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Heart failure with normal LVEF in BIOSTAT-CHF

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ABSTRACT

Aims: Several studies have shown that heart failure (HF) drug treatment seems to benefit patients with preserved ejection fraction (HFpEF) and a left ventricular ejection fraction (LVEF) up to 55–60% but not with higher LVEF. Certain HF drugs are now indicated in patients with HFpEF and a LVEF below normal. However, not much is known about patients with a normal LVEF. Therefore, we investigated the prevalence, clinical characteristics and outcome of patients with HF and a normal LVEF.

Methods and results: Normal LVEF was defined according to the Recommendations for Cardiac Chamber Quantification from the American Society of Echocardiography as a LVEF ≥62% for men and ≥ 64% for women. Preserved ejection fraction was defined as a LVEF ≥50% and reduced ejection fraction as a LVEF <50%. In the total cohort of 1568 studied patients with heart failure (mean age 73 years; 33.6% female) 57 patients (3.6%) had a normal LVEF. These patients least likely had a previous myocardial infarction ($p < 0.001$) or diabetes ($p = 0.045$), had the lowest Left Ventricular End Diastolic Diameter ($p < 0.001$), the highest rate of previous HF hospitalization in the last year ($p = 0.015$), the highest cardiac output ($p < 0.001$) and were most frequently women ($p < 0.001$). Patients with a normal LVEF had the lowest risk for the primary combined outcome of all-cause mortality and HF hospitalization.

Conclusion: Only 3.6% of patients with HF had a sex-adjusted normal LVEF. Despite the sex-adjusted cut-offs they were more frequently female with less ischemic heart disease, higher cardiac output and better clinical outcomes.

Abbreviations and acronyms: ACEi, Angiotensin-converting-enzyme inhibitors; ANOVA, One-way analysis of variance; ARBs, Angiotensin II receptor blockers; BMI, Body mass index; CI, Confidence interval; HF, Heart failure; HFnEF, Heart failure with normal ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; HR, Hazard Ratio; IQR, Interquartile range; IVS, Interventricular septum; LA, Left atrial; LVEDD, Left ventricular end diastolic diameter; LVEDV, Left ventricular end diastolic volume; LVEF, Left ventricular ejection fraction; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association (NYHA) Functional Classification; SD, Standard deviation.

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1. Introduction

In patients with heart failure (HF), left ventricular ejection fraction (LVEF) is the most commonly used metric assessing left ventricular function [1]. LVEF is also used to classify patients as having HF with reduced (HFrEF) or preserved ejection fraction (HFpEF) and this classification is important because it determines treatment recommendations [2,3]. Pharmacological agents effective in improving clinical outcomes in HFrEF, have not convincingly shown to improve outcomes in HFpEF [4].

The FDA recently expanded the indication of sacubitril/valsartan to allow its use in patients with HFpEF. However, the FDA states that the "*benefits are most clearly evident in patients with an LVEF below normal*" [5]. This label extension is based upon data from PARAGON-HF, showing an interaction between treatment efficacy of sacubitril/valsartan and LVEF [6].

Similar interactions, where treatment seems to benefit patients with HFpEF and a LVEF up to 55–60% but not with higher LVEF, were also observed for angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) [7,8].

Interestingly, a normal LVEF for men is defined as 62% and 64% for women [9]. Therefore, the category of patients with HFpEF and a LVEF below these cut-offs can all be considered as "reduced LVEF". Unfortunately, little is known about the prevalence, clinical characteristics and outcomes of patients with a normal LVEF. Therefore, we sought to investigate the characteristics and clinical outcomes of patients with HF and a normal LVEF.

2. Methods

2.1. Patient population

For this study, we utilized patients from BIOSTAT-CHF [10,11] and performed a post hoc analysis of the validation cohort because HFpEF patients in the index cohort were selected based on considerable high NT-pro BNP levels and therefore HFpEF patients in the validation cohort are likely to better represent real-world HFpEF. The validation cohort was a prospective observational study and included 1738 patients from six centers in Scotland, UK. Inclusion criteria were age $\geq$ 18 years, diagnosis with HF and previous documented admission with HF requiring diuretic treatment. Patients had to be treated with furosemide $\geq$20 mg/day or an equivalent and were not previously treated or receiving $\leq$50% of target doses with ACEi/ARBs and/or beta-blockers. Besides an anticipated initiation or uptitration of ACEi/ARBs or beta-blockers they could be enrolled as inpatients or from out-patient clinics. Patients were assigned to three groups based on LVEF examined by transthoracic echocardiography: HF with reduced LVEF (LVEF<50%), HF with preserved EF (LVEF 50–62/64% for male/female; HFpEF) and HF with normal LVEF (LVEF$\geq$62/64% male/female; HFnEF).

