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ORIGINAL ARTICLE

Role of ejection fraction in patients at risk for advanced heart failure: insights from the HELP-HF registry

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Abstract

Aims Patients with heart failure (HF) with reduced ejection fraction (EF) (HFrEF), mildly reduced EF (HFmrEF), and preserved EF (HFpEF) may all progress to advanced HF, but the impact of EF in the advanced setting is not well established. Our aim was to assess the prognostic impact of EF in patients with at least one 'I NEED HELP' marker for advanced HF.

Methods and results Patients with HF and at least one high-risk 'I NEED HELP' criterion from four centres were included in this analysis. Outcomes were assessed in patients with HFrEF (EF $\leq$ 40%), HFmrEF (EF 41–49%), and HFpEF (EF $\geq$ 50%) and with EF analysed as a continuous variable. The prognostic impact of medical therapy for HF in patients with EF $<$ 50% and EF $>$ 50% was also evaluated. All-cause death was the primary endpoint, and cardiovascular death was a secondary endpoint. Among 1149 patients enrolled [mean age 75.1 ± 11.5 years, 67.3% males, 67.6% hospitalized, median follow-up 260 days (inter-quartile range 105–390 days)], HFrEF, HFmrEF, and HFpEF were observed in 699 (60.8%), 122 (10.6%), and 328 (28.6%) patients, and 1 year mortality was 28.3%, 26.2%, and 20.1, respectively (log-rank P = 0.036). As compared with HFrEF patients, HFpEF patients had a lower risk of all-cause death [adjusted hazard ratio (HR_{adj}) 0.67, 95% confidence interval (CI) 0.48–0.94, P = 0.022], whereas no difference was noted for HFmrEF patients. After multivariable adjustment, a lower risk of all-cause death (HR_{adj} for 5% increase 0.94, 95% CI 0.89–0.99, P = 0.017) and cardiovascular death (HR_{adj} for 5% increase 0.94, 95% CI 0.88–1.00, P = 0.049) was observed at higher EF values. Beta-blockers and renin–angiotensin system inhibitors or sacubitril/valsartan were associated with lower mortality in both EF $<$ 50% and EF $\geq$ 50% groups.

Conclusions Among patients with HF and at least one 'I NEED HELP' marker for advanced HF, left ventricular EF is still of prognostic value.

Keywords Heart failure; Advanced heart failure; Ejection fraction; HFpEF; HFrEF; HFmrEF

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Introduction

Heart failure (HF) represents a major cause of morbidity and mortality worldwide.[1] As the disease progresses, patients experience more severe symptoms and need multiple hospitalizations and the prognosis worsens, eventually leading to long-term heart replacement therapies (i.e. heart transplantation or left ventricular assist device), if indicated. 'Advanced'

HF describes a clinical syndrome characterized by persistent or progressive symptoms despite maximal guideline-directed medical therapy (GDMT).[1] It is estimated that 1–10% of the overall HF population is in the 'advanced' disease stage.[2–4] The prevalence of advanced HF is progressively increasing, due to better treatment and hence survival of HF patients, yet prognosis remains poor and therapeutic options are limited in the advanced stage.[5–8] To timely identify patients with HF and a high risk of progression to an advanced stage, the 'I NEED HELP' screening tool has been proposed, which integrates nine markers on clinical history, hospitalizations, and medication intolerance, in addition to symptoms and end-organ dysfunction.[2,9,10] The 'I NEED HELP' criteria are now widely used to define high-risk HF patients.[11,12] Patients with HF with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) may all progress to the advanced HF stage, although these patients have different phenotypes.[2,3] Classification of the patients with HF remains based on left ventricular ejection fraction (LVEF).[1] However, its role is limited in specific settings such as that of the patients hospitalized for acute HF.[13–16] The role of LVEF in patients with signs of advanced HF remains, however, unclear.

In this study, we compared the clinical characteristics and outcomes of patients with HFrEF, HFmrEF, and HFpEF enrolled in a real-world, contemporary, multicentre registry of patients with HF and at least one high-risk marker for advanced HF.

Methods

Study design

The design of the observational, retrospective, multicentre HELP-HF (Assessment of the I NEED HELP markers in HF) registry was already described.[17] In brief, all consecutive patients who were hospitalized for acute HF or were evaluated as outpatients for chronic HF at four Italian high-volume centres between 1 January 2020 and 30 November 2021 and had at least one 'I NEED HELP' high-risk marker were included in the registry. In line with current guidelines,[1] patients were classified as having HFrEF (LVEF $\leq$ 40%), HFmrEF (LVEF 41–49%), and HFpEF (LVEF $\geq$ 50%) according to the LVEF value at inclusion determined by echocardiography.

Anonymized individual patient data on medical history, clinical presentation, medical therapy, echocardiographic and laboratory findings, medical therapy, and clinical outcomes were collected. Institutional review board approval was waived for this study because of its retrospective design with collection of anonymized data and without any study-specific intervention. Follow-up was performed by means of medical records (rehospitalizations or outpatient visits) or phone contact.

