasmil¹, Qassem K. Abdelal¹, Derek Pierce¹, Wilhelmine Wiese-Rometsch¹ and Joel A. Garcia-Fernandez²

¹Department of Medicine, Sarasota Memorial Health Care System, Florida State University College of Medicine, Sarasota, FL, USA; and ²Department of Medicine, Division of Cardiology, Orlando Health, Orlando, FL, USA

Abstract

Aims Temporal conversions among ejection fraction (EF) classes can occur across the heart failure (HF) spectrum reflecting amended structural and functional outcomes unaccounted for by current taxonomy. This retrospective study aims to investigate the differences in serum laboratory values, guideline-directed medical therapy (GDMT), and co-morbidity burden across EF conversion groups.

Methods and results Heart failure patients at least 18-year-old who obtained at least two echocardiograms between January 2018 and January 2020 were identified using ICD-10 codes. Analysis of variance, chi-square tests, and analysis of means for proportions were used as appropriate to identify associations with class conversion groups. A total of 874 patients who underwent 1748 echocardiograms on unique visits were categorized according to initial EF as HF with preserved EF (HFpEF) ($n = 531$, 61%), HF with mildly reduced or midrange EF (HFmrEF) ($n = 132$, 15%), or HF with reduced EF (HFrEF) ($n = 211$, 24%). In accordance with follow-up EF, class conversions were categorized into HF with improved EF (HFief) ($n = 143$, 16%), HF with worsened EF (HFwEF) ($n = 171$, 20%), or HF with stable EF (HFsef) ($n = 560$, 64%). The average age was 75 ± 13 years old; 54% were male, 85% were Caucasian, 11% were African American, and 4% other. The mean time between EF assessments was 208.6 ± 170.2 days. Serum sodium levels were greater in HFwEF (139 ± 3 mmol/L) when compared with HFsef (138 ± 4 mmol/L) ($P = 0.05$). Pro-BNP levels were higher in HFief ($12\,150 \pm 19\,554$ pg/mL) versus HFsef ($6671 \pm 10\,525$ pg/mL) ($P = 0.007$). Angiotensin receptor-neprilysin inhibitors (ARNI) were more frequently ordered on index visit in HFief ($P = 0.03$), but no other significant differences in GDMT were identified. Despite similar Elixhauser Co-morbidity Measure (ECM) scores, ECM categorical analysis revealed that HFwEF was more likely to have an established diagnosis of depression ($P = 0.03$) and a spectrum of psychiatric illnesses ($P = 0.03$) on preliminary visit. HFsef was less likely to have an established diagnosis of blood loss anaemia ($P = 0.04$). Metastatic cancer was more likely to have been diagnosed in HFief and less likely in HFsef ($P = 0.002$).

Conclusions Despite similar ECM scores, EF class conversion groups demonstrated salient differences in average serum sodium and pro-BNP levels. Inpatient ARNI orders, psychiatric, hematologic, and oncologic co-morbidity patterns were also significantly different. Findings demonstrate blood-based biomarker patterns and targetable co-morbid conditions which may play a role in future EF class conversion. Dedicated studies evaluating measurements related to GDMT dose-titration, quality of life, and functionality are the next steps in this field of HF.

Keywords Heart failure; Ejection fraction change; Multiple chronic conditions; Longitudinal; HFief; GDMT

Received: 28 November 2021; Revised: 21 April 2022; Accepted: 27 April 2022

*Correspondence to: Christian J. Lorenzo, Department of Medicine, Sarasota Memorial Health Care System, Florida State University College of Medicine, Graduate Medical Education Office, 3 Waldemere Tower, 1700 South Tamiami Trail, USA. Phone: 727-479-2593. Email: christian.lorenzo16@gmail.com

Introduction

Heart failure (HF), a multidimensional and complex clinical syndrome estimated to affect 64.3 million worldwide, is functionally classified using left ventricular ejection fraction (EF).¹ These classifications currently consist of HF with reduced EF (HFrEF) (EF < 40%), HF with mildly reduced or midrange EF (HFmrEF) (EF 40% to 49%), and HF with preserved EF (HFpEF) (EF ≥ 50%).² Historically, the magnitude of EF emphasis in HF has been appreciated at the clinical trial level, where inclusions have almost exclusively been made based on EF class.³ Across the EF spectrum, management guidelines have been indexed to EF class despite only a modest difference in long-term survival.^{4,5} A discordance is clearly appreciated with the current taxonomy and the progressive understanding that HF is indeed a multifaceted condition, surely not driven solely by an aberrant left ventricle (LV). Regardless, there is fundamentally no other echocardiographic variable more influential than EF, at the present time, used to develop HF treatment plans.

Although cross-sectional measurements of EF often fall short of meaningful prognostic outlook for patient and provider, this is substantially improved with multiple longitudinal assessments. Moreover, temporal conversions from one EF class to another can occur, reflecting amended structural and functional outcomes.⁶ Downward EF changes experienced may lead to worse than expected future HF outcomes. This will depend on a multitude of clinical variables including but not limited to: HF aetiology; HF duration; sex; and likely the occult role of multiple chronic conditions (MCC).