Of the 1738 patients from the validation cohort, 170 patients were excluded because there was no LVEF measured. For the outcome analysis another two patients were excluded because of loss to follow-up.

2.2. Clinical measurements and definition

Demographics, medical history, physical examination, and blood draw were performed and recorded at baseline. We defined normal LVEF according to the Recommendations for Cardiac Chamber Quantification from the American Society of Echocardiography as a LVEF $\geq$62% for men and $\geq$ 64% for women [9]. HFpEF was defined as a LVEF $\geq$50% for male/female, and reduced ejection fraction as a LVEF <50%. Cardiac output was computed from Left Ventricular End Diastolic Diameter (LVEDD) and the given data on heart rate and LVEF using Teichholz Formula for calculating Left Ventricular End Diastolic Volume (LVEDV).

2.3. Outcome analyses

We used the primary combined outcome of all-cause mortality or first hospitalization for HF. The secondary outcome was all-cause mortality alone. HF hospitalizations were determined by the investigators and not independently adjudicated.

2.4. Statistical analyses

Continuous variables are presented as medians with interquartile ranges (IQR) or means with standard deviation (SD), categorical variables as counts and percentages. Differences between continuous variables were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test where appropriate. Categorical variables were compared by Pearson's chi-squared test.

For outcome analysis we performed Cox proportional hazards regression for the different subgroups using the group with the lowest risk as a reference. The cox regression was also adjusted for the BIOSTAT risk model, which has previously been described [12]. Age, NT-proBNP, haemoglobin, use of beta-blockers, HF hospitalization in the year before inclusion, peripheral oedema, systolic blood pressure, high-density lipoprotein cholesterol and sodium were included for the BIOSTAT risk model for predicting the combined endpoint of mortality or HF hospitalization whereas the risk model for predicting mortality included age, blood urea nitrogen, NT-proBNP, haemoglobin and use of beta-blockers.

3. Results

3.1. Demographic and clinical characteristics

In the total cohort of 1568 patients with HF (mean age 73 years; 33.6% female) 1127 (71.9%) had a reduced LVEF. 384 patients (24.5%) had HFpEF with a below normal LVEF and 57 patients (3.6%) showed a normal LVEF. Baseline and clinical characteristics of subgroups are presented in Table 1.

Patients with a normal LVEF were most frequently women (52.6%; $p < 0.001$), had the highest rate of previous HF hospitalization in the last year ($p = 0.015$), were most often in NYHA Class IV ($p < 0.001$), and least likely had a previous myocardial infarction ($p < 0.001$), peripheral artery disease ($p = 0.011$), diabetes ($p = 0.045$) or chronic obstructive pulmonary disease (COPD; $p < 0.001$) compared to patients from other subgroups. Patients with a normal LVEF showed the lowest LVEDD ($p < 0.001$) of all subgroups. In addition, they had the highest cardiac output ($p < 0.001$) compared to patients with reduced LVEF and HFpEF with below normal LVEF (Fig. 1).

3.2. Outcome

602 (38.4%) patients were hospitalized for HF or died after a median follow-up of 21 months. Patients with a normal LVEF showed the lowest risk for the primary combined outcome of all-cause mortality or HF hospitalization (Table 2). Whereas other subgroups HF with reduced LVEF [hazard ratio (HR) 2.05; 95% confidence interval (CI) 1.13–3.73] and HFpEF with below normal LVEF (HR 2.31; 95% CI 1.25–4.25) had twice the risk compared to the group of normal LVEF as the subgroup with the best clinical outcome (Fig. 2B, Table 2). After adjustment for the BIOSTAT-CHF risk model, the risk for the combined endpoint of death or heart failure hospitalization remained statistically significant (see Table 2: reduced LVEF vs. HFnEF: HR 2.58; 95% CI 1.42–4.7; HFpEF vs. HFnEF: HR 2.64; 95% CI 1.43–4.86). All-cause mortality alone did not show significant differences (Fig. 2A, Table 2).