Study endpoints

The primary endpoint of this study was all-cause mortality. Secondary endpoints were the composite of all-cause mortality or first HF hospitalization, cardiovascular (CV) mortality, and first HF hospitalization.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median [inter-quartile range (IQR)], as appropriate, and were compared with the one-way ANOVA test or the Kruskal–Wallis test, respectively. Categorical variables are presented as number and percentages and were compared with the χ^2 test. Baseline characteristics, clinical presentation, medical therapy, echocardiographic data, laboratory data, and clinical outcomes were compared between patients with HFrEF vs. HFmrEF vs. HFpEF. The first occurrence of all-cause mortality, the composite endpoint, and CV mortality was evaluated using the Kaplan–Meier method and compared between groups using the log-rank test. The occurrence of first HF hospitalization in patients with HFrEF vs. HFmrEF vs. HFpEF was evaluated using the Fine–Gray method to account for the competing risk of mortality and was plotted using the cumulative incidence function. For all endpoints, follow-up was evaluated at the date of the event or the last available follow-up. Cox proportional hazards regression analysis was also performed to assess the prognostic impact of LVEF as a continuous variable (per 5% increase) and LVEF categories (HFrEF vs. HFmrEF vs. HFpEF) on all-cause mortality, CV mortality, and the composite endpoint. The Fine–Gray proportional subdistribution hazard model was used to assess the impact of LVEF on first HF hospitalization, accounting for the competing risk of mortality. The impact of LVEF on the primary and secondary endpoints was evaluated by means of univariable and multivariable analyses. The multivariable models included all the covariates of the previously validated models.[17] Results of the Cox regression analyses are reported as unadjusted or adjusted hazard ratio (HR) and 95% confidence interval (CI). Results of the Fine–Gray models are reported as unadjusted or adjusted subhazard ratio (SHR) with 95% CI. The continuous association between the incidence rates of all-cause mortality, CV mortality, and the composite endpoint and LVEF as a continuous variable was assessed by restricted cubic splines with three knots, resulting in the lowest model Akaike information criterion (three to six knots were assessed). To evaluate the predictors of all-cause mortality in patients with LVEF $<$ 50% and in those with LVEF $\geq$ 50%, univariable and multivariable Cox regression analyses were performed separately in these two groups. Covariates with univariable P value $<$0.10 and other covariates considered to be clinically relevant (e.g. age and sex) were included in the multivariable models. The impact of prescribed

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GDMT at inclusion on all-cause mortality was also evaluated in the LVEF $<$ 50% and LVEF $\geq$ 50% groups by means of univariable Cox regression analysis and subsequent adjustment in the same multivariable models. Regarding GDMT, the use and prescribed doses of the following treatments were evaluated: beta-blockers; angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), or angiotensin receptor neprilysin inhibitor (ARNI); and mineralocorticoid receptor antagonist (MRA).

All reported *P* values are two-sided, and a $P < 0.05$ was considered statistically significant.

Statistical analyses were performed with STATA Version 13.0 (StataCorp, College Station, TX).

Results

The HELP-HF registry included 1149 patients with HF and at least one 'I NEED HELP' high-risk marker. The mean age was 75.1 ± 11.5 years, 67.3% of patients were males, and 67.6% of patients were enrolled as inpatients. Median LVEF of the study population was 35% (IQR 25–50%). A total of 699 patients (60.8%) had HFrEF, 122 patients (10.6%) had HFmrEF, and 328 patients (28.6%) had HFpEF.

Patients' characteristics

Baseline characteristics are reported in *Table 1*. As compared with the other two categories, patients with HFrEF were younger, more frequently men, and more likely to be included as inpatients. They also had more frequent history of prior myocardial infarction, prior percutaneous coronary intervention (PCI), and prior implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy with defibrillator implantation. On the contrary, HFpEF patients were more likely to have New York Heart Association Class III–IV, hypertension, history of atrial fibrillation, and prior valve surgery. Patients with HFrEF presented more frequently in cardiogenic shock or acute pulmonary oedema and needed more frequently inotropes/vasopressor, temporary mechanical circulatory support, mechanical ventilation, and intensive care unit (ICU) admission, as compared with the others. Advanced HF according to the 2018 Heart Failure Association of the European Society of Cardiology (HFA-ESC) definition was more frequently observed in HFrEF patients as compared with HFmrEF or HFpEF patients.

Details on medical therapy for HF prescribed at inclusion are reported in *Table 1*. Both beta-blockers and ACEi/ARB/ARNI were less frequently used and prescribed at lower doses in patients with HFpEF, whereas MRAs were less commonly prescribed in the HFmrEF group.

Echocardiographic and laboratory findings are reported in *Table 2*. Median LVEF was 27% (IQR 20–34%), 45% (IQR 43–46%), and 55% (IQR 52–60%) in the HFrEF, HFmrEF, and HFpEF groups, respectively. As compared with the others, patients with HFrEF had more frequently moderate or severe mitral regurgitation and right ventricular dysfunction. Conversely, moderate or severe tricuspid regurgitation was more common in HFpEF patients. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels were significantly higher in patients with HFrEF, whereas estimated glomerular filtration rate (eGFR) was similar between the three groups. Haemoglobin and liver enzymes were slightly higher in the HFrEF group.

Clinical outcomes according to left ventricular ejection fraction categories and prognostic impact of left ventricular ejection fraction

After a median follow-up of 260 days (IQR 105–390 days), 265 patients (23.1%) died for any cause, 179 patients (15.6%) died for CV causes, a first HF hospitalization occurred in 308 patients (26.8%), and a composite outcome event of all-cause death or HF hospitalization occurred in 496 patients (43.2%). The 1 year Kaplan–Meier estimated rates of all-cause death were 28.3% in patients with HFrEF, 26.2% in those with HFmrEF, and 20.1% in those with HFpEF, with a significantly lower unadjusted risk in HFpEF patients as compared with the others (crude HR for HFpEF vs. HFrEF 0.69, 95% CI 0.51–0.92, $P = 0.012$; crude HR for HFmrEF vs. HFrEF 0.98, 95% CI 0.67–1.45, $P = 0.921$; log-rank $P = 0.036$; *Figure 1A*). Among the 777 patients included during their index hospitalization, in-hospital death was similar between patients with HFrEF (12.7%), HFmrEF (14.9%), and HFpEF (8.8%; $P = 0.247$). When evaluating LVEF as a continuous variable, a lower unadjusted risk of all-cause mortality was observed at increasing LVEF values (crude HR for 5% LVEF increase 0.94, 95% CI 0.90–0.98, $P = 0.004$; *Figure 2A*). The 1 year Kaplan–Meier estimated rates of CV death were 20.5% in patients with HFrEF, 17.1% in those with HFmrEF, and 12.3% in those with HFpEF, with a lower unadjusted risk observed in HFpEF patients (crude HR for HFpEF vs. HFrEF 0.64, 95% CI 0.45–0.92, $P = 0.015$; crude HR for HFmrEF vs. HFrEF 0.84, 95% CI 0.51–1.38, $P = 0.493$; log-rank $P = 0.049$; *Figure 1B*). A significant association between LVEF as a continuous variable and CV mortality was observed (crude HR for 5% LVEF increase 0.92, 95% CI 0.87–0.97, $P = 0.001$; *Figure 2B*). The risk of the composite of all-cause death or HF hospitalization and of first HF hospitalization alone (evaluated at competing-risk analysis) was not significantly different between the HFrEF, HFmrEF, and HFpEF groups (*Figure 1C*, Supporting Information, *Figure S1*, and *Table 3*). Similarly, LVEF as a continuous variable did not have a significant impact on the composite endpoint and on HF hospitalization alone (*Figure 2C* and *Table 3*).