Peer-reviewed literature evinces 55% of HF Medicare beneficiaries have 5 or more MCC.⁷ MCC and their effect on HF outcomes can be assessed with a focus on individual co-morbidities or with 'big picture' co-morbidity index calculators. Examples include the Elixhauser Co-morbidity Measure (ECM) and Charlson Co-morbidity Index (CCI), both of which have demonstrated usefulness in studies relying on administrative data. Distinctively, patients with a high calculated MCC burden have demonstrated worse clinical outcomes. This worsened prognosis, irrespective of EF class, occurs because of both the individual and collective effects of MCC on HF.⁷⁻¹⁰ Likewise, the number of underreported co-morbidities, such as depression and cognitive impairment, may play a salient role in patient outcomes.⁷

Haemodynamic stress, LV remodelling, and functional outcomes have been shown to be associated with changes in cardio-centric biomarkers such as amino-terminal pro-B-type natriuretic peptide (NT-pro-BNP).¹¹ Furthermore, even within 'normal' reference intervals, a multitude of serum laboratory values such as potassium, sodium, and bicarbonate have also been shown to pose risk to poor prognostic outcomes.¹²

Significant advancement in HF treatment plans, including guideline-directed medical therapy (GDMT), cardiac devices, coronary revascularization strategies, and valvular repair

have promoted LV reverse remodelling, attempting to ameliorate negative trajectories.^{13,14} However, the extremely relevant 'syndromic' HF patient burdened with MCC and serum biomarker abnormalities (in a background of what appears to be guideline-directed management strategies) is increasingly common and a global health concern. Correspondingly, the role of evaluating index co-morbidity burden, serum biomarker dysregulation, and GDMT on short-term and medium-term bidirectional transitions in EF class warrants further investigation and thus is the purpose of this retrospective study.

Methods

Study design and population

This retrospective, electronic medical record-driven, single-centre, observational study was conducted with the goal of improvement of patient care and safety at Sarasota Memorial Health Care System (SMHCS) in Sarasota, FL, USA. The study was exempted by the Sarasota Memorial Hospital Institutional Review Board as quality improvement. Patients were considered for the study who underwent more than one echocardiogram between January 2018 and January 2020 with results available in the Digisonics DigiView Cardiovascular Image Management and Reporting System at SMHCS. Selection criteria included: (i) patients ≥18 years of age; (ii) at least one of the International Statistical Classification of Disease and Related Health Problems, 10th revision, Clinical Modification (ICD-10-CM) diagnosis codes of HF used in accordance with the Agency for Healthcare Research and Quality (AHRQ) and Healthcare Cost and Utilization Project (HCUP) Elixhauser Co-morbidity Index Software; (iii) at least two consecutive echocardiograms obtained on at least two unique inpatient visits. Exclusion criteria included echocardiograms obtained during (i) visits resulting in hospice care; (ii) visits occurring in the designated SMHCS inpatient rehabilitation pavilion or the SMHCS Bayside Behavioural Health Unit; (iii) inpatient visits without available inpatient medication orders; and (iv) outpatient visits. LVEF was calculated by SMHCS echocardiographic laboratory protocol by means of the modified Simpson's rule in accordance with the American Society of Echocardiography's recommendation.¹⁵ In the event endocardial delineation was sub-optimal or two or more contiguous LV wall segments were poorly visualized, ultrasound enhancing agents were utilized for EF calculation.

Baseline EF data were collected, categorized, and defined as HFpEF (≥50%), HFmrEF (40% to 49%), and HFrEF (<40%). Conversions from HFpEF to HFmrEF, HFpEF to HFrEF, and HFmrEF to HFrEF were pooled and defined as worsened EF (HFwEF). Transitions from HFrEF to HFmrEF, HFrEF to HFpEF, and HFmrEF to HFpEF were pooled and defined as improved

EF (HF_iEF). The absence of EF class conversion among EF groups was defined as stable EF (HF_sEF). Demographic data, serum laboratory data, and inpatient medication orders obtained from Sunrise Clinical Manager were extracted from the index hospital visit in which the first echocardiogram was obtained. Specifically, laboratory data extracted were averaged across the entire index stay. Elixhauser co-morbidities were extracted via ICD-10-CM code search in accordance with AHRQ/HCUP standards.

Figure 1 identifies inclusion and exclusion pathways to delineate the primary cohort. From a database of 20 840 studies obtained during the above allotted time frame, 2913 unique patients were identified to have obtained at least two consecutive studies on at least two consecutive visits between January 2018 to January 2020. Of these patients, 1834 were identified to have carried an AHRQ/HCUP Elixhauser ICD-10-CM code consistent with a diagnosis of heart failure. Pharmacy data extraction excluded outpatient visits and visits to our inpatient rehabilitation pavilion or behavioural health unit. The primary cohort thus yielded 874 heart failure patients which were then grouped according to baseline EF obtained on index visit.

Measures and outcomes

Echocardiographic measurements, blood-based chemistries, and pharmacotherapeutics were obtained from each index echocardiographic inpatient visit. A list of all EF measurements, laboratory traits, and medications is provided in the

Supporting Information, *Tables S1–S3*. Standard HCUP ICD-10-CM codes provided 29 Elixhauser co-morbidity categories to define additional clinical covariates of interest. The primary outcome included the incidence of HF EF class conversion with EF trajectory classification. Secondary outcomes included clinical factors associated with longitudinal EF class change (increased, worsened, or stable) including clinical traits, ECM scores, co-morbidity patterns, blood-based chemistries, and GDMT.

