ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 381–399
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12586

REVIEW

Heart failure with mid-range ejection fraction: pro and cons of the new classification of Heart Failure by European Society of Cardiology guidelines

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Abstract

Currently, the assessment of left ventricular ejection fraction (LVEF) is the cornerstone of the classification of patients with heart failure (HF). The mid-range LVEF (HFmrEF) category was identified in an attempt to uncover specific characteristics of these patients. So far, the analysis of trials, registries, and observational studies have demonstrated that patients with mid-range LVEF belong to a patient cohort with generally intermediate clinical profile as compared with other groups but with a remarkable variety of intrinsic phenotypes. This is due to the limitations of LVEF as the sole criterion to categorize patients with HF and characterize their prognosis, above all when it is >40%. To better define the HFmrEF phenotype, it is reasonable to consider other parameters, such as LVEF changes over time, HF aetiology, co-morbidities, and other imaging parameters. A multiparametric evaluation may contextualize a patient with HFmrEF in a more defined phenotype with a specific prognosis.

Keywords Heart failure with mid-range ejection fraction; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction; Classification

Received: 12 August 2019; Revised: 9 November 2019; Accepted: 12 November 2019
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Highlights

- New guidelines recommend distinguishing HFmrEF from HFpEF and HFrEF.
- Current categorization of patients with heart failure is primarily based on a measure of left ventricular ejection fraction, which has important limitations.
- HFmrEF is in general an intermediate clinical profile between HFpEF and HFrEF but is characterized by a number of distinct phenotypes.

Introduction

The 2016 European Society of Cardiology (ESC) guidelines have introduced a new classification of heart failure (HF) based on the left ventricular ejection fraction (LVEF) in combination with signs and symptoms of HF, elevated levels of natriuretic peptides, and signs of structural heart disease or diastolic dysfunction. The new guidelines classify patients with HF in three categories: heart failure with preserved ejection fraction (HFpEF), defined by an LVEF ≥50%, heart failure with reduced ejection fraction (HFrEF) if the LVEF is <40%, and heart failure with mid-range ejection fraction (HFmrEF) if the LVEF is 40–49%.[1] The 2013 ACC/AHA Heart Failure Guidelines recognized HFpEF and HFrEF categories and identified the group with mid-range LVEF as borderline HFpEF (in the range of 40–49%) or as HFrEF-improved for patients with prior reduced LVEF.[2] Recently, Australian and New Zealand guidelines have not recommended the recognition of the HFmrEF category because of the lack of a clearly defined syndrome for this group of patients, without specific recommendations in clinical management. They classify the patients as HFrEF and HFpEF with 50% as cut-off value between the two categories.[3] Thus, there is currently an ongoing debate about the 'grey area' of HF with mid-range LVEF.

Table 1 Overview of main clinical trials investigating HF patients with mid-range LVEF

Study	Year of pubblication	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
Rickenbacher P. *et al.*[4]	2017	2004–2005; median follow up 794 days	Europe	Symptomatic patients, CHF hospitalization within the last year, and elevated NT-BNP	824	17%	Mortality 39.7% (no significant differences) All-cause hospitalization free survival: $P = 0.08$ Survival: $P = 0.92$ HF hospitalization free survival: $P = 0.29$
Toma M. *et al.*[5]	2014	May 2007–August 2010	America, Europe, Asia, and New Zealand	Inclusion criteria of ASCEND-HF trial with LVEF recorded	5687	11.9%	180 day mortality HFrEF vs. HFpEF: HR 0.96 (0.75–1.24); $P = 0.77$ 180 day mortality HFmrEF vs. HFpEF: HR 0.91 (0.66–1.3); $P = 0.58$ Outcomes (HFrEF, HFmrEF, HFpEF; *P* value) Length of stay (days): 6 (4–10), 7 (4–10), 7 (5–11); 0.007 30 day all-cause rehospitalization: 11.7, 13.6, 18.1; <0.001
Solomon S.D. *et al.*[6]	2005	March 1999–March 2001; follow up: 38 months	Europe, USA, Canada, South Africa, and Australia	Patients enrolled in CHARM programme	7599	17% (LVEF 42–52%)	In patients with LVEF 42–52%: All-cause mortality: 5.2% CV death: 4% Non-CV death: 1.2% Fatal or non-fatal MI (1st episode): 1.7% CHF hospitalization: 5.7% Fatal or non-fatal stroke: 1.3% CV death or CHF hospitalization: 7.9%
Solomon S.D. *et al.*[7]	2016	August 2006–January 2012; follow up through June 2013	Americas (USA, Canada, Brazil, Argentina) and Europe (Russia and Georgia)	Patients with HF and LVEF ≥ 45% enrolled in TOPCAT	3444		CV death, aborted cardiac arrest, or hospitalization HF (per 100 patient-years): EF < 50%: HR 7.2 (6.0–8.7), 50% ≤ EF < 55%: HR 6.0 (5.0–7.0), 55% ≤ EF < 60%: HR 5.5 (4.7–6.4), EF ≥ 60% HR 6.7 (5.9–7.5); $P = 0.02$ HF hospitalization (per 100 patient-years): EF < 50%: HR 3.8 (2.9–5.0), 50% ≤ EF < 55%: HR 4.1 (3.3–5.0), 55% ≤ EF < 60%: HR 3.7 (3.0, 4.5), EF ≥ 60% HR 4.9 (4.2–5.6) ; $P = 0.79$ CV death (per 100 patient-years): EF < 50%: HR 4.1 (3.2–5.2), 50% ≤ EF < 55%: HR 2.8 (2.2–3.6), 55% ≤ EF < 60%: HR 2.7 (2.2–3.3), EF ≥ 60% HR 2.7 (2.2–3.2); $P = 0.002$ Death (per 100 patient-years): EF < 50%: HR 5.6 (4.5–6.8), 50% ≤ EF < 55%: HR 4.0 (3.3–4.8), 55% ≤ EF < 60%: HR 4.3 (3.6–5.0), EF ≥ 60% HR 4.3 (3.7, 4.9); $P = 0.004$

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DOI: 10.1002/ehf2.12586

Table 1 (continued)

Study	Year of pubblication	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
Lund L.H. *et al.*[8]	2018	March 1999–March 2001; follow up: 2.9 years	Europe, USA, Canada, South Africa, and Australia	Patients enrolled in the CHARM programme	7598	17%	Outcomes (HFmrEF vs. HFpEF; HFrEF vs. HFpEF) regardless of any treatment CV death + HF hospitalization: HR 1.00 (0.85–1.17) $P = 0.98$; HR 1.58 (1.40–1.79) $P < 0.001$ HF hospitalization: HR 0.94 (0.78–1.13) $P = 0.55$; HR 1.42 (1.23–1.64) $P < 0.001$ Recurrent HF hospitalization: HR 1.21 (0.98–1.49) $P = 0.07$; HR 1.96 (1.65–2.23) $P < 0.001$ CV death: HR 1.21 (0.98–1.51) $P = 0.08$; HR 2.20 (1.85–2.61) $P < 0.001$ All-cause hospitalization: HR 0.89 (0.81–0.98) $P = 0.02$; HR 0.99 (0.91–1.08) $P = 0.85$ All-cause death: HR 0.98 (0.82–1.19) $P = 0.88$; HR 1.73 (1.49–2.00) $P < 0.001$

CHF, chronic heart failure; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; OR, odds ratio.