After multivariable adjustment for relevant covariates (*Table 3*), HFpEF was independently associated with a lower

Table 1 Baseline characteristics, clinical presentation, and medical therapy at inclusion

	Overall (n = 1149)	HFrEF (LVEF ≤ 40%) (n = 699)	HFmrEF (LVEF 41–49%) (n = 122)	HFpEF (LVEF ≥ 50%) (n = 328)	P value
Age (years)	75.1 ± 11.5	73.2 ± 11.7	76.5 ± 11.7	78.5 ± 10.1	<**0.001**
Male sex	773 (67.3)	529 (75.7)	78 (63.9)	166 (50.6)	<**0.001**
BMI (kg/m^2)	25.7 (22.9–29.4)	25.6 (23.0–29.1)	25.8 (23.0–29.4)	26.1 (22.5–30.9)	0.868
New-onset HF	187 (16.3)	106 (15.2)	22 (18.0)	59 (18.0)	0.446
Time since HF diagnosis (months)	30 (3–84)	48 (5–111)	21 (2–69)	19 (2–48)	<**0.001**
HF hospitalization(s) during last year	415 (36.1)	264 (37.8)	49 (32.0)	112 (34.2)	0.529
NYHA Class III–IV	738 (64.2)	450 (64.4)	65 (53.3)	223 (68.0)	**0.015**
Type of inclusion					**0.004**
Outpatient visit	372 (32.4)	201 (28.8)	48 (39.3)	123 (37.5)	
Inpatient hospitalization	777 (67.6)	498 (71.2)	74 (60.7)	205 (62.5)	
Comorbidities					
Hypertension	817 (71.1)	467 (66.8)	94 (77.1)	256 (78.1)	<**0.001**
Dyslipidaemia	609 (53.0)	328 (54.7)	62 (50.8)	165 (50.3)	0.377
Diabetes	447 (38.9)	273 (39.1)	43 (35.3)	131 (39.9)	0.657
History of AF	641 (55.8)	355 (50.8)	73 (59.8)	213 (64.9)	<**0.001**
Prior myocardial infarction	380 (33.1)	284 (40.6)	37 (30.3)	59 (18.0)	<**0.001**
Prior PCI	336 (29.2)	242 (34.6)	37 (30.3)	57 (17.4)	<**0.001**
Prior CABG	171 (14.9)	114 (16.3)	17 (13.9)	40 (12.2)	0.214
Prior valve surgery	139 (12.1)	69 (9.9)	13 (10.7)	157 (17.4)	<**0.001**
Prior percutaneous valve intervention					<**0.001**
TAVR	28 (2.4)	14 (2.0)	2 (1.6)	12 (3.7)	
Mitral TEER	49 (4.3)	41 (5.9)	1 (0.8)	7 (2.1)	
Known cardiomyopathy	291 (25.3)	175 (25.0)	32 (36.2)	84 (25.6)	0.952
Prior myocarditis	22 (1.9)	16 (2.3)	2 (1.6)	4 (1.2)	0.493
Peripheral artery disease	205 (17.8)	126 (18.0)	21 (17.2)	58 (17.7)	0.973
Prior stroke or TIA	173 (15.1)	101 (14.5)	23 (18.9)	49 (14.9)	0.454
COPD	266 (23.2)	147 (21.0)	33 (27.1)	86 (26.2)	0.103
Chronic kidney disease	650 (56.6)	396 (56.7)	68 (55.7)	186 (56.7)	0.981
Dialysis	28 (2.4)	16 (2.3)	2 (1.6)	10 (3.1)	0.635
MCI or dementia	157 (13.7)	86 (12.3)	16 (13.1)	55 (16.8)	0.149
ADL or IADL impairment	339 (31.3)	199 (30.0)	37 (32.2)	103 (33.9)	0.475
Cardiac implantable electronic devices					<**0.001**
Pacemaker	167 (14.5)	59 (8.4)	33 (27.1)	75 (22.9)	
ICD	183 (15.9)	166 (23.8)	11 (9.0)	6 (1.8)	
CRT-D	168 (14.6)	151 (21.6)	12 (9.8)	5 (1.5)	
CRT-P	15 (1.3)	9 (1.3)	5 (4.1)	1 (0.3)	
Clinical presentation (at inclusion)					
Cardiogenic shock	153 (13.3)	122 (17.5)	13 (10.7)	18 (5.5)	<**0.001**
Acute pulmonary oedema	153 (13.3)	119 (17.0)	12 (9.8)	22 (6.7)	<**0.001**
Rales >1/3 lung fields	490 (42.7)	303 (43.4)	49 (40.2)	138 (42.1)	0.782
Peripheral oedema	673 (58.6)	370 (52.9)	84 (68.9)	219 (66.8)	<**0.001**
Systolic blood pressure (mmHg)	124 ± 26	120 ± 26	128 ± 24	129 ± 26	<**0.001**
Heart rate (b.p.m.)	79 ± 20	81 ± 22	74 ± 17	75 ± 17	<**0.001**
IV loop diuretics	778 (67.7)	489 (70.0)	75 (61.5)	214 (65.2)	0.096
Maximum furosemide dose (mg/day)	110 (0–500)	120 (0–500)	60 (0–500)	80 (0–500)	**0.027**
Use of inotropes/vasopressors	277 (24.1)	228 (32.6)	20 (16.4)	29 (8.8)	<**0.001**
Use of vasodilators	119 (10.4)	86 (12.3)	7 (5.7)	26 (7.9)	**0.021**
Need of temporary MCS					<**0.001**
IABP	40 (3.5)	39 (5.6)	1 (0.8)	0 (0.0)	
Impella	5 (0.4)	5 (0.7)	0 (0.0)	0 (0.0)	
VA-ECMO	3 (0.3)	3 (0.4)	0 (0.0)	0 (0.0)	
Need of mechanical ventilation					<**0.001**
Non-invasive	159 (13.8)	115 (16.5)	12 (9.8)	32 (9.8)	
Invasive	35 (3.1)	29 (4.2)	4 (3.3)	2 (0.6)	
Need of CRRT/ultrafiltration	45 (3.9)	27 (3.9)	9 (7.4)	9 (2.7)	0.079
Need of ICU admission	253 (22.0)	193 (27.6)	21 (17.2)	39 (11.9)	<**0.001**
HFA-ESC advanced HF definition					<**0.001**
4 criteria (advanced HF)	193 (16.8)	152 (21.8)	10 (8.2)	31 (9.5)	
3 criteria	215 (18.7)	134 (19.2)	15 (12.3)	66 (20.1)	
2 criteria	228 (19.8)	149 (21.3)	22 (18.0)	57 (17.4)	
1 criterion	273 (23.8)	159 (22.8)	32 (26.2)	82 (25.0)	
No criteria	240 (20.9)	105 (15.0)	43 (35.3)	92 (28.1)	
INTERMACS Profiles 1–3	104 (9.1)	85 (12.2)	7 (5.7)	12 (3.7)	<**0.001**
ACC/AHA Stage D	185 (16.1)	143 (20.5)	15 (12.3)	27 (8.2)	<**0.001**