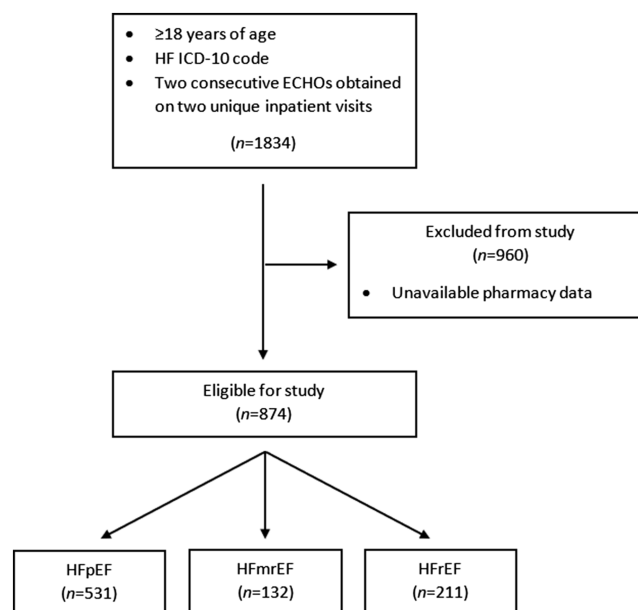
Statistical methods

Analyses were performed using JMP Pro 15.2 (SAS, Cary, NC). The specific methods used to summarize the data included a one-way analysis of variance (ANOVA) to identify differences in the means of numerical data between the three groups. Regarding the MCC, 3-group Pearson's χ^2 test was implemented (carries ICD-10-CM code or not) and evaluated to be significant based on an analysis of means (ANOM) for proportions. As this was a quality improvement project, hypotheses were not tested. Clinical traits, ECM scores, co-morbidity patterns, blood-based chemistries, GDMT, and associations of these traits with class conversion groups were observed.

Results

The baseline characteristics of the 874 patients who underwent 1748 echocardiograms during unique visits be-

Figure 1 Inclusion and Exclusion pathways leading to primary cohort. EF, ejection fraction; ICD-10, International Statistical Classification of Disease and Related Health Problems, 10th revision.



tween January 2018 and January 2020 across the EF spectrum, included an average age of 75 ± 13 years old. Males composed 54% of the cohort. Regarding race, 85% were Caucasian, 11% were African American, and 4% were other. In reference to baseline heart failure class, 24% were HFrEF, 61% were HFpEF, and 15% were HFmrEF. The mean time between EF assessments was 208.6 days and follow-up was greater than or equal to 1 day. Globally, increased EF was observed in 143 patients (16%); EF was noted to be stable in 560 patients (64%); EF was observed to be worsened in 171 patients (20%). *Table 1* lists patient characteristics based on EF class conversion group depending on HFIEF, HFwEF, or HFSEF. In the HFIEF group, 52% originated in the HFrEF group and 48% from the HFmrEF group. In the stable EF group, 71% originated from the HFpEF group, 5% from the HFmrEF group, and 24% from the HFrEF group. In the HFwEF group, 80% originated from

the HFpEF group and 20% originated from the HFmrEF (*Figure 2*).

There was a statistically significant difference in age between HFSEF (75.5 ± 1

2.9 years old) versus HFIEF (72.5 ± 14.2 years old) ($P = 0.04$). The average heart rate (HR) during the index stay was noted to be slightly higher in the HFIEF group (82 ± 12 b.p.m.) when compared with the HFSEF (78 ± 12 b.p.m.) ($P = 0.01$). Diastolic blood pressure of the HFwEF group was noted to be lower (68 ± 10 mmHg) compared with the HFIEF group (71 ± 11 mmHg) ($P = 0.04$). The number of days to the next echocardiogram was not statistically different across the three groups. On index visit, the group who was found to have stable EF on subsequent visit had a shorter length of stay (6.1 ± 7.0 days) than those who were found to be improved on next visit (7.7 ± 7.4 days) ($P = 0.04$).