Left ventricular ejection fraction based classification: Opportunities and limitations

The new classification by ESC was made in a recognition of the lack of knowledge about the patient cohort with LVEF 40–49%, given their exclusion from most of the trials and lack of evidence-based treatment. Trials, prospective, and retrospective observational studies, which included HFmrEF patients and their outcomes, are summarized respectively in *Tables 1*, *2*, and *3*. As acknowledged in the guidelines, the move for this new classification should be seen as an attempt to stimulate research and resolve pending critical questions, rather than an admittance to true phenotypical differences between HFmrEF and other groups. The aim of this review is to identify a clearer profile of the HFmrEF population and to discuss the effective role of the LVEF in the diagnostic and prognostic work up of patients with HF.

Left ventricle ejection fraction remains of fundamental importance for the classification of the patients with HF. The main reason for its pivotal role is that it was used as a main inclusion criterion in trials that identified effective drugs and devices for the treatment of the patients with HF. This is, however, true only for the patients with HFrEF, whereas no treatment has been shown to be effective for the patients with HFpEF, yet.[22] Thus, an LVEF-based classification of the HF population has some notable limitations, and this may be true above all when we have to consider patients with a normal LVEF. First of all, in many instances, the classification of patients as HFmrEF is simply the result of the variability in the measure of LVEF in patient cohorts with different degrees of impairment of myocardial function.[23] The large degree of 'mobility' between the three LVEF categories is due to the heterogeneous aetiology of patients with HFmrEF with several possible LVEF trajectories [e.g. ischaemic aetiology after revascularization, idiopathic dilated cardiomyopathy with different response to drugs or cardiac resynchronization therapy (CRT), myocarditis, HFpEF with progressive decline of LVEF]. Atrial fibrillation (AF) is an additional factor contributing to the mobility across the LVEF categories. AF can worsen pre-existing LV dysfunction or underlying cardiomyopathy, with a partial or complete improvement of the LVEF after the restoration of sinus rhythm.[24–27] A substantial number of patients may move in and out of HFmrEF group on serial echocardiograms, without any change of underlying pathology (*Figure 1*).[11,28]

Although a patient's LVEF underlies a dynamic without a change in underlying pathology, the associated risk can change significantly. Indeed, freedom from death/transplant/cardiac hospitalization in patients with HFmrEF who have recovered from HFrEF is higher than those with HFmrEF who remained stable.[11,29,30] The same applies to patients with HFmrEF with prior preserved LVEF.[15,29] So,

Table 2 Overview of main prospective observational studies investigating HF patients with mid-range LVEF

Study	Year of pubblication	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
Chioncel O. *et al.*[9]	2017	April 2011–January 2015	Europe	Enrolment in ESC-HF-LT Registry	9134 (outpatients) + 6926 (hospitalized)	24.20%	Outcomes (HFmrEF, HFrEF, HFpEF) Mortality at 1 year: 7.6%, 8.8%, 6.3% ($P = 0.005$) All-cause hospitalization: 22%, 31.9%, 23.5% ($P < 0.001$) HF hospitalization: 8.7%, 14.6%, 9.7% ($P < 0.001$) All-cause deaths or HF hospitalization: 15.0%, 21.2%, 14.6% ($P < 0.001$)
Koh A.S. *et al.*[10]	2017	2000-2013	Sweden	Clinician-judged HF	42 061	21%	Outcomes (HFmrEF vs. HFpEF, HFrEF vs. HFpEF) 30 day mortality overall cohort: HR 1.06 (0.86–1.30) $P = 0.573$,HR 1.35 (1.14–1.60) $P < 0.001$ 30 day mortality with CAD: HR 1.01 (0.75–1.36) $P = 0.945$, HR 1.47 (1.16–1.87) $P = 0.002$ 30 day mortality without CAD: HR 1.14 (0.86–1.87) $P = 0.356$, HR 1.21 (0.94–1.55) $P = 0.131$ 1 year mortality overall cohort: HR 1.08 (1.00–1.18) $P = 0.052$, HR 1.26 (1.17–1.35) $P < 0.001$ 1 year mortality with CAD: HR 1.14 (1.02–1.28) $P = 0.026$, HR 1.39 (1.26–1.53) $P < 0.001$ 1 year mortality without CAD: HR 1.05 (0.94–1.18) $P = 0.395$, HR 1.12 (1.01–1.24) $P = 0.034$ 3 year mortality overall cohort: HR 1.06 (1.00–1.12) $P = 0.066$, HR 1.20 (1.14–1.26) $P < 0.001$ 3 year mortality with CAD: HR 1.11 (1.02–1.21) $P = 0.011$, HR 1.34 (1.25–1.44) $p < 0.001$ 3 year mortality without CAD: HR 1.02 (0.94–1.12) $P = 0.592$, HR 1.05 (0.97–1.13) $P = 0.225$
Rastogi *et al.*[11]	2017	March 2010–August 2013	USA	Inpatients and outpatients with HF	168	16%	Death HFmrEF improved vs. HFrEF: HR 0.30 (0.11–0.76) $P = 0.23$ HFmrEF deteriorated vs. HFpEF: HR 1.11 (0.15–7.96) Cardiac hospitalization HFmrEF improved vs. HFrEF: HR 0.21 (0.10–0.45) $P = 0.016$ HFmrEF deteriorated vs. HFpEF: HR 1.08 (0.34–3.37) Death/transplant/any hospitalization HFmrEF improved vs. HFrEF: HR 0.40 (0.25–0.64) $P = 0.011$ HFmrEF deteriorated vs. HFpEF: HR 1.64 (0.62–4.35)
Cheng R.K. *et al.*[12]	2014	1 January 2005–30 December 2011; follow up: end of 2012	USA	Age $\geq$ 65 years hospitalized with a diagnosis of HF	40 239	14%	Outcomes (HFmrEF vs. HFpEF; HFrEF vs. HFpEF) Mortality: HR 0.967 (0.917–1.020) $P = 0.223$, HR 1.040 (0.998–1.084) $P = 0.065$ All-cause readmission: HR 1.032 (0.991–1.074) $P = 0.126$; HR 0.961 (0.930–0.993) $P = 0.016$ CV readmission: HR 1.148 (1.092–1.208) $P < 0.001$; HR 1.179 (1.132–1.228) $p < 0.001$ HF readmission: HR 1.215 (1.142–1.291) $P < 0.001$ HR 1.348 (1.284–1.416) b.001

(*Continues*)

Table 2 (continued)