(*Continues*)

Table 1 (continued)

	Overall (n = 1149)	HFrEF (LVEF ≤ 40%) (n = 699)	HFmrEF (LVEF 41–49%) (n = 122)	HFpEF (LVEF ≥ 50%) (n = 328)	P value
Medical therapy for HF (at inclusion)					
Beta-blockers	882 (76.9)	574 (82.2)	96 (79.3)	212 (64.6)	**<0.001**
Dose ≥50% target dose	438 (38.2)	287 (41.1)	54 (44.6)	97 (29.6)	**0.001**
Fraction of the target dose (%)	37 ± 35	41 ± 36	41 ± 35	28 ± 30	**<0.001**
ACEi/ARB/ARNI	585 (51.0)	381 (54.6)	68 (56.2)	136 (41.5)	**<0.001**
Dose ≥50% target dose	262 (22.9)	153 (21.9)	32 (26.5)	77 (23.6)	0.517
Fraction of the target dose (%)	25 ± 40	25 ± 36	28 ± 36	24 ± 48	0.619
MRA	630 (54.9)	416 (59.6)	56 (46.3)	158 (48.2)	**<0.001**
Dose ≥50% target dose	596 (52.0)	392 (56.2)	53 (43.8)	151 (46.2)	**0.002**
Fraction of the target dose (%)	47 ± 62	51 ± 64	42 ± 63	42 ± 57	**0.050**

Data are presented as n (%), mean ± standard deviation, and median (Q25–Q75). P values in bold are significant.
ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IABP, intra-aortic balloon pump; IADL, instrumental activities of daily living; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IV, intravenous; LVEF, left ventricular ejection fraction; MCI, mild cognitive impairment; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; TEER, transcatheter edge-to-edge repair; TIA, transient ischaemic attack; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 2 Echocardiographic data and laboratory findings

	Overall (n = 1149)	HFrEF (LVEF ≤ 40%) (n = 699)	HFmrEF (LVEF 41–49%) (n = 122)	HFpEF (LVEF ≥ 50%) (n = 328)	P value
Echocardiographic data					
LVEF (%)	35 (25–50)	27 (20–34)	45 (43–46)	55 (52–60)	**<0.001**
Moderate or severe MR	683 (61.3)	464 (68.2)	65 (55.6)	154 (48.4)	**<0.001**
RV dilatation	363 (34.4)	209 (33.0)	34 (30.1)	120 (38.7)	0.134
RV dysfunction	482 (43.4)	338 (50.1)	43 (36.4)	101 (31.8)	**<0.001**
Moderate or severe TR	585 (53.5)	335 (50.5)	64 (56.6)	186 (58.7)	**0.045**
PASP (mmHg)	45 (35–55)	45 (35–55)	42 (35–55)	45 (38–60)	**0.013**
CVP (mmHg)	10 (5–15)	10 (5–15)	5 (5–10)	10 (5–15)	**0.022**
Laboratory findings					
Creatinine (mg/dL)	1.48 (1.08–2.07)	1.51 (1.10–2.14)	1.37 (1.06–1.97)	1.44 (1.05–1.90)	0.060
eGFR CKD-EPI (mL/min/1.73 m^2)	41.9 (27.2–60.6)	42.4 (27.3–60.8)	44.4 (26.6–61.6)	40.9 (27.3–57.3)	0.624
Urea (mg/dL)	69 (47–109)	69 (46–109)	66 (45–96)	69 (50–112)	0.437
NT-proBNP (pg/mL)	5254 (2541–12421)	6750 (3490–15072)	3712 (1880–8583)	3452 (1565–7740)	**<0.001**
BNP (pg/mL)	648 (298–1248)	951 (410–1534)	558 (267–999)	403 (217–808)	**<0.001**
Haemoglobin (g/dL)	12.0 (10.6–13.5)	12.5 (11.1–14.0)	11.3 (10.3–13.0)	11.3 (10.0–12.7)	**<0.001**
Haematocrit (%)	36.8 (32.7–41.0)	38.0 (34.0–42.0)	34.1 (31.5–40.0)	34.5 (30.7–38.7)	**<0.001**
Platelet count (10^9/L)	203 (159–259)	204 (161–258)	195 (161–238)	208 (154–267)	0.527
Sodium (mmol/L)	140 (137–142)	140 (137–142)	140 (138–141)	140 (137–142)	0.689
Potassium (mmol/L)	4.2 (3.8–4.6)	4.1 (3.8–4.6)	4.2 (3.8–4.7)	4.2 (3.8–4.6)	0.413
AST (IU/L)	25 (19–37)	26 (19–41)	23 (19–34)	24 (18–31)	**<0.001**
ALT (IU/L)	20 (14–33)	22 (15–39)	20 (13–30)	18 (13–27)	**<0.001**
Total bilirubin (mg/dL)	0.87 (0.58–1.30)	0.92 (0.61–1.44)	0.80 (0.47–1.10)	0.71 (0.50–1.15)	**<0.001**
INR	1.26 (1.10–1.71)	1.26 (1.10–1.70)	1.20 (1.03–1.56)	1.30 (1.10–1.95)	0.312