Table 1 Baseline characteristics

Characteristic	HF class conversion group			P value		
	HFIEF (N = 143)	HFSEF (N = 560)	HFwEF (N = 171)	HFIEF × HFSEF	HFIEF × HFwEF	HFSEF × HFwEF
Age, years	72.5 (±14.2)	75.5 (±12.9)	76.0 (±12.5)	0.0373	0.0505	0.9158
Body mass index, kg/m ²	30.6 (±8.8)	30.1 (±8.7)	28.6 (±7.3)	0.8294	0.0862	0.0852
Vital signs						
SBP, mmHg	130 (±15)	132 (±17)	130 (±17)	0.5864	0.6565	0.9892
DBP, mmHg	71 (±11)	69 (±11)	68 (±10)	0.1412	0.0372	0.4756
Heart rate, b.p.m.	82 (±12)	78 (±12)	79 (±14)	0.0130	0.4038	0.3546
Respiratory rate, rpm	19 (±2)	19 (±2)	19 (±2)	0.4071	0.5791	0.9965
Haematology						
Haemoglobin, g/dL	11.6 (±2.0)	11.4 (±2.0)	11.3 (±2.0)	0.3308	0.2973	0.9130
RDW, %	15.1 (±2.1)	15.3 (±2.2)	15.0 (±2.0)	0.6633	0.9594	0.4058
Chemistry						
Sodium, mmol/L	138 (±3)	138 (±4)	139 (±3)	0.9656	0.1077	0.0491
Potassium, mmol/L	4.1 (±0.4)	4.1 (±0.4)	4.2 (±0.4)	0.7534	0.4825	0.0618
Carbon dioxide, mmol/L	27 (±3.5)	27 (±3.7)	27 (±3.6)	0.9820	0.9032	0.9298
Blood urea nitrogen, mg/dL	30 (±19)	29 (±16)	32 (±20)	0.4917	0.6816	0.0554
Creatinine, mg/dL	1.79 (±1.64)	1.74 (±1.71)	1.99 (±2.13)	0.9386	0.5893	0.2301
eGFR, mL/min/1.73 m ²	51 (±27)	52 (±26)	51 (±30)	0.9133	0.9992	0.8783
Calcium, mg/dL	8.6 (±0.4)	8.6 (±0.5)	8.6 (±0.5)	0.6259	0.9470	0.8297
Magnesium, mg/dL	2.1 (±0.3)	2.1 (±0.3)	2.1 (±0.3)	0.8968	0.6270	0.2139
Phosphorous, mg/dL	3.6 (±1.0)	3.6 (±1.1)	3.7 (±1.1)	0.9825	0.7494	0.5090
Troponin I, me (IQR), ng/mL	0.07 (0.39)	0.06 (0.29)	0.06 (0.28)	0.9539	0.9217	0.9816
Pro-BNP, ng/mL	12 150 (±19 554)	6671 (±10 525)	10 447 (±20 886)	0.0072	0.7161	0.0694
Glucose, mg/dL	136 (±52)	129 (±43)	130 (±44)	0.1924	0.4812	0.9281
TSH, me (IQR), µIU/mL	1.70 (1.97)	2.00 (2.23)	2.34 (2.99)	0.8063	0.9966	0.8309
LVEF, %	39.0 (±8.2)	52.8 (±17.1)	56.8 (±9.3)	< 0.0001	< 0.0001	0.0042
Delta EF, me (IQR), %	16.4 (14.9)	0.1 (12.40)	19.8 (15.1)	< 0.0001	< 0.0001	< 0.0001
Visit 1 length of stay, days	7.7 (±7.4)	6.1 (±7.0)	6.6 (±6.9)	0.0353	0.2900	0.7584
Echo1/Echo2 interval, days	199.1 (±163.2)	210.1 (±172.0)	211.6 (±170.7)	0.5871	0.6128	0.5943
Characteristic	HF class conversion group			P value		
	HFIEF (N = 143)	HFSEF (N = 560)	HFwEF (N = 171)			
Sex, n (%)				0.3262		
Female	59 (41.3)	267 (47.7)	75 (43.9)			
HF clinic establishment, n (%)	21 (14.7)	81 (14.5)	21 (12.3)	0.7522		

Values are presented in means ± SD unless otherwise indicated. Items in bold indicate statistically significant values.

Continuous data were compared by one-way analysis of variance. Categorical data were compared by 3-group Pearson's χ^2 test.

b.p.m., beats per minute; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFIEF, heart failure with improved ejection fraction; HFSEF, heart failure with stable EF; HFwEF, heart failure with worsened EF; LVEF, left ventricular ejection fraction; IQR, interquartile range; me, median; mmHg, millimetre of mercury; pro-BNP, pro-B-type natriuretic peptide; RDW, red blood cell distribution width; rpm, respirations per minute; SBP, systolic blood pressure; TSH, thyroid stimulating hormone.

Figure 2 Proportion of baseline EF classes among follow-up conversion class. HFIEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced or mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFReF, heart failure with reduced ejection fraction; HFwEF, heart failure with worsened ejection fraction; HFSEF, heart failure with stable ejection fraction.

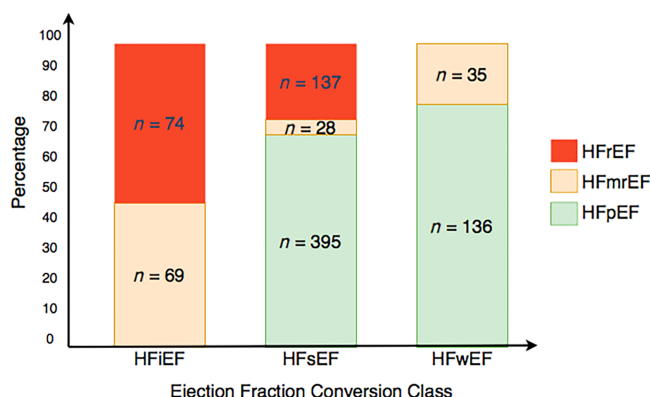


Table 2 Baseline Elixhauser co-morbidity measures

	HFIEF (N = 143)	HFSEF (N = 560)	HFwEF (N = 171)	P value
ECM score, mean (SD)	22.1 (±13.9)	22.9 (±12.4)	23.9 (±12.3)	>0.0500
Health condition(s), index only, n (%)				
Congestive heart failure	143 (100)	560 (100)	171 (100)	0.0000
Valvular disease	85 (59)	354 (63)	109 (64)	0.6729
Pulmonary circulation disorders	22 (15)	69 (12)	22 (13)	0.6218
Peripheral vascular disorders	67 (47)	285 (51)	93 (54)	0.4130
Hypertension	121 (85)	493 (88)	149 (87)	0.5468
Paralysis	21 (15)	91 (16)	25 (15)	0.8228
Neurodegenerative disorders	58 (41)	239 (43)	87 (51)	0.1127
Chronic pulmonary disease	76 (53)	314 (56)	92 (54)	0.7596
Diabetes, uncomplicated	39 (27)	143 (26)	45 (26)	0.9086
Diabetes, complicated	15 (11)	66 (12)	12 (7)	0.2084
Hypothyroidism	18 (13)	58 (10)	23 (14)	0.4681
Renal failure	85 (60)	337 (60)	113 (66)	0.3415
Liver disease	19 (13)	93 (17)	28 (16)	0.6208
Peptic ulcer disease, excluding bleeding	16 (11)	37 (7)	18 (11)	0.0886
AIDS/HIV	1 (1)	1 (0)	2 (1)	0.2184
Lymphoma	5 (4)	22 (4)	4 (2)	0.6161
Metastatic cancer	13 (9)	15 (3)	7 (4)	0.0023
Solid tumour without metastasis	26 (18)	82 (15)	30 (18)	0.4572
Coagulopathy	38 (27)	174 (31)	54 (32)	0.5434
Rheumatoid arthritis/collagen vascular diseases	12 (8)	56 (10)	23 (14)	0.2982
Obesity	57 (40)	191 (34)	48 (28)	0.0875
Weight loss	34 (24)	128 (23)	52 (30)	0.1295
Fluid and electrolyte disorders	30 (21)	146 (26)	42 (25)	0.4506
Blood loss anaemia	18 (13)	42 (8)	22 (13)	0.0387
Deficiency anaemia	98 (69)	388 (69)	126 (74)	0.4994
Alcohol abuse	18 (13)	70 (13)	23 (14)	0.9471
Drug abuse	17 (12)	55 (10)	17 (10)	0.7613
Psychoses	12 (8)	37 (7)	22 (13)	0.0319
Depression	43 (30)	176 (31)	71 (42)	0.0340