Study	Year of pubblication	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
							Composite readmission/mortality: HR 1.022 (0.985–1.061) $P = 0.247$; HR 0.988 (0.958–1.018) 0.420
He K.L. *et al*.[13]	2009	September 2005–February 2008	China	Inpatients or outpatients seen at the People's Liberation Army General Hospital with and without HF	564	14% (LVEF 40–55%)	In patients with LVEF 40–55%: LVEDD 55 ± 7, FS 24 ± 4 ($P < 0.005$ vs. HFrEF and HFpEF) LVESD 42 ± 6, IVSd12 ± 2, PWTd 11 ± 2 ($P < 0.005$ vs. HFrEF) LVEDV 148 ± 38, LVEDVI 82 ± 20, LVESV 81 ± 24, LVESVI 45 ± 13, SVI 38 ± 8, LVEDV/mass ratio 0.57 ± 0.14 ($P < 0.005$ vs. HFrEF and HFpEF) SV 67 ± 16 ($P < 0.005$ vs. HFrEF) LVM 264 ± 74, LVM/BSA 145 ± 36 ($P < 0.005$ vs. HFpEF) E 75 ± 28, A 82 ± 22, E/A 1.07 ± 0.7, DT 217 ± 65, E' 7 ± 2 ($P < 0.005$ vs. HFrEF) S' 8 ± 2 ($P < 0.005$ vs. HFrEF and HFpEF)
Sweitzer *et al*.[14]	2008	1 January 2004	America	Patients hospitalized for acute decompensated HF and enrolled in ADHERE database	74 863	23% (LVEF 40–55%)	Outcomes in HF with LVEF 40–55%: In-hospital mortality: 3.2% ICU/CCU admission: 19.0% (significantly different from LVEF >55% at $P = 0.017$ level) ICU/CCU length of stay (days): 2.6 Total hospital length of stay (days): 4.7 Increase in creatinine 0.5 mg/dL during hospitalization: 14.9%
Nadruz *et al*.[15]	2016	July 2007–June 2013; median follow up: 4.4 years (through 31 December 2014)	USA	Patients with HF and CPET	944	29% (LVEF 40–55%)	Outcomes (improved-LVEF 40–55% vs. HFrEF; stable LVEF 40–55% vs. HFrEF) Death[a]: HR 0.32 (0.17–0.61) $P = 0.001$; HR 0.74 (0.45–1.21) $P = 0.23$ Death[b]: HR 0.42 (0.21–0.82) $P = 0.011$; HR 0.87 (0.51–1.46) $P = 0.59$ Left ventricular assistant device implantation, heart transplantation, or all-cause mortality[a]: HR 0.19 (0.10–0.36) $P < 0.001$; HR 0.25 (0.13–0.47) $P < 0.001$ Left ventricular assistant device implantation, heart transplantation, or all-cause mortality[b]: HR 0.60 (0.38–0.95) $P = 0.029$; HR 0.79 (0.49–1.28) $P = 0.34$
Löfman I. *et al*.[16]	2017	11 May 2000–3 October 2013	Sweden HF	Clinician-judged HF	40 230	21%	In HFmrEF with eGFR ≥ 60: 1 year mortality: 7.8%; 5 year mortality: 32.0%; death/100 patient-years: 2.23 In HFmrEF with eGFR < 60: 1 year mortality: 22.4%; 5 year mortality: 63.1%; death/100 patients years: 4.79 Association CKD-mortality: HFpEF: HR 1.32 (1.24–1.42); HFmrEF: HR 1.51 (1.40–1.63); HFrEF: HR 1.49 (1.42–1.56)

(*Continues*)

Table 2 (continued)

Study	Year of pubblication	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
Kapoor J.R. *et al*.[17]	2016	January 2005–September 2013	USA	HF admission in the Get With The Guidelines-HF (GWTG-HF) database	99 825	13%	In-hospital death: HFmrEF 2.62%, HFrEF 3.21%, HFpEF 3.02% ($P = 0.0020$) Length of stay >4 days: HFmrEF 46.61%, HFrEF 45.24%, HFpEF 48.74% ($P < 0.0001$) Factors associated with length of stay >4 days in HFmrEF: Pneumonia/respiratory process: OR 1.31(1.18–1.45) $P < 0.0001$ Dyspnoea: OR 1.31 (1.18–1.45) $P < 0.0001$ Dietary non-compliance: OR 0.72 (0.58–0.88) $P = 0.0015$ Medication non-compliance: OR 0.86 (0.75–0.99) $P = 0.032$ Factors associated with in-hospital death in HFmrEF: Worsening renal failure: OR 1.53 (1.02–2.28) $P = 0.039$ Pneumonia/respiratory process: OR 1.48 (1.05–2.10) $P = 0.025$ Medication non-compliance: OR 0.52 (0.27–0.98) $P = 0.043$
Tsuji *et al*.[18]	2017	October 2006–March 2010; follow up: 1–3 years	Japan	Patients enrolled in CHART-2 Study with previous history of symptomatic HF and echocardiographic available data at the registration	3480	17%	HFmrEF: intermediate incidences of all-cause death, CV death, and HF admission (all *P* values for trend <0.001); non-significant differences for non-CV death, acute MI, or stroke 1 year transition HFmrEF → HFpEF: 44% and HFmrEF → HFrEF: 16% 3 year transition HFmrEF → HFpEF: 45% and HFmrEF → HFrEF: 21% 1 year transition HFrEF → HFmrEF: 22% 3 year transition HFrEF → HFmrEF: 21% 1 year transition HFpEF → HFmrEF: 8% 3 year transition HFrEF → HFmrEF: 8% All-cause death according to the transitions after registration to 1 year (vs. HFpEF → HFpEF): HFmrEF → HFpEF: HR 0.81 (0.57–1.16) $P = 0.259$ HFmrEF → HFmrEF: HR 1.07 (0.74–1.54) $P = 0.717$ HFmrEF → HFrEF: HR 1.60 (1.05–2.44) $P = 0.026$ HFpEF → HFmrEF: HR 1.32 (0.96–1.81) $P = 0.078$ HFrEF → HFmrEF: HR 1.17 (0.73–1.89) $P = 0.502$

(*Continues*)

DOI: 10.1002/ehf2.12586

Table 2 (continued)

Study	Year of pubblication	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
Lupòn *et al*.[19]	2017	August 2001–December 2015; mean follow up: 5.6 ± 3.1 years	Europe	All consecutive ambulatory patients referred to HF unit with echocardiography assessment at the baseline and at 1 year of follow up	1057		(HF recovered = baseline LVEF <45% → LVEF ≥45% at 1 year follow up; HFpEF = stable LVEF ≥ 45% throughout the follow up; HFrEF = stable LVEF <45% throughout the follow up) Outcomes (HFpEF vs. HF recovered, HFrEF vs. HF recovered) CV death + HF hospitalization: HR 1.83 (1.27–2.65) $P = 0.001$, HR 1.74 (1.31–2.32) $P < 0.001$ All-cause death: HR 1.77 (1.20–2.61) $P = 0.004$, HR 1.54 (1.16–2.04) $P = 0.003$ CV death: HR 2.17 (1.23–3.82) $P = 0.007$, HR 2.23 (1.44–3.43) $P < 0.001$ HF death: HR 2.74 (1.34–5.58) $P = 0.006$, HR 2.94 (1.68–5.14) $P < 0.001$ Sudden death: HR 1.14 (0.26–5.05) $P = 0.87$, HR 2.16 (0.83–5.61) $P = 0.11$ At 1 year: HFrEF → HFmrEF: 22.%, HFrEF → HFpEF: 13.9%, HFrEF → HFrEF: 63.5% Outcomes (HFrEF → HFmrEF vs. HFrEF → HFpEF, HFrEF → HFrEF vs. HFrEF → HFpEF) CV death + HF hospitalization: HR 1.09 (0.69–1.72) $P = 0.700$, HR 2.19 (1.50–3.22) $P < 0.001$ All-cause death: HR 1.40 (0.89–2.20) $P = 0.151$, HR 2.23 (1.50–3.31) $P < 0.001$ CV death: HR 1.43 (0.71–2.89) $P = 0.310$, HR 3.34 (1.83–6.12) $P < 0.001$ HF death: HR 1.80 (0.72–4.50) $P = 0.210$, HR 4.93 (2.20–11.05) $P < 0.001$ Sudden death: HR 2.17 (0.45–10.36) $P = 0.330$, HR 4.61 (1.12–18.96) $P = 0.034$

BSA, body surface area; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic Kidney disease; CPET, cardiopulmonary exercise testing; CV, cardiovascular; CV, cardiovascular; DT, deceleration time; E/A ratio, ratio between mitral early and late wave velocity; E, Mitral early wave velocity; E', Tissue Doppler E = -wave velocity; eGFR, estimated glomerular filtration rate; FS, fractional shortening; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICU/CCU, intensive care unit/coronary care unit; IVSd, interventricular septal diameter; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; LVESVI, left ventricular end systolic volume index; LVM, left ventricular mass; MI, myocardial infarction; OR, odds ratio; PWTd, posterior wall thickness diameter; S', Tissue Doppler S = -wave velocity.

