

# Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines?

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## Abstract

**Aims** The main terminology used to describe heart failure (HF) is based on measurement of the left ventricular ejection fraction (LVEF). LVEF in the range of 40–49% was recently defined as HF with mid-range EF (HFmrEF) by the 2016 European Society of Cardiology guidelines. The purpose of our study was to assess the clinical profile and prognosis of patients with HF according to this new classification.

**Methods and results** A total of 482 patients referred for HF were retrospectively included over a period of 1 year. There were 258 (53%), 115 (24%), and 109 (23%) patients with HF with reduced EF (HFrEF), HFmrEF, and HF with preserved EF (HFpEF), respectively. Patient age increased, whereas left block bundle branch, brain natriuretic peptide level, and the use of beta-blocker and furosemide decreased from HFrEF to HFpEF. After adjustment for the age, patients with HFpEF and HFmrEF were more likely to have NYHA stage 2 dyspnea, had a higher systolic blood pressure, were less likely to have spironolactone, had lower furosemide dose, and had lower haemoglobin than those with HFrEF. Cardiovascular risk factors and medical history were similar in the three groups of patients. There was a 33% death rate after a mean follow-up of  $32.2 \pm 14.3$  months. The survival was the same among patients whatever the group of HF ( $P = 0.884$ ).

**Conclusions** Patients with HFrEF, HFmrEF, and HFpEF share the same cardiovascular risk factors, medical history, and prognosis. Patients with HFmrEF have a different clinical profile, which is nearly the same as patients with HFpEF, except for sex. These results question the relevance of this new classification of HF to stimulate research into this new group of patients.

**Keywords** Heart failure; Heart failure with mid-range ejection fraction; European Society of Cardiology Guidelines; Baseline characteristics; Mortality

Received: 22 August 2016; Accepted: 8 December 2016

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## Introduction

The main terminology used to describe heart failure (HF) is based on measurement of the left ventricular ejection fraction (LVEF). Historically, HF was divided in patients with normal LVEF [HF with preserved EF (HFpEF), typically with a LVEF  $\geq 50\%$ ] and those with reduced LVEF [HF with reduced EF (HFrEF), typically with a LVEF  $< 40\%$ ]. Patients with a LVEF in the range 40–49% were in a ‘grey area’, which was recently defined as HF with

mid-range EF (HFmrEF) by the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF.<sup>1</sup> Few data are available on the phenotype and prognosis of patients with HF according to this new classification, because most HF studies and clinical trials included patients with EF below 35–40% or above 50%.

The purpose of our study was to assess the clinical profile and the prognosis of patients with HF according to this new classification.

## Methods

### Study population

Patients referred to the HF Unit Care of the University Hospital of Rangueil, Toulouse, France, between June 2012 and June 2013 for assessment of HF by invasive coronary angiography were retrospectively included. HF was defined according to the ESC Guidelines for the diagnosis and treatment of acute and chronic HF 2012 by the association of typical symptoms of HF (breathlessness at rest or at exercise, fatigue, tiredness, ankle swelling) and typical signs of HF (tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly).<sup>2</sup> All patients were screened by systematic transthoracic echocardiography within 30 days, and LVEF was assessed using the conventional apical two- and four-chamber views and the modified Simpson's method. Patients were classified according to the new terminology of the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF as HFpEF (LVEF  $\geq 50\%$ ), HFmrEF (LVEF 40–49%), and HFrEF (LVEF  $< 40\%$ ).<sup>1</sup> All patients underwent invasive coronary angiography, and data were extracted electronically from our local database. Coronary artery disease was defined as the presence or the history of coronary stenosis  $> 50\%$  of at least one principal coronary artery at coronary angiography. Dyspnea was quantified according to the New York Heart Association (NYHA) functional class. Current smoking was defined by a smoking habitus persisting during the last month. Systemic hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg or a diastolic blood pressure  $\geq 90$  mmHg without treatment; hypercholesterolemia in patients without atherosclerotic cardiovascular disease as a total plasma cholesterol or LDL cholesterol above 5 mmol/L and 3 mmol/L, respectively, or in patients with atherosclerotic cardiovascular disease or diabetes above 4 mmol/L and 2.5 mmol/L, respectively; obesity as a body mass index  $\geq 30$  kg/m<sup>2</sup> and chronic renal insufficiency as an estimated glomerular filtration rate by modification of diet in renal disease formula  $< 60$  mL/min.