Values are presented in means ± SD unless otherwise indicated. Items in bold indicate statistically significant values.

Continuous data were compared by one-way analysis of variance. Categorical data were compared by 3-group Pearson's χ^2 test.

AIDS, acquired immunodeficiency syndrome; ECM, Elixhauser Co-morbidity Measure; HFIEF, heart failure with improved ejection fraction; HFSEF, heart failure with stable EF; HFwEF, heart failure with worsened EF; HIV, human immunodeficiency virus.

Regarding co-morbidity patterns, most co-morbidities were not significantly associated with EF shift, with a few exceptions (Table 2). The HFSEF group was less likely to carry an established diagnosis of blood loss anaemia versus

the HFIEF or HFwEF groups ($\chi^2(df = 2, n = 874) = 6.50, P = 0.04$) (Figure 3). The HFwEF group was more likely to carry an established diagnosis of depression on index visit compared with the HFSEF or HFIEF groups ($\chi^2(df = 2,$

Figure 3 Analysis of means for proportions – statistically significant ECM categories. HFIEF, heart failure with improved ejection fraction; HFwEF, heart failure with worsened ejection fraction; HFSEF, heart failure with stable ejection fraction.

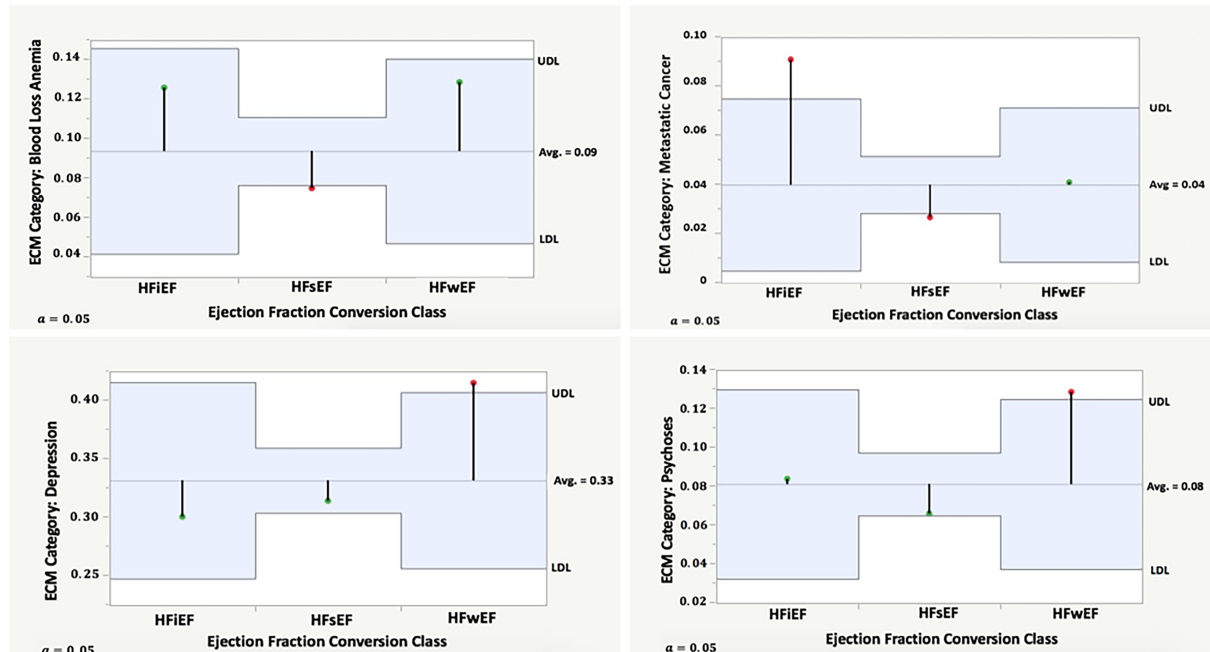


Table 3 Prevalence of guideline-directed medical therapy orders during index hospitalization

Pharmacologic class/medication, n (%)	HFIEF (N = 143)	HFSEF (N = 560)	HFwEF (N = 171)	P value
ACEi/ARB	69 (48)	270 (48)	69 (40)	0.1681
ARNI	13 (9)	22 (4)	7 (4)	0.0322
Beta-blocker	127 (89)	453 (81)	144 (84)	0.0705
Diuretic	77 (54)	246 (44)	68 (40)	0.0814
Isosorbide dinitrate/hydralazine	16 (11)	77 (14)	23 (14)	0.7207
Aldosterone antagonist	30 (21)	86 (15)	22 (13)	0.1304

Values are presented in means \pm SD unless otherwise indicated.