Data are presented as n (%) and median (Q25–Q75). P values in bold are significant.
ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RV, right ventricular; TR, tricuspid regurgitation.

risk of all-cause mortality as compared with HFrEF (adjusted HR 0.67, 95% CI 0.48–0.94, P = 0.022), whereas a similar risk between HFrEF and HFmrEF was observed (adjusted HR 1.13, 95% CI 0.75–1.70, P = 0.556). Higher LVEF values were independently associated with a lower risk of all-cause mortality (adjusted HR for 5% increase 0.94, 95% CI 0.89–0.99,

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Figure 1 Clinical outcomes at 1 year in patients with HFrEF vs. HFmrEF vs. HFpEF. The figure shows Kaplan–Meier curves for (A) 1 year all-cause mortality, (B) cardiovascular mortality, and (C) the composite of all-cause mortality or first heart failure (HF) hospitalization in patients with HF with reduced ejection fraction (HFrEF) vs. HF with mildly reduced ejection fraction (HFmrEF) vs. HF with preserved ejection fraction (HFpEF) enrolled in the HELP-HF registry.

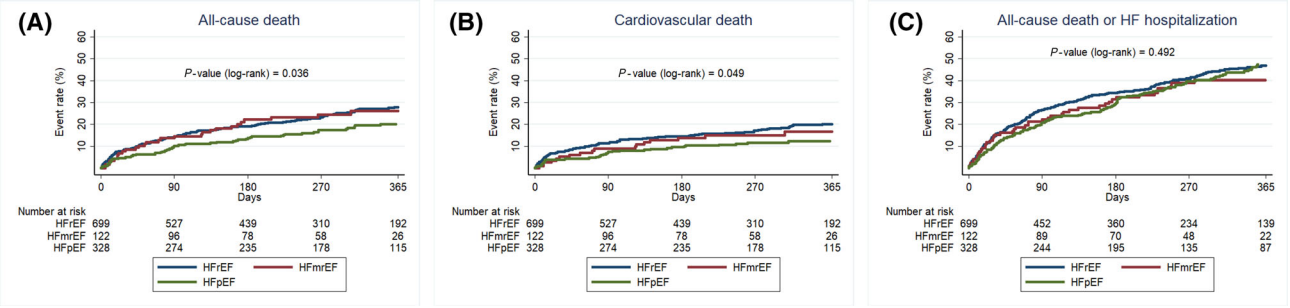
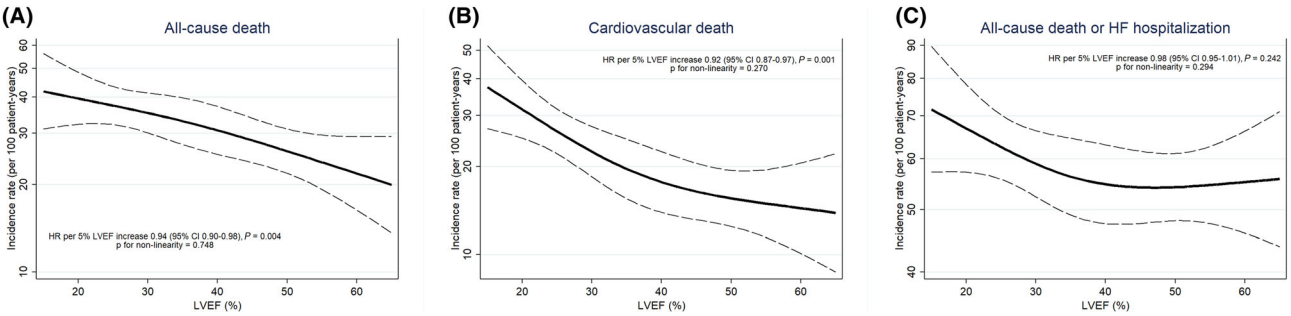


Figure 2 Indidence rate of clinical outcomes according to LVEF. The figure shows restricted cubic spline curves reporting the incidence rate of (A) all-cause mortality, (B) cardiovascular mortality, and (C) the composite of all-cause mortality or first heart failure (HF) hospitalization according to left ventricular ejection fraction (LVEF) values in patients enrolled in the HELP-HF registry. CI, confidence interval; HR, hazard ratio.



P = 0.017). The significantly lower risk of CV mortality in HFpEF patients was not confirmed after multivariable analysis (adjusted HR for HFpEF vs. HFrEF 0.72, 95% CI 0.47–1.09, *P* = 0.123), whereas LVEF as a continuous variable was independently associated with CV mortality (adjusted HR for 5% increase 0.94, 95% CI 0.88–1.00, *P* = 0.049). The risk of the composite endpoint and of first HF hospitalization alone was not significantly different between the HFrEF, HFmrEF, and HFpEF groups, and LVEF as a continuous variable did not have a significant impact on these endpoints also after multivariable adjustment (*Table 3*).

