Heart failure with mid-range or mildly reduced ejection fraction

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Abstract | Left ventricular ejection fraction (EF) remains the major parameter for diagnosis, phenotyping, prognosis and treatment decisions in heart failure. The 2016 ESC heart failure guidelines introduced a third EF category for an EF of 40–49%, defined as heart failure with mid-range EF (HFmrEF). This category has been largely unexplored compared with heart failure with reduced EF (HFrEF; defined as EF <40% in this Review) and heart failure with preserved EF (HFpEF; defined as EF ≥50%). The prevalence of HFmrEF within the overall population of patients with HF is 10–25%. HFmrEF seems to be an intermediate clinical entity between HFrEF and HFpEF in some respects, but more similar to HFrEF in others, in particular with regard to the high prevalence of ischaemic heart disease in these patients. HFmrEF is milder than HFrEF, and the risk of cardiovascular events is lower in patients with HFmrEF or HFpEF than in those with HFrEF. By contrast, the risk of non-cardiovascular adverse events is similar or greater in patients with HFmrEF or HFpEF than in those with HFrEF. Evidence from post hoc and subgroup analyses of randomized clinical trials and a trial of an SGLT1–SGLT2 inhibitor suggests that drugs that are effective in patients with HFrEF might also be effective in patients with HFmrEF. Although the EF is a continuous measure with considerable variability, in this comprehensive Review we suggest that HFmrEF is a useful categorization of patients with HF and shares the most important clinical features with HFrEF, which supports the renaming of HFmrEF to HF with mildly reduced EF.

Heart failure (HF) is a global pandemic with an increasing prevalence. Drivers of the growing prevalence of HF are ageing of the population, improved survival after myocardial infarction, and improved treatment and survival of patients with HF[1–4]. As a result, the burden of HF-related hospitalizations and costs are increasing[5,6], with the total costs for HF in 2012 estimated to be US$30.7 billion, of which more than two-thirds is attributable to direct medical costs, and projections suggesting an increase of 127% by 2030 (REF.[7]). Despite the availability of effective therapies, the prognosis of patients with HF remains poor[8]. HF is the leading cause of hospitalization among adults, and 1-year mortality is 10–35% in various population-wide registries, and is much higher in patients with advanced HF[9–12].

Left ventricular ejection fraction (EF), generally measured by echocardiography, remains the cornerstone of HF diagnosis, characterization, prognosis, patient triage and treatment selection. The clinical use of EF has flaws, which are described below in detail. Advanced multivariable analytics (such as machine learning and other methods for patient clustering and phenotyping) as well as other parameters have demonstrated a better calibration and discrimination for survival than the use of EF alone[13]. Nevertheless, EF remains the primary parameter for HF characterization and the primary inclusion criterion for clinical trials of HF. Until better measurements than the EF are available that meet all the needs for HF characterization, the data described in this Review might be relevant for both clinicians and clinical trialists[6,14–16].

HF with reduced EF (HFrEF; defined as EF <40%) is well characterized, and effective therapies for patients with HFrEF are available. The term HF with preserved EF (HFpEF) has long been used to describe patients with HF signs and symptoms and an EF that was variably defined as >40%, >45% or ≥45%, or >50% or ≥50%. For these patients, no clinical trial to date has demonstrated clear benefits of therapy[17]. In the 2016 ESC HF guidelines, a separate entity, HF with mid-range EF (HFmrEF; defined as EF 40–49%), was introduced to foster research in this EF range, which has been less investigated than HFrEF (EF <40%) and HFpEF (EF ≥50%)[6]. Extensive subsequent research confirms that HFmrEF has some intermediate features between HFrEF and HFpEF but also suggests distinct similarities between HFmrEF and HFrEF that warrant the term HF with 'mildly reduced' EF, as has also been proposed by other authors in the past 2 years[18–20]. In this Review, we provide a comprehensive overview of the epidemiology, clinical profile,

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Key points

- Heart failure (HF) with mildly reduced ejection fraction (EF) (HFmrEF) has been extensively studied, generally using an EF of 40–49%, and accounts for up to 25% of patients with HF.
- On the basis of contemporary trials and definitions, HFmrEF might be defined as an EF of 41–49%.
- HFmrEF is an intermediate HF type between HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF) for some characteristics but is more similar to HFrEF for others, especially for the high prevalence of ischaemic heart disease.
- HFmrEF and HFpEF are milder forms of HF than HFrEF and are associated with a lower risk of cardiovascular and HF events but with a similar or greater risk of non-cardiovascular adverse events.
- Clinical trials on therapies for HFpEF enrolled patients with an ejection fraction of >40% or ≥45% and did not demonstrate a clear treatment effect; however, subgroup and post hoc analyses suggest that some therapies for HFrEF might also be effective in HFmrEF.
- These arguments support the current redefinition of HFmrEF as HF with mildly reduced EF instead of HF with mid-range EF.

prognosis and potential treatment of HFmrEF, which we define as HF with mildly reduced EF.