The study was approved by our institutional review board.

### Follow-up

Clinical follow-up was assessed in June 2016 by phone interview of patient's general practitioner/cardiologist, patient, or family. The outcome event examined was total mortality. Patients without contact up to 6 months were considered as lost to follow-up.

### Statistical analysis

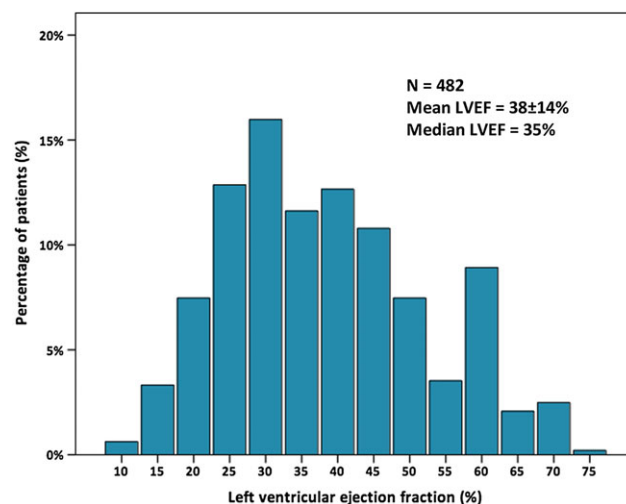
Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and expressed as

mean  $\pm$  standard deviation. Biomarkers and posology of furosemide were not normally distributed, and results are, therefore, presented as medians with interquartile ranges. Categorical variables were expressed as numbers and percentages. The study population was categorized into three groups: patients with HFrEF, patients with HFmrEF, and patients with HFpEF. Group comparisons were made using nonparametric Kruskal–Wallis tests or ANOVA for continuous variables and  $\chi^2$  test for categorical variables, using Bonferroni corrections for multiple comparisons. Regression model was used to adjust for the effect of age on the differences in baseline characteristics among groups. All-cause mortality was summarized using Kaplan–Meier survival curve, and log rank test was used for initial comparisons. Patients were censored at the time of death. Cox proportional-hazards regression was used to adjust for the effect of age on survival. Differences were considered statistically significant for  $P$  values of  $< 0.05$ . All analyses were performed using standard statistical software SPSS version 20 (SPSS Inc., Chicago, Illinois).

## Results

A total of 482 patients were referred for invasive coronary angiography for assessment of HF from June 2012 through June 2013, who constituted the study population. Echocardiographic assessment of EF within 30 days was available for all patients. The distribution of LVEF across the population is illustrated in the *Figure 1*. There were 258 (53%), 115 (24%), and 109 (23%) patients with HFrEF, HFmrEF, and HFpEF, respectively.

**Figure 1** Distribution of left ventricular ejection fraction across the population of patients with heart failure referred for invasive coronary angiography.



## Patient characteristics

Patient age increased, whereas prevalence of LBBB, brain natriuretic peptide level, and the use of beta-blocker and furosemide decreased from HFrEF to HFpEF (Table 1).

Patients with HFpEF or HFmrEF were older, were more likely to have NYHA stage 2 dyspnea, had a higher systolic blood pressure, were less likely to have ACEI/ARB and spironolactone, had lower furosemide dose, and had lower haemoglobin than those with HFrEF. Except for ACEI/ARB treatments, these differences remained significant after adjustment for the age difference between groups.

Patients with HFrEF or HFmrEF were more likely to be male and to have less history of hypertension than those with HFpEF. After adjustment for the age difference between groups, only sex difference between groups remains significant.

Overall, and after adjustment for age differences, cardiovascular risk factors and medical history were similar in the three groups of patients.