Continuous data were compared by one-way analysis of variance. Categorical data were compared by 3-group Pearson's χ^2 test.

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFIEF, heart failure with improved ejection fraction; HFSEF, heart failure with stable EF; HFwEF, heart failure with worsened EF.

$n = 874$) = 6.76, $P = 0.03$) (Figure 3). Similarly, an established diagnosis of a wide spectrum of psychiatric illnesses inclusive of bipolar disorders, dysthymia, cyclothymia, schizoaffective disorders, and schizophrenia was more likely to be seen in patients with HFwEF as opposed to the other two groups ($\chi^2(df = 2, n = 874) = 6.89, P = 0.03$) (Figure 3). Metastatic disease was more likely to have been established in HFIEF and less likely to be established in HFSEF ($\chi^2(df = 2, n = 874) = 12.19, P = 0.002$) (Figure 3). ECM scores between HF groups were not significantly different.

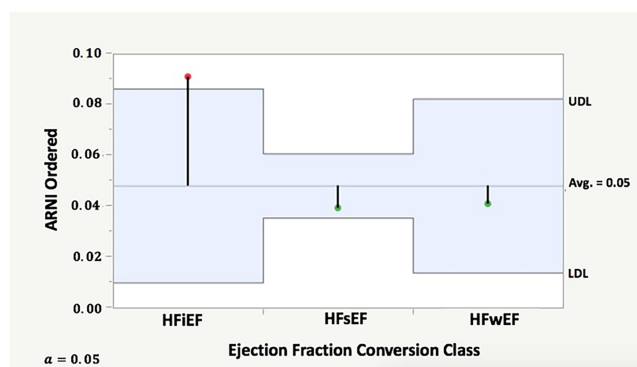
In the HFIEF group, a significantly higher pro-BNP level ($12\ 150 \pm 19\ 554$ pg/mL) was noted when compared with the HFSEF group ($6671 \pm 10\ 525$ pg/mL) ($P = 0.007$). Serum sodium levels were found higher in HFwEF (139 ± 3 mmol/L) when compared with HFSEF (138 ± 4 mmol/L) ($P = 0.05$).

Additional serum chemistries, troponin I, and haemogram studies were not significantly different among classes (Table 1). Separately, the prevalence of GDMT orders is listed in Table 3. Angiotensin receptor-neprilysin inhibitor (ARNI) orders during index visit were more likely to be seen in the HFIEF group ($\chi^2(df = 2, n = 874) = 6.87, P = 0.03$) (Figure 4). Otherwise, there was no significant difference in medication prescribing across medication classes.

Discussion

Heart failure clinical course is indeed individualized and LV function may oscillate between a wide spectra of EF values.

Figure 4 Analysis of means for proportions – statistically significant medications. ARNI, angiotensin receptor-neprilysin inhibitor; HFIEF, heart failure with improved ejection fraction; HFwEF, heart failure with worsened ejection fraction; HFSEF, heart failure with stable ejection fraction.



Eminent threats imposing downward class conversions are of value to identify, study, risk stratify against, and ultimately prevent. These temporal conversions from one EF class to another frequently occur in clinical practice. Therefore, this study aimed to identify associations between easily accessible data points including medical history, medication usage, biomarker evaluation, and echocardiographic outcomes. Briefly, results show that despite similar objective ECM scores, index visit serum laboratory values, and GDMT usage across the EF spectrum, salient differences among conversion classes were observed.

Co-morbidity burden

Heart failure with worsened EF, on index visit, more frequently carried an established diagnosis of psychiatric illness such as major depressive disorder. This suggests an association between short and medium-term changes in LV function and affect disorders. Depression, especially common in hospitalized patients with HF, has shown to be independently associated with poor self-care.¹⁶ The term 'self-care' is broad and encompasses many aspects of HF maintenance. These include behaviours such as dietary restrictions, medication adherence, and HF symptom recognition. Self-care also includes dynamic HF management behaviours such as maintaining adequate communication with one's provider and follow-up. These important behaviours, in conjunction with the ability to understand the nuances of HF and cope with its facets, are foundational. Developing treatment plans tailored to address the cumulative culprits of self-care deterioration including depression, heightened anxiety, stress, and lack of social support is warranted. This, coupled with GDMT and the reinforcement of good self-care behaviours, may have the potential to mitigate downward trajectories in EF.

Additionally, there was a lower prevalence of chronic blood loss anaemia and metastatic disease in the HFSEF group and, paradoxically, a higher prevalence of metastatic disease in

the HFIEF group. It is known that anaemia is independently associated with HF disease severity and lack of this co-morbid condition is not surprisingly associated with EF stability.⁴ The increased prevalence of metastatic disease in HFIEF when compared with HFSEF and HFwEF has an unclear explanation. This may be due to close follow-up, frequent provider surveillance, and therefore multiple opportunities to evaluate for good HF maintenance. Although there was no statically significant correlation, a trend reflecting the highest ECM scores in HFwEF and the lowest ECM scores in HFIEF was observed.

Biomarker dysregulation

The HFSEF group had significantly lower average inpatient sodium levels than the HFwEF group. A prior abstract demonstrated a protective effect (odds ratio <1) against the composite outcome of hospital death and hospice discharge for HF patients with average serum sodium levels between 134–142 mmol/L.¹² These outcomes were not studied in this analysis, and these minor variances may be related to inter-provider management differences in fluid restriction and diuresis strategies.