4. Discussion

Patients with a normal LVEF were (1) most commonly women with less ischemic heart disease and diabetes, and (2) had better outcomes

Table 1
Baseline characteristics of the different heart failure subgroups in the BIOSTAT-CHF validation cohort. Data are mean (SD), n (%), or median (IQR). BMI, body-mass index; NYHA,New York Heart Association.; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

Characteristics	Reduced LVEF N = 1127	HFpEF (LVEF below normal) N = 384	HFnEF N = 57	p-value
Clinical				
Age	72.6 (10.7)	75.9 (9.9)	74.1 (11.0)	<0.001
Female sex	331 (29.4%)	166 (43.2%)	30 (52.6%)	<0.001
BMI (kg/m^2)	27.5 (24.3–31.7)	29.6 (25.2–34.7)	27.3 (24.1–32.8)	<0.001
Edema				<0.001
Not present	428 (42.1%)	108 (31.1%)	10 (19.2%)	
Ankle	301 (29.6%)	119 (34.3%)	19 (36.5%)	
Below knee	240 (23.6%)	90 (25.9%)	16 (30.8%)	
Above knee	48 (4.7%)	30 (8.7%)	7 (13.5%)	
Crackles				<0.001
No	642 (59.4%)	183 (49.2%)	19 (35.2%)	
Single base	58 (5.4%)	26 (7.0%)	6 (11.1%)	
Bi-basilar	381 (35.2%)	163 (43.8%)	29 (53.7%)	
NYHA class				<0.001
NYHA I	12 (1.1%)	4 (1.0%)	0 (0.0%)	
NYHA II	502 (44.6%)	115 (29.9%)	23 (40.4%)	
NYHA III	480 (42.6%)	191 (49.7%)	20 (35.1%)	
NYHA IV	132 (11.7%)	74 (19.3%)	14 (24.6%)	
Medical history				
Previous HF hosp. (last year)	273 (24.7%)	107 (28.1%)	23 (41.1%)	0.015
Atrial fibrillation	498 (44.5%)	177 (46.3%)	25 (43.9%)	0.813
Myocardial infarction	607 (54.0%)	158 (41.1%)	13 (22.8%)	<0.001
Hypertension	615 (54.8%)	266 (69.3%)	33 (57.9%)	<0.001
Diabetes mellitus	350 (31.2%)	144 (37.8%)	16 (28.1%)	0.045
Renal disease	494 (44.4%)	189 (50.4%)	23 (41.8%)	0.108
Stroke	205 (18.4%)	78 (20.4%)	7 (12.5%)	0.337
Peripheral artery disease	234 (21.3%)	106 (28.5%)	10 (17.5%)	0.011
COPD	176 (15.8%)	107 (27.9%)	7 (12.3%)	<0.001
Hyperthyroidism	7 (0.6%)	6 (1.6%)	1 (1.8%)	0.137
Smoking (past and current)	559 (49.9%)	182 (48.0%)	20 (35.1%)	0.087
Echocardiography				
LVEF (%)	34.9 (8.9)	55.9 (4.4)	67.7 (5.3)	NA
LVEDD (mm)	56.6 (8.8)	48.2 (7.2)	47.0 (6.9)	<0.001
LVESD (mm)	47.3 (10.5)	33.3 (9.1)	26.0 (6.7)	<0.001
LA diameter (mm)	45.6 (7.4)	44.2 (7.1)	43.0 (7.2)	0.005

than patients with reduced LVEF or patients with HFpEF and a below normal LVEF. In addition, they showed the highest cardiac output. This is the first study utilizing a heart failure cohort to explore the characteristics and clinical outcome of patients with HF and a normal LVEF.

4.1. Patient characteristics

Patients with normal LVEF were more likely women, even though we used sex-adjusted LVEF cut-offs. Patients with HFpEF are more commonly women and there are important sex differences in HF – women often have a different etiology of HF and show in general higher LVEF [13–15].

Our findings support frequently postulated assumptions that patients with HFpEF more often are female and show less ischemic heart disease as a central role in the development of cardiovascular disease [16,17]. The small number of patients with a normal LVEF in our study could also be influenced by the low proportion of women in the total cohort (33.6%) once more underlining a consistent underrepresentation of women in clinical studies and trials [18] but also emphasizing the importance of our finding that more than 52% of patients with a normal LVEF are female in this subgroup. Interestingly, the PARAGON-HF trial indicates that especially women might obtain more benefit from therapy with sacubitril/valsartan in the normal LVEF range [19].