## Mortality

Survival data were available for 452 of the 482 patients (94%), with a mean ( $\pm$ SD) follow-up of  $32.2 \pm 14.3$  months. There were 17 (7%), 9 (8%), and 4 (4%) patients lost for follow-up among patients with HFrEF, HFmrEF, and HFpEF, respectively ( $P = 0.390$ ). A total of 147 (33%) deaths occurred during follow-up.

The survival rate was no different among patients with HFrEF, HFmrEF, and HFpEF (Figure 2). The respective mortality rates were 15, 9, and 9% at 6 months ( $P = 0.061$ ); 18, 15, and 13% at 1 year ( $P = 0.337$ ); and 33, 32, and 32% at the time of follow-up ( $P = 0.903$ ).

The unadjusted hazard ratios for death in the group of patients with HFmrEF and HFpEF as compared with the patients with HFrEF were 0.88 (95% confidence interval, 0.58 to 1.35;  $P = 0.560$ ) and 0.95 (95% confidence interval, 0.63 to 1.43;  $P = 0.820$ ), respectively. After adjustment for age, the likelihood of survival was still the same among groups (hazard ratio for death among patients with HFmrEF as compared with patients with HFrEF, 0.78; 95% confidence interval, 0.51 to 1.20,  $P = 0.259$  and hazard ratio for death among patients with HFpEF as compared with patients with HFrEF, 0.78; 95% confidence interval, 0.51 to 1.18,  $P = 0.242$ ).

## Discussion

As previously described,<sup>3</sup> the distribution of the LVEF across our population of patients with HF referred for invasive

coronary angiography observed a unimodal bell shaped including 24% of HFmrEF, which is substantially more than previous big series.<sup>4–6</sup> Anyway, the bell-shaped distribution is relatively constant and we can assume that the prevalence of HFmrEF depends on the patient recruitment method.<sup>3</sup>

The new ESC terminology was done because patients with LVEF that ranges from 40 to 49% were in a grey area between HFrEF and HFpEF and, consequently, were excluded from HF clinical trials of HF.<sup>4</sup> Identifying HFmrEF as a separate group has the aim of stimulating research into the underlying characteristics, pathophysiology, and treatment of this group of patients. The main question is to know if differentiation of patients with HF based on LVEF can make the difference between underlying aetiologies, demographics, and comorbidities with the ulterior motive of a common response to therapies. In our cohort of HF patients referred for coronary angiography, except for sex where patients with HFpEF are more likely to be female than those with HFrEF and HFmrEF, we found that patients with HFmrEF and HFpEF share the same clinical profile: they are older, are more likely to have NYHA stage 2 dyspnea, have a higher systolic blood pressure, are less likely to have spironolactone, have lower furosemide dose, and have lower haemoglobin than those with HFrEF. All these differences remained significant after adjustment for age. In summary, our study shows that patients with HFmrEF have the same clinical profile as patients with HFpEF, which is different from HFrEF mainly for age, symptoms, and systolic blood pressure. Finally, patients with HFrEF, HFmrEF, and HFpEF share the same cardiovascular risk factors and medical history. Previous large cohorts of patients with HF have reported that HFpEF and HFrEF have different epidemiological and etiological profiles. Compared with HFrEF, patients with HFpEF are older, more often women, are more likely to be obese, have lower haemoglobin, and more commonly have a history of hypertension and atrial fibrillation, while a history of myocardial infarction is less common.<sup>7,8</sup> Several previous studies that have focused on HFmrEF reported intermediate clinical characteristics of patients with HFmrEF, between those of HFrEF and HFpEF: patients were younger and more predominantly male compared with those with HFpEF.<sup>4,6</sup> Several cardiovascular risk factors were shared among HFmrEF, HFrEF, and HFpEF, but patients with HFmrEF were more likely to have hypertension compared with those with HFrEF. The recent study of Kapoor *et al.* found that patients with HFmrEF are closer to patients with HFpEF in terms of mean age and comorbidities as anaemia, atrial fibrillation, diabetes, hypertension, or renal disease.<sup>6</sup> These results confirm the difference in demographics and co-morbidities among patients with HF, according to their LVEF, and suggest that our study has probably not enough power to highlight slight differences. Interestingly, patients with HFmrEF were more likely to have ischaemic heart disease compared with those with HFpEF, and similar to those with HFrEF<sup>4</sup> suggesting that ischemic burden could play a role in the time course of a potential transition