Medical therapy

The HFwEF group, when compared with the HFIEF group, was older and had lower mean diastolic blood pressures on index visit. Prior literature has demonstrated an association with lower diastolic blood pressure values and increased risk for adverse cardiovascular outcomes. This has previously been studied by evaluating HFpEF outcomes including death and cardiovascular death.¹⁷ The stable EF group had significantly lower average heart rates and pro-BNP levels during index visit and left the hospital 1.6 days earlier than HFIEF. Although there was no statistically significant difference in inpatient GDMT orders between these two groups, these find-

ings may reflect GDMT chronicity, tolerance, and dose titration levels which were likely higher in the HFseEF group.

Echocardiographic measurements

In the longitudinal evaluation of HF patients, important attention should be directed towards the accurate reproducibility of EF measurements. To capture clinically significant EF shifts, only patients admitted or readmitted to the hospital were studied. However, in the era of chemotherapy-related cardiac dysfunction, implantable defibrillators, and cardiac resynchronization therapy, precise reproducibility of EF measurements will affect inpatients and outpatients alike. Although the gold standard for LVEF evaluation is cardiac magnetic resonance imaging (CMR), a practical and commonly utilized modality is transthoracic echocardiography. Interobserver variability of echocardiography is significantly reduced with the use of ultrasound-enhancing agents, which provides similar intraclass correlation coefficients seen with CMR.¹⁸

Evolving taxonomy

In addition to the recent introduction of the term HFmrEF, proposed by Lam and Solomon,¹⁹ two additional transition phenotypes have also sparked interest: HFrecEF-recovered (HFrecEF), (classified here as HFief), and HFpEF-declined (classified here within HFwEF).²⁰ These two classes, at a certain point in time, may exhibit the same LVEF. However, they likely differ in pathophysiology and clinical outcomes.

A study published in *JAMA Cardiology* by Kalogeropoulos *et al.*²¹ showed that in the outpatient setting, HFrecEF (HFief) patients were found to have different clinical courses than HFpEF or HFrecEF; with less frequent hospitalizations and lower mortality. Another study of HF patients followed with echocardiography over 15 years demonstrated high mortality in patients who showed earlier deterioration of LVEF.⁶ A recent medium-term study performed by Savarese *et al.*²² identified important resiliency factors associated with longitudinal increases in EF. Echocardiogram intervals ranged from 6 months to 3 years. These factors include the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), female sex, indicators of less severe HF (New York Heart Association Class I-II), specialized HF follow-up, the absence of ischaemic heart disease, and the presence of several other modifiable co-morbidities (anaemia and atrial fibrillation) and preserved renal function.

Despite being mentioned in the existing literature and alluded to in current guidelines, management of these subtypes is not well established and requires further investigation. Analyses between HF sub-types may help reveal risk and resiliency patterns to refine patient-centric diagnosis, prognosis, and prediction of treatment response.

Conclusions

In supplement to a gap in the literature, we studied several non-cardiac co-morbidities including psychiatric illness, hematologic conditions, neurocognitive disorders, and liver disease, among others. Specifically, it was of special interest to identify covariates associated with HFwEF, a subgroup previously identified to have poorer outcomes.⁶ In contrast to Savarese *et al.*, this study found the absence of chronic blood loss anaemia to be associated with stable EF. Our data show that distinct psychiatric co-morbidity patterns, inclusive of diagnoses such as major depressive disorder, schizophrenia, and bipolar disorder, were associated with worsening EF class upon follow-up visit. These may reflect amendable targets which may have the potential to mitigate functional and prognostic outcomes.

It was shown, in the absence of statistical significance, that ECM scores were the highest in the HFwEF group and the lowest in the HFief group. Perhaps with a larger patient population, this finding may yield statistical significance, supporting the notion that a higher co-morbidity burden may be a risk factor for worsening EF over time. Separately, HFief patients were observed to have a significantly higher pro-BNP level on index stay when compared with the HFseEF group, hypothesized to be secondary to haemostatic dysregulation en route to the clinical plateau reached at a state of 'healthy' or stable HF.

Ultimately, there has been a call for forthcoming HF studies to include repeated EF measurements of all-comers HF patients to be able to identify patterns of EF class conversions and the clinical determinants of such changes. This study responds to that call by identifying salient differences across EF class conversion groups inclusive of both the individual and summative impact (or lack thereof) of MCC, biomarker dysregulation, and the presence of GDMT. Although further investigations are needed to evaluate the plausible mechanisms related to these changes, this study yields practical markers of myocardial resiliency and vulnerability. The prognostic significance of such changes appears more feasible at this juncture and dedicated studies evaluating measurements related to quality of life, functionality, hospital readmissions, and mortality are the next steps in this field of HF.

Limitations

Regarding limitations, no CMR LVEF calculations were obtained in this study. Anthropometrics, vital signs, and laboratory data were obtained from only the first visit and are averaged throughout the entire stay. Selection bias is a major limitation of the study given the scarcity of extractable pharmacologic data. This reduced the cohort size substantially, which is subject to potential confounding. Additionally,

GDMT dosing data and New York Heart Association functional classes were not available.