Predictors of all-cause mortality and impact of guideline-directed medical therapy in left ventricular ejection fraction <50% and ≥50% groups

At multivariable analysis, the independent predictors of all-cause mortality among patients with LVEF < 50% were older age, inpatient status at inclusion, peripheral artery disease, chronic obstructive pulmonary disease (COPD), lower systolic blood pressure (SBP), advanced HF according to the HFA-ESC definition, and lower eGFR (*Table 4*). In the group of patients with preserved LVEF (LVEF ≥ 50%), the independent predictors of all-cause mortality were inpatient status at enrolment, lower SBP, and advanced HF according to the HFA-ESC definition. The results of the univariable analyses are reported in Supporting Information, *Table S1*.

Regarding the prognostic impact of GDMT, use of beta-blockers and use of ACEi, ARB, or ARNI at inclusion were independently associated with a lower risk of all-cause mortality both in patients with LVEF < 50% and in those with LVEF ≥ 50%. Higher prescribed doses of beta-blockers and of ACEi/ARB/ARNI were independently associated with a lower likelihood of all-cause mortality in the LVEF < 50% group, whereas only higher doses of ACEi/ARB/ARNI were protective in the LVEF ≥ 50% group (*Table 4*). Use of MRA was not independently associated with mortality in both LVEF < 50% and LVEF ≥ 50% groups.

Table 3 Impact of ejection fraction on clinical outcomes

	All-cause death		Cardiovascular death		All-cause death or HF hospitalization		First HF hospitalization	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	SHR (95% CI)	*P* value
LVEF (per 5% increase)								
Univariable analysis	0.94 (0.90–0.98)	**0.004**	0.92 (0.87–0.97)	**0.001**	0.98 (0.95–1.01)	0.242	1.00 (0.97–1.04)	0.850
Multivariable analysis	0.94 (0.89–0.99)[a]	**0.017**	0.94 (0.88–1.00)[a]	**0.049**	0.98 (0.95–1.02)[b]	0.265	1.02 (0.97–1.06)[c]	0.427
LVEF categories								
HFmrEF vs. HFrEF								
Univariable analysis	0.98 (0.67–1.45)	0.921	0.84 (0.51–1.38)	0.493	0.85 (0.62–1.15)	0.284	0.73 (0.48–1.11)	0.139
Multivariable analysis	1.13 (0.75–1.70)[a]	0.556	1.04 (0.62–1.77)[a]	0.876	0.87 (0.63–1.21)[b]	0.417	0.77 (0.50–1.42)[c]	0.248
HFpEF vs. HFrEF								
Univariable analysis	0.69 (0.51–0.92)	**0.012**	0.64 (0.45–0.92)	**0.015**	0.93 (0.76–1.13)	0.466	1.04 (0.82–1.33)	0.736
Multivariable analysis	0.67 (0.48–0.94)[a]	**0.022**	0.72 (0.47–1.09)[a]	0.123	0.90 (0.72–1.13)[b]	0.371	1.09 (0.84–1.42)[c]	0.521

Data are presented as HR or SHR with 95% CI. *P* values in bold are significant.
CI, confidence interval; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; SHR, subhazard ratio.
[a]Adjusted for age, sex, inpatient vs. outpatient status, HFA-ESC advanced HF definition, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association Class III–IV, systolic blood pressure, heart rate, and estimated glomerular filtration rate.
[b]Adjusted for age, sex, inpatient vs. outpatient status, HFA-ESC advanced HF definition, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association Class III–IV, systolic blood pressure, and estimated glomerular filtration rate.
[c]Adjusted for age, sex, HFA-ESC advanced HF definition, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association Class III–IV, left ventricular ejection fraction <40%, and estimated glomerular filtration rate.

Discussion

Our study, based on the analysis of 1149 patients with HF and at least one 'I NEED HELP' marker for advanced HF, enrolled in a multicentre, contemporary, real-world registry, demonstrates the independent prognostic impact of LVEF also in these patients. In our high-risk population, higher LVEF values at inclusion were independently associated with a lower risk of all-cause mortality, and higher survival was observed in HFpEF as compared with HFrEF patients. An independent association was also observed between LVEF and CV mortality, although the lower unadjusted risk of CV death in HFpEF as compared with HFrEF patients was not confirmed after multivariable adjustment. No significant differences in HF hospitalization according to LVEF were observed. Several differences emerged in terms of comorbidities, clinical profile, and echocardiographic and laboratory findings. Beyond its role in differentiating the therapeutic strategies, our study suggests that LVEF still has a prognostic role in a population with HF and markers of advanced stage. Furthermore, inpatient status at inclusion, lower SBP, and advanced HF according to the HFA-ESC definition were independent predictors of all-cause mortality both in patients with LVEF $< 50\%$ and in those with LVEF $\geq 50\%$, whereas older age, peripheral artery disease, COPD, and lower eGFR were independently associated with mortality only in the LVEF $< 50\%$ group. Use of beta-blockers, use of ACEi/ARB/ARNI, and ACEi/ARB/ARNI up-titration were independently associated with lower mortality in both LVEF $< 50\%$ and LVEF $\geq 50\%$ groups, whereas beta-blockers up-titration was protective only in the LVEF $< 50\%$ group.