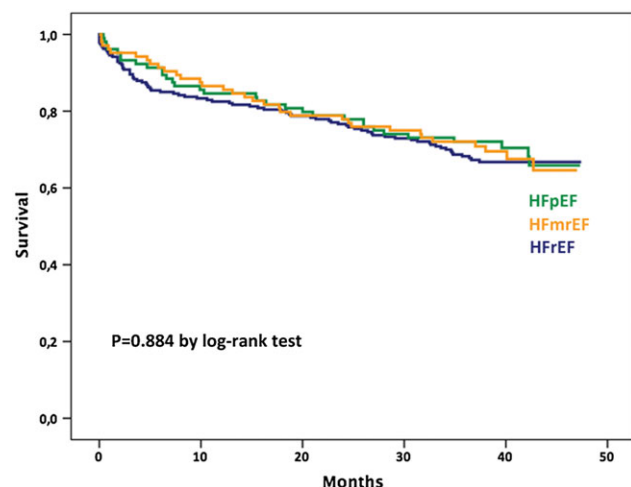
Table 1 Characteristics of patients with heart failure and reduced, mild range, or preserved EF

	HFpEF (1) n = 258	HFmrEF (2) n = 115	HFpEF (3) n = 109	P value	Adjusted P value <sup>a</sup>	Post-hoc analysis		
						1 vs. 2	2 vs. 3	3 vs. 1
Age (years)	66 ± 12	69 ± 13	71 ± 12	<0.001	NA	0.061	0.501	<0.001
65 years old and older	134 (52)	78 (68)	73 (67)	0.002	NA	0.003	0.502	0.005
Male [n (%)]	186 (72)	83 (72)	60 (55)	0.004	0.016	0.546	0.006	0.001
Body mass index (kg/m <sup>2</sup> )	28 ± 14	27 ± 5	27 ± 5	0.419	0.412			
Obesity	63 (24)	29 (25)	31 (28)	0.441	0.153			
NYHA class [n (%)]								
I	65 (25)	29 (25)	21 (19)	0.269	0.443			
II	73 (28)	46 (40)	45 (41)	0.008	0.007	0.018	0.476	0.011
III	75 (29)	25 (22)	24 (22)	0.106	0.069			
IV	45 (17)	15 (13)	19 (17)	0.812	0.676			
Mean	2.4 ± 1.0	2.2 ± 1.0	2.4 ± 1.0	0.346	0.443			
LVEF (%)	28 ± 6	43 ± 3	58 ± 6	<0.001	<0.001	<0.001	<0.001	<0.001
Systolic arterial pressure (mmHg)	127 ± 25	138 ± 24	145 ± 26	<0.001	<0.001	<0.001	0.103	<0.001
Diastolic arterial pressure (mmHg)	77 ± 16	77 ± 13	77 ± 15	0.972	0.402			
Heart rate (bpm)	84 ± 21	79 ± 22	78 ± 22	0.023	0.022	0.139	1.000	0.048
LBBB	87 (34)	24 (21)	10 (9)	<0.001	<0.001	0.008	0.011	<0.001
Smoking habitus [n (%)]								
Current smoking	49 (19)	12 (10)	17 (16)	0.232	0.798			
Previous smoking	94 (36)	44 (38)	49 (45)	0.117	0.190			
Medical history								
Hypertension [n (%)]	131 (51)	61 (53)	71 (65)	0.017	0.072			
Diabetes [n (%)]	64 (25)	35 (30)	31 (28)	0.367	0.359			
Hyperlipidemia [n (%)]	103 (40)	52 (45)	43 (39)	0.891	0.880			
Paroxysmal atrial fibrillation [n (%)]	62 (22)	20 (17)	26 (24)	0.727	0.477			
Permanent atrial fibrillation [n (%)]	30 (10)	21 (18)	15 (14)	0.381	0.901			
Renal insufficiency [n (%)]	111 (43)	36 (31)	52 (48)	0.728	0.350			
Coronary artery disease [n (%)]	140 (54)	57 (50)	59 (54)	0.835	0.485			
Myocardial infarction	69 (27)	26 (23)	25 (23)	0.373	0.469			
COPD [n (%)]	19 (7)	10 (9)	14 (13)	0.105	0.245			
Sleep disordered breathing	11 (4)	8 (7)	9 (8)	0.113	0.087			
Biology [95% CI]								
BNP (pg/mL)	819 [667–971]	597 [396–799]	395 [264–526]	0.004	<0.001	0.003	0.020	<0.001
Haemoglobin (g/dL)	13.5 [13.3–13.8]	12.6 [12.2–12.9]	12.4 [12.0–12.8]	<0.001	<0.001	<0.001	0.622	<0.001
eGFR (mL/min)	71 ± 62	74 ± 35	68 ± 33	0.683	0.679			
Medication at discharge								
Furosemide [n (%)]	208 (81)	80 (70)	59 (54)	<0.001	<0.001	0.014	0.012	<0.001
Posology (mg/day) [95% CI]	89 [71–106]	59 [24–93]	52 [32–71]	0.044	0.011	0.001	0.118	<0.001