Despite a relatively short maximum period between echocardiogram 1 and 2, ICD codes of patients evaluated in this study were indexed to a medical record number and not visit identification numbers, therefore potentially overlooking co-morbidities acquired between echocardiogram 1 and 2. Also, various ICD codes may indeed be indicative of a patient with HF which may not have been included in the ECM categories. Importantly, it is not specified whether visit one was the patient's first heart failure hospitalization, in which the patient would be potentially naïve to GDMT. These patients, expectedly, would likely have a substantial improvement in EF in comparison with those admitted for a chronic heart failure relapse.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline Characteristics¹.

Table S2. Baseline Elixhauser Comorbidity Measures².

Table S3. Prevalence of Guideline-Directed Medical Therapy Orders During Index Hospitalization³.

References

- Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail.* 2020; **22**: 1342–1356.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Böhm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021; **42**: 3599–3726.
- Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, Backs J, Bauersachs J, Burkhoff D, Bonow RO, Chopra VK, De Boer RA, De Windt L, Hamdani N, Hasenfuss G, Heymans S, Hulot JS, Konstam M, Lee RT, Linke WA, Lunde IG, Lyon AR, Maack C, Mann DL, Mebazaa A, Mentz RJ, Nihoyannopoulos P, Papp Z, Parissis J, Pedrazzini T, Rosano G, Rouleau J, Seferovic PM, Shah AM, Starling RC, Tocchetti CG, Trochu JN, Thum T, Zannad F, Brutsaert DL, Segers VF, De Keulenaer GW. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J.* 2019; **40**: 2155–2163B.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld JA, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol.* 2017; **70**: 776–803.
- Goyal P, Loop M, Chen L, Brown TM, Durant RW, Safford MM, Levitan EB. Causes and temporal patterns of 30-day readmission among older adults hospitalized with heart failure with preserved or reduced ejection fraction. *J Am Heart Assoc.* 2018; **7**: 1–9.
- Lupón J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, López-Ayerbe J, Domingo M, Núñez J, Zamora E, Moliner P, Díaz-Ruata P, Santesmases J, Bayés-Genís A. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol.* 2018; **72**: 591–601.
- Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen S, Jankowska EA, Atar D, Butler J, Fiuzat M. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction Robert. *J Am Coll Cardiol [Internet].* 2014; **64**: 2281–2293.
- Formiga F, Moreno-Gonzalez R, Chivite D, Franco J, Montero A, Corbella X. High comorbidity, measured by the Charlson comorbidity index, associates with higher 1-year mortality risks in elderly patients experiencing a first acute heart failure hospitalization. *Aging Clin Exp Res [Internet].* 2018; **30**: 927–933.
- Tamaki S, Yamada T, Morita T, Furukawa Y, Iwasaki Y, Kawasaki M, Kikuchi A, Kawai T, Seo M, Ikeda I, Fukuhara E, Abe M, Nakamura J, Kayama K, Tanabe K, Kawahira M, Fukunami M. Prognostic value of Charlson comorbidity index in patients admitted for acute decompensated heart failure with reduced or preserved left ventricular ejection fraction: a prospective study. *J Am Coll Cardiol [Internet].* 2018; **71**: A829.
- Simard M, Sirois C, Candas B. Validation of the combined comorbidity index of Charlson and Elixhauser to predict 30-day mortality across ICD-9 and ICD-10. *Med Care.* 2018; **56**: 441–447.
- Daubert MA, Adams K, Yow E, Barnhart HX, Douglas PS, Rimmer S, Norris C, Cooper L, Leifer E, Desvigne-Nickens P, Anstrom K, Fiuzat M, Ezekowitz J, Mark DB, O'Connor CM, Januzzi J, Felker GM. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFREF. *JACC Hear Fail.* 2019; **7**: 158–168.
- Abdelal QK, Conte J, Lorenzo C, George J, Wiese-Rometsch W. A method to personalize blood chemistry reference intervals: getting to patient-centric laboratory medicine using electronic medical record data in chronic heart failure patients. *J Card Fail [Internet].* 2020; **26**: S121.
- De Groote P, Fertin M, Pentiah AD, Goémine C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β -blocker therapy. *Circ Heart Fail.* 2014; **7**: 434–439.
- Basuray A, Fang JC. Management of patients with recovered systolic function. *Prog Cardiovasc Dis [Internet].* 2016; **58**: 434–443.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015; **16**: 233–271.
- Freedland KE, Skala JA, Steinmeyer BC, Carney RM, Rich MW. Effects of depres-

- sion on heart failure self-care. *J Card Fail.* 2021; **27**: 522–532.
17. Sandesara PB, O'Neal WT, Kelli HM, Topel M, Samman-Tahhan A, Sperling LS. Diastolic blood pressure and adverse outcomes in the TOPCAT (treatment of preserved cardiac function heart failure with an aldosterone antagonist) trial. *J Am Heart Assoc.* 2018; **7**: e007475.
 18. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M, Choy J, Gaibazzi N, Gillam LD, Janardhanan R, Kutty S, Leong-Poi H, Lindner JR, Main ML, Mathias W, Park MM, Senior R, Villanueva F. Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography guidelines update. *J Am Soc Echocardiogr.* 2018; **31**: 241–274.
 19. Bayés-Genís A, Núñez J, Lupón J. Heart failure with mid-range ejection fraction: a transition phenotype? *Eur J Heart Fail.* 2017; **19**: 1635–1637.
 20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013; **128**: e240–e327.
 21. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol.* 2016; **1**: 510–518.
 22. Savarese G, Vedin O, D'Amario D, Uijl A, Dahlström U, Rosano G, Lam CSP, Lund LH. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. *JACC Hear Fail.* 2019; **7**: 306–317.