In the HELP-HF registry, most patients had HFrEF (60.8%), whereas HFmrEF and HFpEF accounted for 10.6% and 28.6%, respectively. These proportions seem consistent with the large HFA-ESC EURObservational Research Programme (EORP) HF Long-Term registry, which reported rates of HFrEF, HFmrEF, and HFpEF of 60%, 24%, and 16% for outpatients with chronic HF and of 53%, 18%, and 29% for inpatients with acute HF, respectively.[14,18] In a recent population-based cohort study of all Olmsted County including 936 patients with advanced HF according to the HFA-ESC criteria, the proportions of HFrEF, HFmrEF, and HFpEF were 42.3%, 14.3%, and 43.4%, respectively.[3] The selection of patients with at least one 'I NEED HELP' marker in our registry may have determined a higher rate of HFrEF as compared with a study only including patients with HFA-ESC-defined advanced HF, because some 'I NEED HELP' criteria facilitate the selection of HFrEF patients (i.e. LVEF $< 20\%$, ICD shocks, or need of inotropes).[9] Furthermore, HFpEF patients are older, commonly have non-CV comorbidities,[1] and are often admitted and followed up in internal medicine or geriatric departments; hence, we may have missed several HFpEF patients that were not admitted or visited in our cardiology departments and were not included in our registry.

Table 4 Multivariable Cox regression analysis for the independent predictors of all-cause mortality and impact of GDMT in patients with LVEF < 50% and in those with LVEF ≥ 50%

	LVEF < 50%		LVEF ≥ 50%	
	HR_{adj} (95% CI)	*P* value	HR_{adj} (95% CI)	*P* value
Independent predictors of all-cause death				
Age (years)	1.05 (1.03–1.07)	**<0.001**	1.01 (0.98–1.04)	0.410
Female sex	1.10 (0.79–1.51)	0.576	1.14 (0.68–1.93)	0.619
Inpatients vs. outpatients	3.36 (2.19–5.14)	**<0.001**	1.83 (1.01–3.31)	**0.046**
Peripheral artery disease	1.49 (1.06–2.08)	**0.020**	—	—
History of AF	1.11 (0.82–1.49)	0.504	—	—
Prior myocardial infarction	1.32 (0.99–1.77)	0.061	—	—
COPD	1.37 (1.00–1.87)	**0.047**	—	—
NYHA Class III–IV	1.28 (0.90–1.80)	0.168	1.51 (0.79–2.90)	0.216
Systolic blood pressure (mmHg)	0.99 (0.98–1.00)	**0.001**	0.98 (0.97–0.99)	**0.002**
HFA-ESC advanced HF definition	1.80 (1.28–2.53)	**0.001**	3.33 (1.82–6.08)	**0.002**
eGFR CKD-EPI (mL/min/1.73 m^2)	0.99 (0.98–1.00)	**0.002**	—	—
Impact of GDMT[a]				
Beta-blocker (any dose)	0.51 (0.37–0.69)	**<0.001**	0.52 (0.31–0.86)	**0.012**
Beta-blocker ≥50% target dose	0.74 (0.54–1.01)	0.059	0.94 (0.52–1.70)	0.840
Beta-blocker—fraction of the target dose (%)	0.49 (0.30–0.79)	**0.004**	0.45 (0.16–1.26)	0.128
ACEi/ARB/ARNI (any dose)	0.65 (0.48–0.89)	**0.007**	0.43 (0.24–0.77)	**0.005**
ACEi/ARB/ARNI ≥ 50% target dose	0.76 (0.51–1.13)	0.176	0.36 (0.16–0.81)	**0.013**
ACEi/ARB/ARNI—fraction of the target dose (%)	0.57 (0.34–0.97)	**0.039**	0.22 (0.07–0.72)	**0.013**
MRA (any dose)	0.83 (0.62–1.10)	0.194	0.89 (0.52–1.53)	0.682
MRA ≥ 50% target dose	0.86 (0.64–1.15)	0.307	0.84 (0.48–1.44)	0.519
MRA—fraction of the target dose (%)	1.09 (0.86–1.38)	0.465	0.92 (0.59–1.43)	0.700

Data are presented as adjusted HR (HR_{adj}) with 95% CI. *P* values in bold are significant.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; AF, atrial fibrillation; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
[a]The impact of each GDMT variable on all-cause death was adjusted for all the covariates entered in the two multivariable models: age, sex, inpatient vs. outpatient status, peripheral artery disease, history of AF, prior myocardial infarction, COPD, NYHA Class III–IV, systolic blood pressure, HFA-ESC advanced HF definition, and eGFR (for LVEF < 50%); age, sex, inpatient vs. outpatient status, NYHA Class III–IV, systolic blood pressure, and HFA-ESC advanced HF definition (for LVEF ≥ 50%).

Similarly to other studies,[14,18–20] in our cohort, patients with HFpEF were older and more likely to be female as compared with HFrEF (mean age 78.5 vs. 73.2 years). Patients with HFpEF were less likely to be included during a hospitalization for acute HF and to have history of prior myocardial infarction and PCI, while they were more prone to have hypertension and history of atrial fibrillation. As previously reported,[14,19] HFrEF patients needed more frequently inotropes/vasopressors and had higher NT-proBNP or BNP values. Interestingly, HFA-ESC-defined advanced HF was more common in patients with HFrEF. As already described,[21,22] the HFmrEF group shared features of both other groups.

Beyond the differences observed between the LVEF groups in terms of clinical characteristics, in our study, we also found relevant differences in terms of patients' prognosis. When analysed as a continuous variable, higher LVEF was independently associated with a lower risk of all-cause mortality (adjusted HR for 5% increase 0.94, 95% CI 0.89–0.99, *P* = 0.017) and CV mortality (adjusted HR for 5% increase 0.94, 95% CI 0.88–1.00, *P* = 0.049). As compared with patients with HFrEF, those with HFpEF had a lower risk of all-cause mortality at multivariable analysis, whereas their lower risk of CV mortality was only observed at univariable analysis and not confirmed after extensive multivariable adjustment. The risk of both all-cause and CV mortality was similar between HFmrEF and HFrEF. These findings are consistent with the HFA-ESC EORP HF Long-Term registry, which reported lower 1 year all-cause mortality in HFpEF as compared with HFrEF among both outpatients with chronic HF[18] and inpatients with acute HF.[14] A lower adjusted risk of mortality for each 5% LVEF increase in patients with acute HF was also reported in this registry.[23] The incidence of CV mortality was significantly lower in HFpEF vs. HFrEF patients with acute HF at inclusion,[14] but this difference was not observed among patients with chronic HF.[18] Some studies consistently reported a higher survival in unselected patients with HFpEF as compared with HFrEF,[24,25] whereas others showed a similar survival between HFpEF and HFrEF patients.[19,20,26–28]