ACEI and ARB [n (%)]	213 (83)	85 (74)	78 (72)	0.012	0.050			
Beta-blockers [n (%)]	225 (87)	90 (78)	67 (61)	<0.001	<0.001	0.022	0.005	<0.001
Spirolactone [n (%)]	111 (43)	22 (19)	13 (12)	<0.001	<0.001	<0.001	0.096	<0.001
Ivabradine [n (%)]	8 (3)	6 (5)	3 (3)	0.939	0.542			
Aspirin [n (%)]	166 (64)	80 (70)	73 (67)	0.508	0.904			
Statin [n (%)]	150 (58)	67 (58)	62 (57)	0.871	0.792			
Insulin [n (%)]	35 (14)	17 (15)	16 (15)	0.746	0.877			
Devices [n (%)]								
ICD	38 (15)	4 (3)	0 (0)	<0.001	<0.001	0.001	0.068	<0.001
ICD + CRT	24 (9)	3 (3)	2 (2)	0.002	0.001	0.013	0.525	0.006

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; LBBB, left block bundle branch.

<sup>a</sup>The P values are adjusted for age. NA denotes not applicable.

**Figure 2** Kaplan–Meier survival curves for patients with heart failure and reduced, mild, range or preserved ejection fraction.



between HFpEF and HFrEF. The role of coronary artery disease in the course of HFpEF and the transition from HFpEF to HFrEF is supposed to be determinant: patients with coronary artery disease have greater deterioration of LVEF and may have been more likely to transition to HFrEF following a myocardial infarction.<sup>9</sup> These findings led the authors to suggest that HFmrEF could constitute a subset of HFpEF enriched with coronary artery disease and representing an early stage of HFrEF.<sup>4</sup> Our results contradict this hypothesis by showing the same prevalence rates of myocardial infarction and artery coronary disease among the three groups of patients with HF.

Beyond the difference of phenotype between groups of patients with HF, our study shows that patients have the same mortality over a follow-up period of 2.7 years, whatever their group of EF. Previous data suggest that the mortality rate of HFmrEF is intermediate between that of HFrEF and HFpEF. These data show a graded relationship between lower EF and higher risk of events.<sup>3,5</sup> Finally, in regard of these data and in terms of outcomes, chronic stable HFmrEF resembles HFpEF more than HFrEF. Our results are slightly different showing the same prognosis and the high mortality rate among the three groups of patients with HF. There is only a trend of increased mortality among patients with HFrEF as compared with those with HFmrEF and HFpEF, but this trend disappears in the first year to join the general prognosis of HF.<sup>4</sup> These results confirm that beyond the simple EF, symptoms and congestive signs of HF carry a poor prognosis.