HFpEF is strongly associated with higher prevalence of hypertension [16,17]. Interestingly, in our study the rate of hypertension in patients with a normal LVEF was comparatively low. Furthermore, diabetes as a common etiology and comorbidity of HF associated with worse morbidity and mortality in HFpEF [20] was least likely to be seen in patients with a normal LVEF. These patients also tended to have a lower body mass index (BMI), whereas especially HFpEF is related to higher BMI and obesitiy [21,22]. These findings might indicate a lack of typical causes for HF in patients with normal LVEF, who do not demonstrate common etiologies of either HFpEF or HFrEF as other subgroups. They show no strong evidence for ischemic heart disease or diabetes as a central etiology nor signs of a more important influence of hypertension or obesity. This might also be a potential reason for failing of conventional HF therapy to improve their outcome. Despite that, they have substantial burden of disease showing a higher rate of previous HF hospitalizations in the last year and more patients classified in NYHA Class IV than other subgroups. However, also COPD as a further risk factor is least prevalent in this subgroup and atrial fibrillation or renal disease as other potential causes for their condition did not show significant differences between subgroups.

The highest cardiac output observed in the subgroup of normal LVEF is another interesting finding. A high-output state in HF as congestive HF with a normal or higher cardiac output is caused by reduced systemic vascular resistance [23]. Reddy et al. found that high-output HF is associated with excessive vasodilation, often caused by obesity and should especially be considered as a differential diagnosis in patients with symptoms of HF and a normal LVEF [24]. Although in our study cardiac output was remarkably high in patients with a normal LVEF, characteristics of this subgroup, such as prevalence of hypertension and diabetes and BMI do not point in this direction. Still, the notable high cardiac output might suggest a certain pathophysiological mechanism of HFnEF that differs from usual mechanisms of congestive HF all of which are characterized by some kind of ventricular dysfunction resulting in low cardiac output. Patients with HFnEF might have a different underlying pathophysiology without ventricular dysfunction.

4.2. Outcome

In our study patients with a normal LVEF had the lowest rate of all-cause mortality or HF hospitalizations. Wehner et al. recently described an U-shaped curve with increasing risk of death in both the higher and lower LVEF ranges [25]. Bhatia et al. have shown that both types of heart failure HFrEF and HFpEF have similar survival rates [17]. Other studies indicate that mortality is lower in HFpEF than in HFrEF [14,22]. HRs for the primary combined outcome of HF hospitalization and mortality of both other subgroups interestingly were very close. Especially after adjustment for the BIOSTAT risk model, they were at an almost similar level both showing a more than twofold increased risk compared to the group of patients with normal LVEF. This might suggest that the similar or even better outcome of HFpEF patients could mainly be caused by the better prognosis of those with a normal LVEF and might indicate a potential need for looking at these two groups within HFpEF differently. This is also supported by the results from PARAGON-HF as Solomon et al. have shown lacking effect of sacubitril/valsartan on reducing the composite of total heart failure hospitalization and mortality in the higher LVEF range [6].

Remarkably, patients with a normal LVEF while showing the lowest risk for the primary outcome of HF hospitalization and all-cause mortality had the highest rate of previous HF hospitalizations and the most patients in NYHA Class IV compared to other subgroups. This could be caused by a general underdiagnosis of heart failure in patients with normal LVEF, thus only patients with really severe heart failure symptoms and a high burden of disease get diagnosed with it at a later stage and were therefore more often treated in the hospital previously [26,27]. In addition, the differentiated profile of these patients might raise the question of whether they are typical heart failure patients or