[a]Adjusted for age, sex, glomerular filtration rate, coronary artery disease, post-chemotherapy, diabetes mellitus, race and haemoglobin with death as outcome and for age, sex, glomerular filtration rate, coronary artery disease and post-chemotherapy with composite endpoint as outcome.

[b]Further adjusted for use of pacemaker, diuretics, statins and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with death as outcome and for use of diuretics, aldosterone antagonists, anticoagulation and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with composite endpoint as outcome.

Table 3 Overview of main retrospective observational studies investigating HF patients with mid-range LVEF

Study	Year of pubblication	Type of study	Enrolment/ follow up	Geography	Inclusion criteria	Patient number	Prevalence of HFmrEF	Outcomes for HFmrEF
Coles A.H. *et al.*[20]	2014	Retrospective review of study population	Years of 1995, 2000, 2002, and 2004	USA	Patients hospitalized for acute decompensated HF	3604	14%	Mortality at 1 year after discharge (HFmrEF vs. HFpEF; HFrEF vs. HFpEF) HR 1.37 (1.14–1.65); HR 1.17 (1.07–1.28) Mortality at 2 years after discharge (HFmrEF vs. HFpEF; HFrEF vs. HFpEF) HR 1.36 (1.20–1.55); HR 1.17 (1.09–1.24) Mortality at 5 years after discharge (HFmrEF vs. HFpEF; HFrEF vs. HFpEF) HR 1.04 (0.98–1.10); HR 1.02 (0.99–1.05)
Coles A.H. *et al.*[21]	2015	Retrospective review of study population	Years of 1995, 2000, 2002, 2004, and 2006	USA	Patients hospitalized for acute decompensated HF	4025	13%	Deaths rates at 1 year after discharge: 34% (HFrEF), 30% (HFmrEF), and 29% (HFpEF) ($P = 0.03$) Factors significantly associated with 1 year mortality after discharge in HFmrEF and according to age: COPD in >75 years: HR 1.63 (1.07–2.47) Serum sodium >135 mEq/L in <75 years: HR 0.22 (0.10–0.51) Systolic blood pressure (150–159 mmHg) in >75 years: HR 0.47 (0.24–0.91)

COPD, chronic obstructive pulmonary disease; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.

beyond the baseline LVEF assessment, the prognostic implications of longitudinal LVEF changes are becoming increasingly clear, and specific factors have been identified as predictors of increasing or decreasing LVEF.[31] Therefore, the attempt to classify patients in LVEF categories does not appropriately account for the spectrum of diverse phenotypes within the LVEF categories.[31]

Because LVEF is not a static measurement, HFmrEF is certainly a heterogenous condition with variable evolutions rather than a stable phenotype. Only slightly more than one-third of the HFmrEF population remains in the same category during the long-term follow up.[19,31] Conversely, the remaining patients reclassify into HFpEF (25–33%) and HFrEF categories (25–37%). LVEF measurements are subject to a wide intra-variability and inter-variability and vary between modalities. Further, several variables, such as preload, afterload, contractility, valvular diseases, systolic blood pressure, and heart rate, can temporarily influence the value of LVEF.[28] However, evaluation of cardiac function is complex and goes beyond the LVEF and contractility. For example, diastolic dysfunction is more severe in patients with HFmrEF and prior HFpEF than in those with prior HFrEF, indicating its greater value as a determinant of the clinical course of these patients.[11] LVEF alone is also not an accurate marker of remodelling. Left ventricular volumes, mass, stroke volume, and their changes in time are more accurate index of maladaptive remodelling and correlate better with the prognosis and response to the therapy.[28,32] Thus, the current use of LVEF for HF classification to some extent impairs our ability to discern true myocardial recovery from myocardial remission in which there are signs of reverse remodelling but without a complete reversal of damage[33].

Beyond the LVEF, delayed times of contraction and dyssynchrony are important independent signs of LV dysfunction.[28,34,35] The assessment of myocardial deformation, such as the strain and strain rate, through the tissue Doppler or global longitudinal strain (GLS)[28] or on gated single-photon emission computed tomography myocardial perfusion imaging could be alternative methods to classify HF patients.[34,35] The GLS is measured on the basis of the LV longitudinal shortening in systole, and it is an index of systolic function.[36] It may become abnormal at an earlier stage before a decrease in LVEF.[37,38] GLS has an independent prognostic value in the mid-range and preserved LVEF group, because of the loss of prognostic value of LVEF in this HF population.[39] In particular, GLS is a stronger predictor of all-cause mortality and outcomes (cardiac death, HF hospitalization, and malignant arrhythmias) than LVEF,[40] and the additional predictive value over LVEF for mortality is more pronounced for LVEF >35%.[39] GLS allowed a better risk prediction independent of and incremental to the LVEF also in patients with acute myocardial infarction, including those with HFmrEF.[41] In addition, peri-infarct strain is the only independent predictor of malignant cardiac arrhythmias, and GLS could identify

Figure 1 Heart failure phenotypes based on left ventricle ejection fraction. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

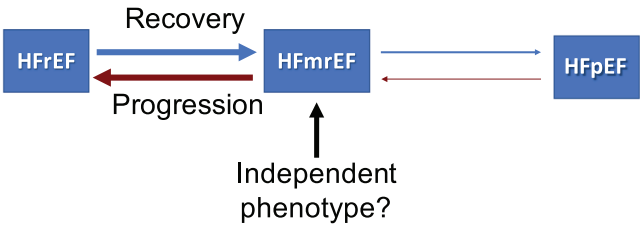
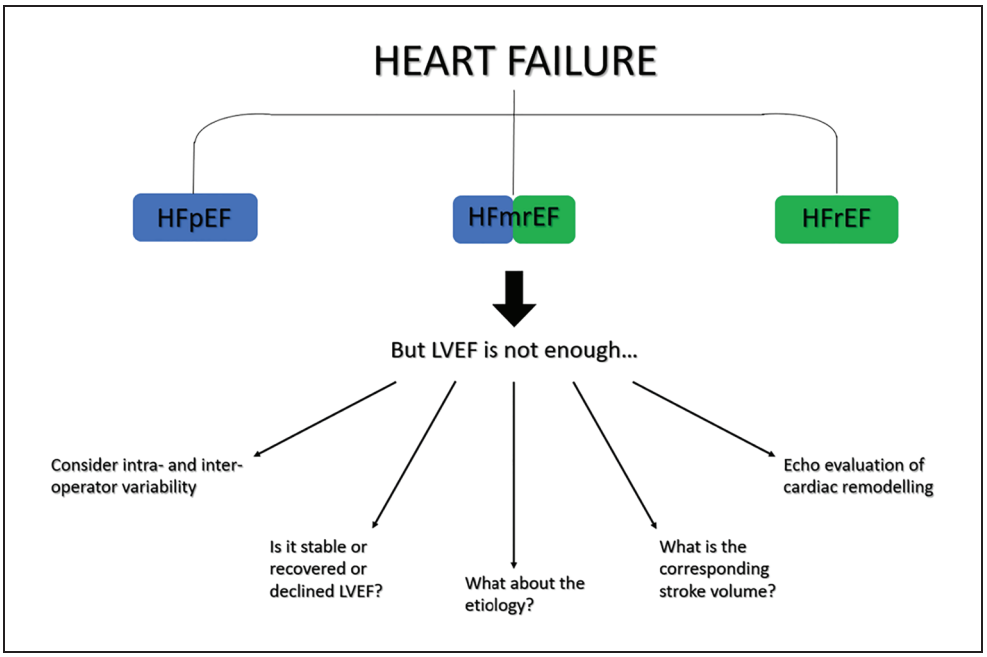