Differently from most studies reporting data from unselected patients with acute and/or chronic HF, we focused on a high-risk population with at least one 'I NEED HELP' marker for advanced HF.[17] Criteria for defining advanced HF have changed over time, and several classification systems have been proposed in order to achieve a timely referral of

these patients.[7,10,29,30] The 'I NEED HELP' classification represents a nine-item useful mnemonic that has been proposed as a screening tool for advanced HF, including easy-to-record clinical, laboratory, and imaging parameters.[9] Therefore, we explored the differences in terms of clinical presentation and outcomes between LVEF categories in our high-risk and selected population enriched of patients with signs of advanced HF. In the already mentioned population-based Olmsted County cohort study including patients meeting the 2018 HFA-ESC advanced HF definition, all-cause mortality was similar between HFrEF, HFmrEF, and HFpEF (adjusted HR for HFmrEF vs. HFrEF 1.00, 95% CI 0.81–1.24; adjusted HR for HFpEF vs. HFrEF 0.99, 95% CI 0.84–1.16), whereas patients with advanced HFpEF had a lower risk of CV mortality as compared with advanced HFrEF (adjusted HR 0.79, 95% CI 0.65–0.97).[3] The significant difference that we observed between HFpEF and HFrEF patients in terms of all-cause mortality could be secondary to the different nature of our cohort, because we included less advanced patients not fulfilling the strict 2018 HFA-ESC definition[2] and therefore being more similar to other unselected HF populations.[14,18] However, a lower risk of CV mortality for higher LVEF values was also reported in our high-risk HF population.

Because we observed similar outcomes between HFrEF and HFmrEF patients, we evaluated the predictors of mortality and the impact of GDMT separately in the LVEF $<$ 50% group (either HFrEF or HFmrEF) and in the LVEF $\geq$ 50% group (HFpEF). Along with inpatient status at inclusion and lower SBP, the presence of HFA-ESC-defined advanced HF was independently associated with higher mortality both in patients with LVEF $<$ 50% and in those with LVEF $\geq$ 50%, in line with recent evidence supporting the prognostic impact of this definition.[17,31] Older age, peripheral artery disease, COPD, and lower eGFR were predictors of mortality in the LVEF $<$ 50% group, consistently with previous studies.[14,18] Interestingly, in our study, use of beta-blockers and use of ACEi/ARB/ARNI were independently associated with lower mortality in both LVEF $<$ 50% and LVEF $\geq$ 50% groups. The effectiveness of GDMT in advanced HFrEF, when tolerated, has already been described,[8] whereas the benefits of these drugs in patients with HFpEF are debated.[1,32] In the recent Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial, a high-intensity care strategy with rapid GDMT up-titration and close follow-up after an acute HF episode improved quality of life and reduced the risk of 180 day all-cause death or HF rehospitalization as compared with usual care, independently of the LVEF value.[13,33] Although our findings suggest that use of beta-blockers, use of ACEi/ARB/ARNI, and ACEi/ARB/ARNI up-titration might be beneficial in patients with HF, at least one high-risk marker for advanced HF, and either reduced or preserved LVEF, further dedicated studies are needed to prospectively test this hypothesis.

Limitations

The main limitation of our study is represented by its retrospective design, as already described.[17] Although the reported outcomes (mortality and HF hospitalization) are not likely to be biased, clinical events were reported by local investigators and not externally adjudicated. Furthermore, LVEF at inclusion was determined by echocardiography according to local clinical practice at the four participating centres and was consequently recorded by local investigators. Data on the impact of medical therapy on outcomes should be interpreted with caution due to the retrospective nature of the registry. Considering the study period (January 2020–November 2021), the available follow-up was relatively limited and sodium–glucose co-transporter 2 inhibitors were still not approved in our country, and therefore, their use was not evaluated. Finally, the sub-analysis focused on predictors of mortality and impact of medical therapy in the HFpEF group may be underpowered because of the relatively low number of patients (n = 328).

Conclusions

In our contemporary, real-world, multicentre cohort including patients with HF and at least one high-risk 'I NEED HELP' marker for advanced HF, different clinical profiles were observed between patients with HFrEF, HFmrEF, and HFpEF, and mortality was lower in the HFpEF group. A lower risk of both all-cause and CV mortality was demonstrated at higher LVEF values. Use of beta-blockers and ACEi/ARB/ARNI was associated with lower mortality both in patients with LVEF $<$ 50% and in those with LVEF $\geq$ 50%. Future studies are needed to further explore the impact of LVEF among patients with advanced HF.

Conflict of interest

M. Pagnesi reports personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, and Vifor Pharma, all outside the submitted work. D.S. reports personal fees from Novartis, Merck, GSK, and Acceleron, all outside the submitted work. M.A. reports speaker fees from Abbott Vascular and Medtronic. M. Merlo reports personal fees for congresses from Novartis, Vifor Pharma, and Pfizer and unrestricted research grant from Pfizer, all outside the submitted work. G.S. reports consulting fees from Novartis, Impulse Dynamics, and Biotronik and speaker fees and honoraria from Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini, and Akcea Therapeutics, all outside the submitted work. M. Metra reports personal consulting honoraria of minimal amount from Abbott, Amgen, Bayer, Edwards

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Supporting information

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

Figure S1. First HF hospitalization at 1 year in patients with HFrEF vs. HFmrEF vs. HFpEF.

Table S1. Univariable Cox regression analysis for the predictors all-cause mortality and impact of GDMT in patients with LVEF <50% and in those with LVEF ≥50%.

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