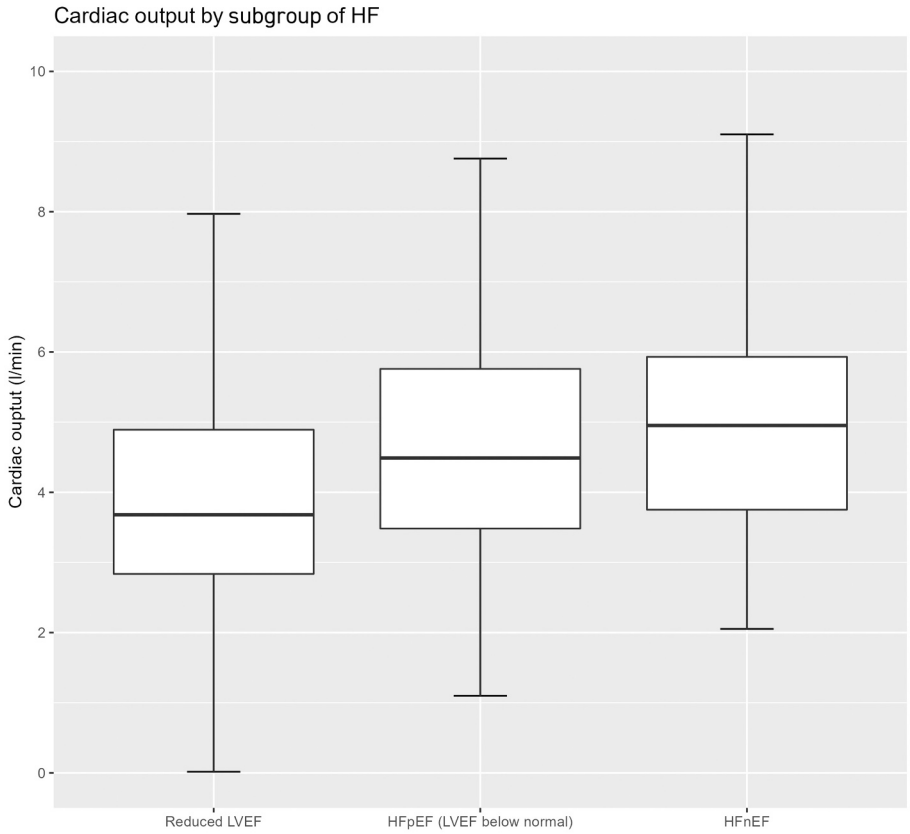

Fig. 1. Cardiac output for the different subgroups, LVEDV was calculated using Teichholz Formula ($p < 0.001$).

Table 2
Subgroups hazard ratios for all-cause mortality and the combined outcome of all-cause mortality and HF hospitalization, adjusted for the BIOSTAT risk model (*$p < 0.05$).

Subgroup	Unadjusted HR (CI)	Adjusted HR (CI)
All-cause mortality		
Reduced LVEF	1.51 (0.78–2.93)	1.56 (0.8–3.03)
HFpEF (LVEF below normal)	1.83 (0.93–3.62)	1.86 (0.95–3.68)
HFnEF	1.0 (referent)	1.0 (referent)
Combined mortality and hospitalization		
Reduced LVEF	2.05 (1.13–3.73)*	2.58 (1.42–4.7)*
HFpEF (LVEF below normal)	2.31 (1.25–4.25)*	2.64 (1.43–4.86)*
HFnEF	1.0 (referent)	1.0 (referent)

whether they suffer from another underlying related condition. Furthermore, it might be necessary for clinical studies and trials to not only further distinguish between men and women but also between a below normal and normal LVEF. However, our study suggests a certain clinical profile of HF with normal LVEF. This subgroup needs to be further examined to reveal underlying etiologies or conditions because these patients might benefit from a specific diagnosis and a differentiated treatment.

4.3. Limitations

This study has several limitations. Our findings are based on a post hoc analysis. Although we studied a large cohort of HF patients from the BIOSTAT-CHF validation cohort only a small group of patients had a normal LVEF and thereby could be examined. These patients also had to meet the BIOSTAT-CHF inclusion criteria, which makes them a selected cohort and, in combination with the small number of patients, could limit heterogeneity. Additionally, we had to utilize definite thresholds for the definition of "normal LVEF". Even though that was according to acknowledged guidelines those can and should be discussed in context of the extended approval of sacubitril/valsartan and in general. However, LVEF assessment by transthoracic echocardiography was not standardized and - especially in the normal or higher LVEF ranges - is examiner dependent and by that comes with a certain degree of inaccuracy. In addition, derivation of LVEF can differ depending on the imaging method. Although, all LVEF measurements were centrally performed by one experienced echo technician. Furthermore, calculating cardiac output from echocardiographic data can also result in impreciseness. Lastly, BIOSTAT-CHF included mainly Caucasian patients and the validation cohort only consists of patients from one country, which makes transferring results particularly to other ethnicities difficult.

5. Conclusions

This study showed that only a small percentage of patients with HF had a sex-adjusted normal LVEF. Despite the sex-adjusted cut-offs they were more frequently female with less ischemic heart disease, higher cardiac output and had a better clinical outcome.