Figure 2 Evaluation of HFmrEF beyond LVEF. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricle ejection fraction.



patients at risk of ventricular arrhythmias despite LVEF is >35%.[39] Even in the setting of acute HF, for a given LVEF, there is a wide distribution of LV dyssynchrony, and LV dyssynchrony appears to have a greater prognostic role than LVEF.[42]

The current LVEF-based HF classification does not take into account the underlying HF aetiology and its influence on prognosis.[32,43] Cardiac magnetic resonance (CMR) imaging and late gadolinium enhancement add notable diagnostic and prognostic information in patients with HF, especially in the diagnostic workup of LV hypertrophy. The CMR allows an accurate study of myocardial extracellular volume (ECV) and the detection of fibrosis, interstitial oedema, or deposition of proteins, lipids, or iron. It is a superior imaging method for the identification of the right underlying aetiology of HF.[36] The correlation between the ECV and the echocardiographic parameters, such as LVEF, LV volumes, peak ejection, and peak filling rate, is clearer for the HFpEF group but has not been demonstrated for patients with reduced EF.[36] Moreover, the ECV expansion is significantly linked with higher rates of mortality and worsening of HF.[36] Finally, the epicardial fat detected by CMR is reduced in the HFrEF and increased in the HFmrEF and HFpEF populations compared with healthy controls, suggesting a possible role of fat-associated inflammation in the mechanisms of HF in the upper value of the LVEF spectrum.[44] Given that LVEF is an imaging-based parameter, it is unable to fully account for the disease trajectory, including predisposition to malignant arrhythmias and the risk of sudden cardiac death.[32] Nowadays, it is clear that a better stratification of the arrhythmic risk requires genetic testing, especially in dilated cardiomyopathy. Genetic mutations involved in the cardiomyopathies

Table 4 Summary of clinical characteristics, medication pattern, and echocardiographic parameters of HFmrEF population included in the main clinical trials considered for our review

	Rickenbacher P. *et al.*[4]	Toma M. *et al.*[5]	Solomon S.D. *et al.*[6a]	Solomon S.D. *et al.*[7b]	Lund LH *et al.*[8]
Age, years, mean ± SD	79.0	73	66.3 ± 10.8	66 ± 9	65 ± 11
Female gender, %	46.3	41.1	32	36.5	
BMI, kg/m^2, mean ± SD or median (IQR)	25.5			31.5 ± 7.2	27.8 (25.0–31.2)
SBP, mmHg, mean ± SD or median (IQR)	127	130 (117–147)	135.2 ± 18.9	128 ± 14	130 (120–145)
Heart rate, b.p.m., mean ± SD or median (IQR)	76	78 (68–90)	71.4 ± 12.4	69.98 ± 10.17	
eGFR, mL/min/1.73 m^2, mean ± SD or median (IQR)	49	53.8 (38.5–69.9)		69.6 ± 19.9	
Creatinine, mg/dL, mean ± SD or median (IQR)	1.39				1.16 ± 0.43
Sodium, mmol/L, mean ± SD or median (IQR)	139	140 (137–142)			
NT-proBNP, median (IQR), ng/L	3941 (2247–6760)	3931 (1933-8269)			
BNP, median (IQR), ng/L		898 (557–1435)			
NYHA class III/IV, %	71.3		36.8	35.4	42.3
Hypertensive heart disease, %	27.8				12.7
Ischaemic aetiology, CAD, %	56.5	69.0	72		66.9
Idiopathic dilated CMP, %	8.3				13.1
Valve disease and other, %	7.4				
CABG or PCI, %	32.4	29.2	36		43.6
CRT, %					
ICD, %	2.8	3.9			1.6
Smoker, current, or previous %	60.2	50.7	15		15.9
Hypertension, %		81.9	60	86.5	56.2
PAOD, %	18.5	19.3			
Hyperlipidaemia, %	48.1				
Diabetes mellitus, %	39.8	50.2	27	28.7	28.6
COPD, asthma, and lung disease, %	21.3	20.3			
Prior stroke/TIA and cerebrovascular disease, %	15.7	14.2			9.3
CKD, %	63.9				
Anaemia, %	38.0				
Depression, %	13.0	11.1			
Atrial fibrillation, flutter %	39.6	49.9			25.6
LVEDD, mm, mean ± SD	52				
LVESD, mm, mean ± SD	42				
Beta-blocker, %	73.1	65.4	57	78.3	57.7
ACE-I/ARBs, %	90.7	60.7	21	88.1	27.2
Aldosterone receptor blocker, %	33.3	21.2	11		11.4
Nitrates, %	32.4	24.5			
Diuretics %	89.8	97.2	64	76.2	74.4
Statin and lipid-lowering therapy %					44.7
Digoxin and digitalis, %	13.9	8.0	32		35.2
Calcium channel blocker, %			26		24.1

ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CMP, cardiomiopathy; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquantile range; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; PAOD, peripheral arterial occlusive disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD,standard deviation.

[a]population of patients with HF and LVEF 43–52%.

[b]population of patients with HF and LVEF 45–50%.

DOI: 10.1002/ehf2.12586

Table 5 Summary of clinical characteristics, medication pattern, and echocardiographic parameters of HFmrEF population included in the main prospective observational studies considered for our review