HF is a heterogeneous disorder resulting of the interaction of multiple aetiologies, comorbidities, and cardiovascular risk factors, where imbalance can lead to maintain or decrease of LVEF. The discrepancy among studies in terms of prevalence, comorbidities, clinical profile, and prognosis of patients with HFmrEF among large cohorts suggests that the link between

pathophysiology of HF and LVEF is not so linear and simple. HF includes multiple diverging patient-oriented time trajectories, resulting in a wide spectrum of different phenotypes.<sup>10</sup> Following any form of cardiac dysfunction, each patient will follow his individual trajectory within a large spectrum of LVEF, depending on the number of disease modifiers.<sup>10</sup> This questions if the patients with HFmrEF are truly a distinct pathophysiologic entity or a transitional phenotype between HFrEF and HFpEF as suggested by previous big cohort.<sup>6</sup> The new ESC classification of HF does not imply that patients will inevitably progress from HFpEF to HFmrEF then HFrEF. The recent study of Nadruz *et al.* regarding patients with previously reduced and then recovered EF suggests that mild range LVEF is not necessarily a transition step of the progression from normal LVEF to HFrEF or vice versa.<sup>11</sup> HFrEF, HFmrEF, and HFpEF are probably different phenotypes of the same disease whose final common pathway is the decrease of cardiac output and the onset of congestive signs leading to neurohormonal activation and poor prognosis. The recognition of a new group for the patients with mid-range LVEF occurred due to historical development of HF trials rather than due to a strong pathophysiological basis for a third entity in HF.<sup>4</sup> An ideal HF classification system would group together pathophysiologically similar individuals who may respond in the same way to clinical management and targeted therapy. Any classification that can guide treatment will be useful in clinical practice. Among measurements and indices of the left ventricular pump, LVEF has emerged as one of the most sensitive ones leading to the most therapeutic evidence, including effective pharmacological and device therapies. But LVEF is probably not the ideal parameter to stratify patients with HF. The remaining question is: is left ventricular pump performance 'preserved' in patients with HFmrEF and HFpEF? Other measures of myocardial function such as myocardial deformation imaging may be better parameters.<sup>12,13</sup>

## Limitations

As previously discussed, the sample of our study, as compared with large clinical trials in HF, is probably too small for allowing enough power to discriminate slight differences among groups of patients with HF. Trends of difference in the prevalence rates of obesity, hypertension, and sleep disorder breathing among groups suggest that a bigger sample would be able to show a significant difference. However, we think that these differences among studies are the results of the heterogeneity of the different phenotypes of the same disease.

Our study is an observational study, and therefore unmeasured confounding factors may influence the observed associations and prognosis. Thus, our study does not integrate echocardiographic and haemodynamic features, as well as right ventricular function, which are key determinants in

clinical practice for phenotyping and assessing prognosis of patients with HF. We did not distinguish the subset of patients with previously reduced and then recovered EF, which have been recently described as a distinct group from the residual population with similar clinical characteristics but better prognosis.<sup>11</sup> The difference in prognosis between these subsets of patients with HFmrEF may explain some reported discrepancies on prognosis in patients with HFmrEF.

Finally, we did not distinguish compensated and decompensated HF, or changes in medical therapy over time, which have a strong impact on prognosis. We did not distinguish cardiovascular mortality from all-cause mortality, which can be different among groups of HF and according to the LVEF, and could explain the difference of prognosis observed in previous studies.

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## Conclusions

Despite overlapping features with HFrfEF, as cardiovascular risk factors and medical history, patients with HFmrEF have a different clinical profile, which is nearly the same than patients with HFpEF, except for sex. HFrfEF, HFmrEF, and HFpEF carry the same poor prognosis of HF. Given the failure of clinical trials in the field of HFpEF, these results question the relevance of this new classification of HF to stimulate research into the new group of patients with HFmrEF.

## Conflict of interest

None declared.