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Conflicts of interest

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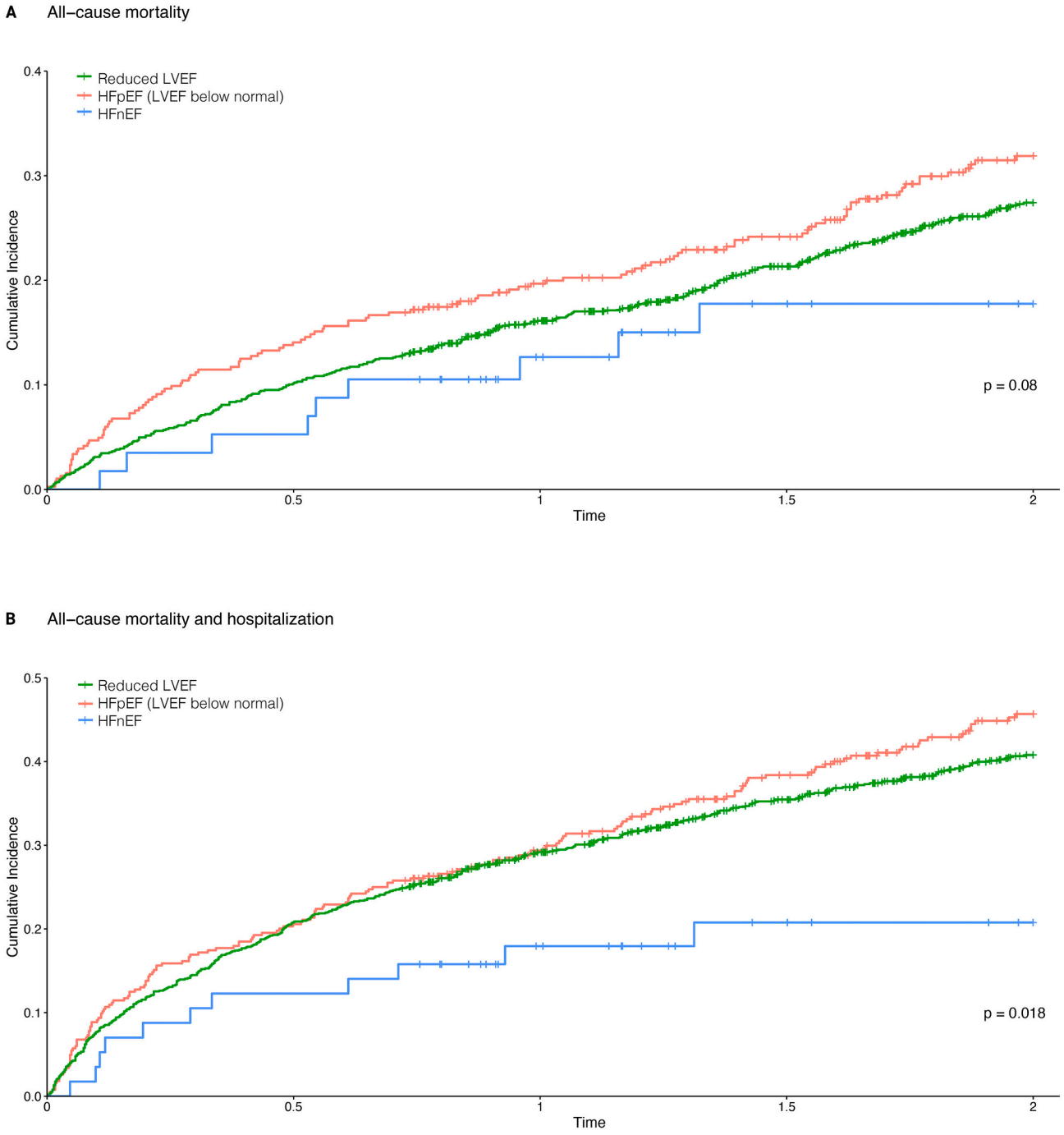

Fig. 2. Kaplan-Meier time to event curve for all-cause mortality ($p = 0.08$) and for the combined outcome of all-cause mortality and HF hospitalization ($p = 0.018$) for the different subgroups.

served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Actelion, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., Us2.ai, Janssen Research & Development LLC, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe Group Ltd., Roche Diagnostics, Sanofi and WebMD Global LLC; and serves as co-founder & non-executive director of Us2.ai. AAV and/or his institution received consultancy fees and/or research grants from: Amgen Astrazeneca, Bayer AG, Boehringer Ingelheim, BMS, Cytokinetics, Myokardia, Merck, Novo Nordisk, Novartis, Roche Diagnostics. All other authors declare no conflict of interest.

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