	Chioncel O. *et al.*[9]	Koh A.S. *et al.*[10]	Rastogi *et al.*[11]	Cheng R.K. *et al.*[12]	He K.L. *et al.*[13c]	Sweitzer *et al.*[14c]	Kapoor J.R. *et al.*[17]	Tsuji *et al.*[18]	Lupòn et al.[19a]
Age, years, mean ± SD	64.2 ± 14.2	74	56 ± 13.09	81	66 ± 10	73.8 ± 12.9	74.44 ± 13.31	69.0 ± 12.7	63.2 ± 12.4
Female gender, %	26.4	39	46	50.5	21	54.3	48.85	28.2	
BMI, kg/m^2, mean ± SD, or median (IQR)	28.6 ± 5.4	27		26.5	25 ± 4	29.9 ± 7.9		22.8 ± 5.3	27.7 ± 4.9
SBP, mmHg, mean ± SD, or median (IQR)	126.5 ± 21.1	131	119 ± 18.65	142	141 ± 31	129 ± 22[b]		124.7 ± 19.3	129.3 ± 22.9
Heart rate, b.p.m., mean ± SD, or median (IQR)	73.2 ± 15.9	73	74 ± 12.88	81	69 ± 8	62 ± 19[b]		73.4 ± 14.7	70.1 ± 15.5
eGFR, mL/min/1.73 m^2, mean ± SD, or median (IQR)		62	76 ± 29.46		71 ± 28			58.6 ± 22.1	64.2 ± 24.1
Creatinine, mg/dL, mean ± SD, or median (IQR)		1.22	1.0	1.3	1.33 ± 1.07	1.3 (1.0–1.9)		1.1 ± 0.8	
Sodium, mmol/L, mean ± SD, or median (IQR)			140 ± 2.97	138					138.3 ± 3.3
NT-proBNP, median (IQR), ng/L		2160 (938-4763)			2037 ± 3484				994 (465–2165)
BNP, median (IQR), ng/L				790 (421–1487)	500 ± 627			164.5 (83.4–310.7)	
NYHA class III/IV, %	18.4	31	22					11.8	18.5
Hypertensive heart disease, %	9.6							14.3	9.4
Ischaemic aetiology, CAD, %	41.8	53	20	56.7	65	59.7	68.95	52.9	35.2
Idiopathic dilated CMP, %	27.6		65					20.3	19.3
Valve disease and other, %	11.5	21	20	14.4		24.8		7.2	18.9
CABG or PCI, %	35.8			17.1				43.1	
CRT, %	8.4	0.9		1.8				1.8	4.3
ICD, %	13.4	1.6		5.5				3.9	5.6
Smoker, current, or previous, %	10.7	55		8.7		12.1	14.11		
Hypertension, %	82.4	64	51	77.9	77		82.18	89.8	
PAOD, %		10	4	15.5		19.9	15.84		61.4
Hyperlipidaemia, %			35	48.2		38.0	54.02	80.2	
Diabetes mellitus, %	30.5	27	26	41.5	48	47.7	50.16	36.1	33.0
COPD, asthma, and lung disease, %	11.6	30	9	29.6		31.5	36.43		
Prior stroke/TIA and cerebrovascular disease, %	8.3		8	17.1		18.0	17.10	22.1	
CKD, %	16.5			21.1		30.9	25.78		42.0
Anaemia, %		35		21.3			27.02		40.3
Depression, %	7.1			10.0			12.86		
Atrial fibrillation, flutter %	22.3	58	26	40.2	8	32.9	45.00	43.5	21.0

(*Continues*)

Table 5 (continued)

	Chioncel O. *et al.*[9]	Koh A.S. *et al.*[10]	Rastogi *et al.*[11]	Cheng R.K. *et al.*[12]	He K.L. *et al.*[13c]	Sweitzer *et al.*[14c]	Kapoor J.R. *et al.*[17]	Tsuji *et al.*[18]	Lupòn et al.[19a]
LVEDD, mm, mean ± SD	58.0 ± 8.4		54 ± 7.4		55 ± 7			55.8 ± 7.9	
LVESD, mm, mean ± SD			41 ± 7.6		42 ± 6			42.9 ± 6.9	
Beta-blocker, %	86		88	86.5[b]	58	62.2		63.8	93.1
ACE-I/ARBs, %	84		86	83.5[b]	68	71.8		80.0	92.7
Aldosterone receptor blocker, %	24		42	13.0[b]				29.3	55.8
Nitrates, %	17		5			52.0			
Diuretics, %			69		45			63.3	89.3
Statin and lipid-lowering therapy, %			42					39.6	
Digoxin and digitalis, %			30		23				37.3
Calcium channel blocker, %			3		39	30.5		27.0	

ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CMP, cardiomiopathy; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquantile range; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; PAOD, peripheral arterial occlusive disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD,standard deviation.
[a]Only for HFmrEF with recovery of LVEF.
[b]After discharge.
[c]Population of patients with HF nad LVEF 40–55%.

interfere with the encoding of proteins necessary for the contraction of myocytes or ion channel function in the myocardiac tissue.[45] In particular, LMNA and DSP mutations (implicated respectively in the encoding of laminin and desmoplakin) are associated with higher risk of sudden cardiac death.[45] These findings suggest that the outcomes correlate more specifically with primary arrhythmia mechanisms than with the degree of left ventricular dysfunction.[45] Thus, a complete evaluation of heart chamber sizes, geometry, and function with genetic, clinical, and biomarker data is more appropriate than the measurement of LVEF alone[46] (*Figure 2*). Given the limitations of LVEF, the recognition of phenotypes across the LVEF spectrum should consider the disease mechanisms and/or the bio-profiling of the patients.[47] In addition, co-morbidities, such as diabetes and kidney dysfunction, may have a major role and influence outcomes more than the LVEF itself[48].

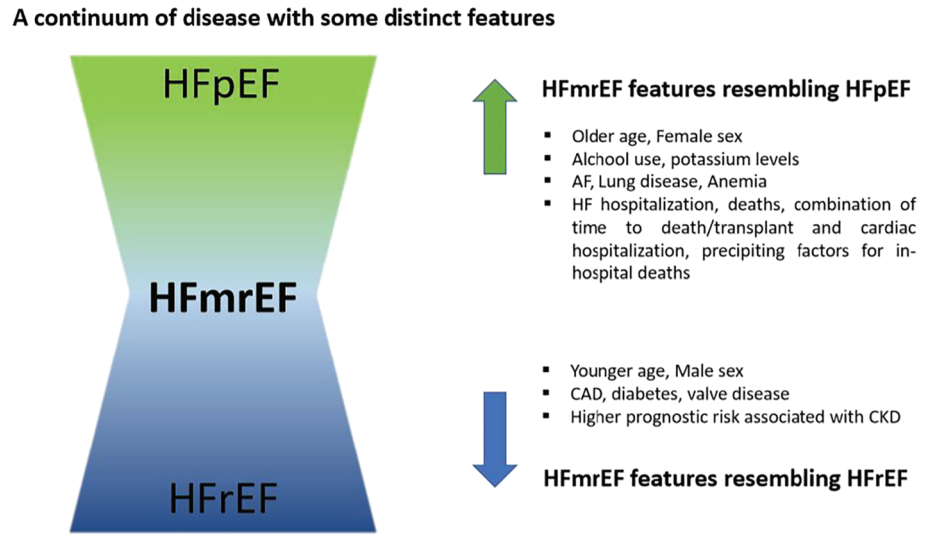
Demographic and clinical characteristics

Real-world registries and clinical trial data suggest a HFmrEF prevalence of 14–24% among the overall HF population.[4,9,10,19,31] Up until recently, HFmrEF was commonly considered a clinical condition more similar to HFpEF than HFrEF, with higher rates of female patients and more common history of hypertension and atrial fibrillation/flutter.[12,20,21] With an increased attention to the HFmrEF group, the clinical profile of these patients is becoming clearer. Currently, it seems like the three groups show a continuous relationship of most clinical characteristics. Clinical features, co-morbidities, medication pattern, and echocardiographic parameters of this population in the different studies are compared in *Tables 4* and *5*. In *Figure 3*, we highlight the intermediate clinical profile of HFmrEF, specifying the aspects of resemblance with the other two HF categories.