EF in heart failure

EF is a normally distributed, continuous measure in the general population[21], but has a bimodal distribution among patients with incident HF[22,23], which supports the current concept that HF has distinct forms. According to the definition in European and US guidelines, the normal EF range is 52–72% in men and 54–74% in women, with normal values plus or minus standard deviation being 62 ± 5% for men and 64 ± 5% for women[24,25]. Given that HFmrEF is defined by a tighter EF range than HFrEF and HFpEF, measurement variability in EF quantification can have important implications for HFmrEF[26] (BOX 1).

The EF became the predominant tool to characterize, risk stratify and select patients with HF in clinical trials in the 1980s as a result of the design of these trials to select for enrolment only of patients with reduced EF as an enrichment strategy. Although the concept of HF with 'normal' or 'intact' EF was introduced in the 1980s[27,28], these patients were included in interventional trials only much later.

Various cut-off values for EF have been proposed and used to differentiate reduced from preserved EF for trial design purposes, with most trials of HFrEF considering an EF of <45%[29], <40% or ≤40%[30–36] but also ≤35%[37–42], ≤30%[43,44] or even <25%[45], to target patients with more severe HF and/or as an enrichment strategy (for example, to increase the rates of cardiovascular events and therefore reduce the sample size needed to observe an effect of the tested treatment if such an effect is present)[46]. The rationale for the clinical use of EF for HF classification is supported by evidence from large, randomized clinical trials (RCTs), and ensuing guidelines and regulatory approvals, showing that drugs and devices for the treatment of HF improve outcomes in patients with reduced EF (EF ≤40%), whereas no equivalent evidence is available in patients with higher EF[6]. Therefore, the EF identifies two different HF phenotypes according to treatment response. Additionally, the choice of using the cut-off value of EF = 40% to define HFrEF is further supported by the higher risk of adverse cardiovascular outcomes in patients with EF <40% than in patients with EF ≥40% observed in several studies[47–50]. The definition of preserved EF has varied across different trials, with HFpEF defined as EF >40% or ≥40% in the CHARM-Preserved[51], EMPEROR-Preserved[52], DELIVER[53], SPIRIT-HF[54] and SPIRRIT-HFpEF[55] trials[56], as EF ≥45% in the TOPCAT[57], I-PRESERVE[58] and PARAGON-HF[59] trials, and as EF ≥50% in the 2020 SOLOIST-WHF trial[60]. The inconsistent inclusion in trials of HFpEF of patients with EF of 40–49%, together with the above reported definition of normal EF, led to questions over how to characterize patients with EF 40–49%[24]. Therefore, in 2016 the ESC guidelines on HF introduced the term 'mid-range' EF and acknowledged a new HF phenotype between HFpEF and HFrEF, which was named HF with mid-range EF (HFmrEF) and defined as an EF of 40–49% in combination with the presence of signs and symptoms of HF, elevated levels of natriuretic peptides in the plasma and evidence of structural heart disease (left ventricular hypertrophy or left atrial remodelling) or the presence of diastolic dysfunction, to ensure a diagnosis of HF in a setting in which the EF is not markedly reduced[6]. However, given that the EF in HFmrEF is below the normal range, why HFmrEF should require more supportive criteria than HFrEF is not readily apparent. The aim of the guidelines committee was to stimulate research into the "underlying characteristics, pathophysiology and treatment of this group of patients"[6]. Analogously, the 2013 ACCF/AHA guidelines on HF defined an EF of 41–49% as HF with borderline EF to differentiate this entity from HFrEF but not include HFpEF[61]. Finally, in the universal