Biomarkers

Natriuretic peptides (NPs) and other biomarkers can help improve the current HF classification. Recent large randomized controlled trials used specific biomarkers, such as elevated levels of NP, as an enrolment criterion. There is a significant variability in NPs levels across the spectrum of HF.[49] Similar to troponin, NPs achieve higher levels in HFrEF, intermediate levels in HFmrEF, and lower concentrations in HFpEF. The association between high N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and increased mortality and hospitalization rates is independent from LVEF. In addition to its absolute values, their changes over time have an important role also in the HFmrEF group.[50] The prognostic

Figure 3 HFmrEF on a continuum of disease. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



role of NT-proBNP is even greater in HFmrEF and HFpEF than in HFrEF, although its absolute levels are lower and more affected by some confounding factors, particularly AF.[51] AF has also a major role on NPs trajectories in HFrEF.[52]

Natriuretic peptides allow a differentiation of HF subtypes in patients with HFmrEF. For example, patients with HFmrEF and recovered LVEF have lower baseline NT-proBNP levels than patients with a downtrending LVEF.[19] Troponin is another commonly used biomarker. Troponins have a prognostic role, regardless of LVEF.[53] Generally, the biomarker profile of HFmrEF is intermediate between the two extremes of the LVEF spectrum. In HFmrEF group, both biomarkers of cardiac stretch (NT-proBNP), typical of HFrEF, and the biomarkers of inflammation, typical of HFpEF, such as endothelin-1 and galectin-3, are well represented in the acute and chronic HF setting.[54]

Co-morbidities

The ESC Heart Failure Long-Term Registry showed a comparable prevalence of non-cardiac co-morbidities in the three LVEF groups,[4,9] except for chronic obstructive pulmonary disease, renal, and hepatic dysfunction, which were more commonly associated with HFrEF.[9] Coronary artery disease (CAD) is a leading aetiology of HF in both HFmrEF and HFrEF patients, as compared with HFpEF.[4,10,13] HFmrEF patients are less often diabetic and anaemic, with less frequent atrial fibrillation, lung disease, or chronic kidney disease (CKD) when compared with HFpEF. HFmrEF is characterized by a higher prevalence of atrial fibrillation, respiratory disease, and aortic stenosis than HFrEF.[10,13,14] In HFmrEF, the prevalence of CKD is around 50%.[16] CKD has a prognostic role in all the three LVEF categories, but the correlation with a mortality seems stronger for the mid-range and reduced LVEF groups.[16] This could be explained by the tight connection between CKD and a more advanced HF stage. In this scenario, both the backward and forward haemodynamic failure and the neurohormonal activation compromise the renal function, and CKD in turn contributes to further cardiac deterioration. Similar to CKD, the prognostic influence of diabetes mellitus on the mortality seems greater in HFmrEF and HFrEF.[55] On the contrary, AF has the same prognostic impact across all the EF spectrum, with a similarly increased risk of death, HF hospitalization, and stroke/TIA, regardless of LVEF.[56] An analysis of a community-based prospective observational study has shown a similar impact of co-morbidities regardless the LVEF values with a linear increase in events rates with an increased number of co-morbidities and with a major contribution of anaemia, CKD, chronic obstructive pulmonary disease, diabetes mellitus, and peripheral artery disease.[57]

Outcomes

The ESC Long-Term registry and other studies[7,58] have shown an intermediate rate of mortality at 1 year (7.6%) as compared with reduced and preserved LVEF (8.8% and 6.4%, respectively).[9] Most of the data show better outcomes for the patients with HFmrEF, compared with those with HFrEF. Event rates of the patients with HFmrEF are better than in HFrEF and similar to those of the patients with HFpEF, above all after adjustments for patients' characteristics.[6,10,59] Yet other studies have found similar rates of HF hospitalization

Table 6 Summarize results of landmark trials stratified for LVEF

Study	Prevalence (%)			Main outcomes	Outcomes stratified for LVEF		
	HFrEF	HFmrEF	HFpEF		HFrEF	HFmrEF	HFpEF
DIG trial[60]	75.42	15.34	9.23	Digoxin/placebo HR for HF hospitalization	0.71 [95% CI 0.65–0.77]	0.80 [95% CI 0.63–1.03]	0.85 [95% CI 0.62–1.17]
				Digoxin/placebo HR for the composite of HF death or HF hospitalization	0.74 [95% CI 0.68–0.81]	0.83 [95% CI 0.66–1.05]	0.88 [95% CI 0.65–1.19]
CHARM programme[8]	57	17	26	Cardiovascular death or HF hospitalization	15.9 per 100 p-y	8.5 per 100 p-y	8.9 per 100 p-y
				Candesartan/placebo HF for the composite of cardiovascular death or HF hospitalization	0.82 [95% CI 0.75–0.91; $P < 0.001$]	0.76 [95% CI 0.61–0.96; $P = 0.02$]	0.95 [95% CI 0.79–1.14; $P = 0.57$]
				Candesartan/placebo incident RR for recurrent HF hospitalization	0.68 [95% CI 0.58–0.80; $P < 0.001$]	0.48 [95% CI 0.33–0.70; $P < 0.001$]	0.78 [95% CI 0.59–1.03; $P = 0.08$]
TOPCAT[7]	0	15[a]	85	Composite of CV death, aborted cardiac arrest, or HF hospitalization	—	1.37 [95% CI 1.09–1.72]	Referent[b]
				HF hospitalization	—	1.06 [95% CI 0.79–1.44]	Referent[b]
				CV death	—	1.86 [95% CI 1.35–2.55]	Referent
				Spironolattone/placebo HR for composite of CV death, aborted cardiac arrest, or HF hospitalization	—	0.72 [95% CI 0.50–1.05]	0.97 [95% CI 0.76–1.23; $P = 0.046$][b]
				Spironolattone/placebo HR for HF hospitalization	—	0.76 [95% CI 0.46–1.27]	0.98 [95% CI 0.74–1.30; $P = 0.039$][b]
PARAGON-HF[61]	0	52[c]	48[c]	ARNI/valsartan RR for HF hospitalizations and CV death	—	0.78 [95% CI 0.64–0.95]	1.00 [95% CI 0.81–1.23]
Meta-analysis on beta-blockers (Cleland *et al.*)[62]	94	4	2	All-cause mortality HR for each 5% lower LVEF	1.16 [95% CI 1.26–1.19; $P < 0.0001$]	1.16 [95% CI 1.26–1.19; $P < 0.0001$]	1.16 [95% CI 1.26–1.19; $P < 0.0001$]
				Beta-blockers/placebo HR for all-cause mortality in sinus rhythm	0.67 [95% CI 0.50–0.90]; $P = 0.007$[d]	0.59 [95% CI 0.34–1.03]; $P = 0.066$	1.79 [95% CI 0.78–4.10]; $P = 0.17$
				Beta-blockers/placebo HR for CV death in sinus rhythm	0.72 (0.52–0.99); $P = 0.041$[d]	0.48 [95% CI 0.24–0.97]; $P = 0.040$	1.77 [95% CI 0.61–5.14]; $P = 0.29$
				Beta-blockers/placebo mean change in LVEF from baseline to follow up in sinus rhythm (SE)	+4.9% (0.9)[d]	+1.9% (1.1%)	+0.1% (1.2%)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; p-y, patient-years; RR, rate ratio; SE, standard error.
[a]LVEF values are ≥45% and <50%.
[b]For LVEF, ≥60%.
[c]In the analysis of pre-specified groups of PARAGON-HF trial, the cut-off value of LVEF is 57% (45–57% and >57%).
[d]These results belong to the subgroups of patients with LVEF 35–39%; for the other subgroups of HFrEF (LVEF <20%, 21–25%, and 26–34%), the HR are superimposable.

Table 7 Summary of positive (↑) and negative (↓) effect of HF medication on adverse outcomes (mortality and HF hospitalization) in the HFmrEF

Study	MRA	ACE-i	ARB	Beta-blocker	Diuretics	Statin
Pitt *et al*. TOPCAT[63]	↑					
Xiang *et al*.[64]	↑					
Fonarow *et al*. OPTIMIZE-HF[65]			=	=		
Tsuji *et al*.[18]		=	=	↑	↓	=
Yusuf *et al*. CHARM-PRESERVED[66]			↑			
Koh *et al*.[10]		↑	↑	↑		↑
Lund *et al*. CHARM programme[8]			↑			

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

and survival between the three LVEF categories.[4] In the presence of CAD, HFmrEF group has higher all-cause death rates at 3 years as compared with HFpEF, probably because of an incomplete myocardial revascularization.[10] In the in-hospital setting, patients with HFmrEF have lower rates of in-hospital death (2.6%) than preserved and reduced LVEF populations (3.0% and 3.2%, respectively).[17] Moreover, precipitating factors for HF decompensation vary by EF group and are independently associated with clinical outcomes.[17]

Medical and non-medical treatment

Since the introduction of the new LVEF-based classification of HF, several retrospective analyses have explored differences in medication use and treatment response. In general, the use of medication is comparable between HFmrEF and HFrEF. The use of digoxin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers is higher in HFrEF, while patients with HFpEF are more likely to receive calcium channel blockers.[10,11,29] The proportion of patients on mineralocorticoid receptor antagonists has a wide range (23–55%).[9,10,29] Retrospective analysis of clinical trials and observational studies has explored the effects of drugs and devices in patients with HFmrEF. The results of landmark HF trials stratified for LVEF are reported in *Table 6*; meanwhile, the summary of the effect of the main HF therapies on outcomes specifically in the HFmrEF population is reported in *Table 7*. Spironolactone was associated with decreased hospitalization rates in HF patients with LVEF ≥45%, with a stronger benefit for the range of LVEF values from 45% up to 50%.[63,67] HFmrEF patients benefit from spironolactone treatment also in terms of improvement of NYHA class and reduction of BNP and indices of myocardial fibrosis.[64] Despite some analyses of observational studies,[18,65] an analysis of CHARM[8] showed a reduction of HF hospitalization,[66] mortality,[10] and of the composite endpoint (cardiovascular death and HF hospitalization)[8] with candesartan in the mid-range LVEF category. Finally, the benefit of beta-blockers in this population appears still unclear. While the OPTIMIZE-HF registry[65] did not show a benefit from beta-blockers, other data demonstrated a reduction in mortality in all the EF categories.[18] Particularly, beta-blockers increase the LVEF for the patients with LVEF <50% and reduce the CV death both in HFrEF and in HFmrEF.[62] The improvement of the prognosis with beta-blockers is greater in specific subgroups, such as HFmrEF with CAD.[10] Diuretics seem to have negative influence on the prognosis also in patients with HFmrEF.[18] In spite of HFrEF, digoxin does not significantly reduce HF hospitalization rates in the HFmrEF population.[60] The current evidence for HFmrEF treatment has been summarized in a recent consensus article. It states that candesartan and spironolactone may be considered for ambulatory patients with symptomatic HFmrEF in order to reduce the risk of HF hospitalization and CV death and that beta-blockers may be considered in ambulatory patients with HFmrEF in sinus rhythm, to reduce all-cause and cardiovascular death.[68]

Recently, the PARAGON-HF has failed to demonstrate a significant reduction of HF hospitalization and CV death with Sacubutril/Valsartan in HF patients with LVEF ≥45%.[61] The

Table 8 Pros and cons of an LVEF-based classification for patients with HFmrEF

Pros	Cons
Standardize the clinical approach	Large mobility of patient with HF between LVEF categories
Standardize the care	Lack of consideration of the underlying HF aetiology
The LVEF is a simple criterion to plan and design randomized trials	Poor information about the ventricular remodelling and/or ventricular dyssynchrony
Acknowledgement of a subgroup with a specific bio-clinical profile that is different from HFrEF and HFpEF	Intra-variability and inter-variability of the echo LVEF measurement
Lack of other classifiers and targets that are reproducible and/or treatable	Intrinsic limitations of LVEF alone
	HFmrEF patient cohort is a heterogeneous population with many phenotypes
	Loss of prognostic power of LVEF proportionally to the increase of LVEF values

inconclusive results from TOPCAT (spironolactone in HFpEF) will hopefully be soon corrected by the two ongoing spironolactone in HFpEF trials (SPIRRIT-HFpEF and SPIRIT).[7] Notably, across PARAGON-HF and TOPCAT, lower LVEF was associated with improved outcomes. For PARAGON-HF, the HR of the primary outcomes was 0.76 (95% CI 0.63–0.92) per 10% decrease in LVEF suggesting that in respect to neurohormonal blocker therapy. In the same category of patients, also Vericiguat did not show a change of NT-proBNP and of left atrial volume [69]. Currently, one of the most interesting area of research in the HF concerns the sodium glucose cotransporter 2 inhibitors. Given the reduction of HF hospitalizations and CV death with sodium glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus regardless of history of HF,[70,71] the ongoing EMPEROR-Preserved, DELIVER, and SOLOIST-WHF trials have the aim to study the effect of this drug category on the HF outcomes in patients with LVEF $\geq$45%.

The rates of implanted implantable cardioverter defibrillator (ICD)/CRT-D in the three LVEF categories have a wide variability.[4,5,8,9,19,29] Regarding the use of pacemakers, CRT, and/or ICD, HFmrEF resembles more HFpEF.[10] Specifically, HFmrEF patients with improved or recovered LVEF have intermediate rates of implanted pacemakers and/or ICD/CRT when compared with HFrEF and HFpEF patients.[15,19]

Conclusions

The new category of HFmrEF does not simply indicate an intermediate category between HFrEF and HFpEF but comprises a heterogenous population of patients with distinct and heterogeneous prognostic profiles. Thus, HFmrEF represents a new area of investigation and future research. The complexity of this population lies in the heterogeneity of its clinical profile, prognosis, and the underlying pathophysiological substrate. Before the current ESC guidelines, clinical trials and registries often lumped HFpEF and HFmrEF together, potentially introducing a high degree of variability in clinical phenotypes. The complexity of cardiac and extra-cardiac factors in HF demands a more comprehensive evaluation and classification of patients across the whole spectrum of cardiovascular diagnostic and therapeutic metrics. The current HF classification is based on LVEF measurement alone, but, as demonstrated earlier, there are many limitations to this method. Thus, a more detailed phenotyping may allow to better characterize patients, provide greater prognostic differentiation, help for more precise targeting of therapies to patients, and stimulate the discovery of new more effective treatments. It is reasonable to consider an alternative and more reliable classification, including other imaging parameters or their changes over time and taking into account biomarkers and the phenotype migration. HFmrEF may occur either as a recovery from HFrEF or, less often, as a progression from HFpEF. It may also be the first presentation of HF, although it may move to HFrEF or HFpEF in its clinical course. In each instance, the HFmrEF phenotype has a different clinical makeup and prognosis. LVEF alone is insufficient to capture which phenotype HFmrEF belongs to and what the trajectory/prognosis of the phenotype is (*Table 8*).

Conflict of interest

None declared.

Funding

Dr Fudim is supported by an American Heart Association (grant 17MCPRP33460225) and National Institutes of Health T32 post-doctoral training (grant 5T32HL007101-42) and consults for Axon Therapies and Galvani.

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