Box 1 | **Implications of variability in EF measurements**

- Intraobserver and interobserver variability of standard echocardiographic left ventricular ejection fraction (EF) assessment is reported to be 8–21% and 6–13%, respectively[173]
- Sources of measurement variability include
  - Digit-rounding bias: the tendency is to report EF with numbers ending in 0 or 5, for example as 40% instead of 39% or 41%. Therefore, whether heart failure with mildly reduced EF (HFmrEF) is defined as EF 40–49% or 41–49% can have major implications for estimating the prevalence of HFmrEF
  - Regression to the meanVisual estimation: although reliability has been reported as sufficient[174,175], visual estimation can underestimate true EF values
  - Poor image quality
  - Measurement error, in particular in the setting of rapid and/or irregular ventricular rhythm
- Consequences of measurement variability
  - Misclassification: in randomized clinical trials, estimation of EF at local sites can lead to the misclassification of patients for enrolment. In the TOPCAT trial[176], core laboratory measurements would have reclassified about 20% of the EF measurements
- Future perspectives
  - Optimization of automated algorithms for the analysis of EF
  - Systematic adoption of core laboratories fulfilling standard requirements for randomized clinical trials that are based on EF[66]
  - Improved agreement between imaging techniques: substantial variability in the estimation of EF has been reported across imaging modalities even when quantified by core laboratories[177]
  - Integrating EF with additional criteria (such as biomarkers and multivariable scores and algorithms) for more accurate and precise categorization of heart failure

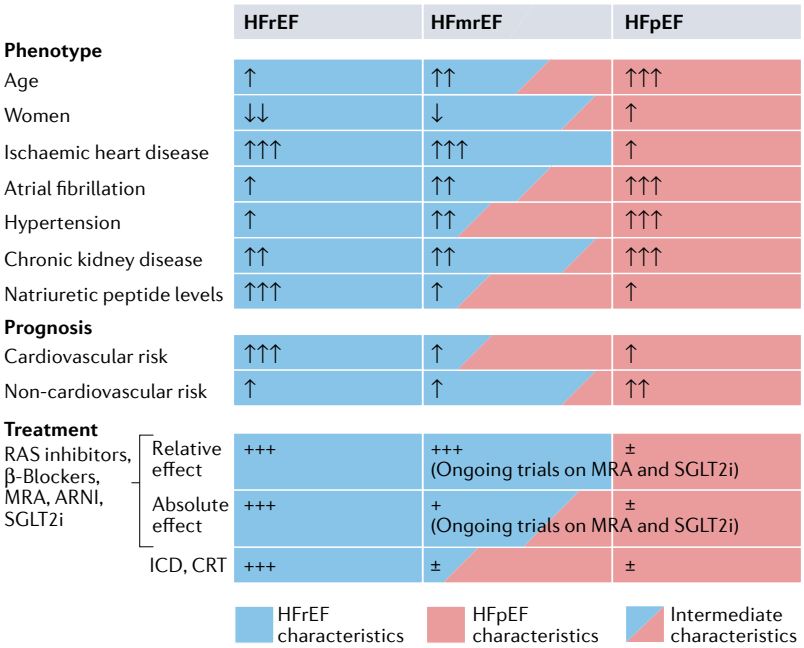


Fig. 1 | **Phenotype, risk of cause-specific outcomes and effect of therapies in HFrEF, HFmrEF and HFpEF.** Phenotype, risk of cause-specific outcomes and demonstrated or potential effect of treatments across the left ventricular ejection fraction categories of heart failure. Heart failure with mildly reduced ejection fraction (HFmrEF) shares features with both heart failure with reduced ejection fraction (HFrEF), such as a higher prevalence of ischaemic heart disease and less frequent renal impairment, and heart failure with preserved ejection fraction (HFpEF), such as hypertension, milder heart failure symptoms and lower levels of natriuretic peptides. HFmrEF is intermediate between the two categories for age and prevalence of atrial fibrillation. Cardiovascular mortality is lower in patients with HFmrEF and those with HFpEF than in patients with HFrEF. Non-cardiovascular mortality is lower in patients with HFmrEF and those with HFrEF than in patients with HFpEF. Post hoc and subgroup analyses of trials of heart failure suggest a potential benefit of therapy with a mineralocorticoid-receptor antagonist (MRA), angiotensin-receptor blocker–neprilysin inhibitor (ARNI) or sodium–glucose cotransporter 2 inhibitor (SGLT2i) in patients with HFmrEF. ↑ and ↓ denote higher or more common and lower or less common, respectively, than in an age-matched control population, with the exception of age, in which ↑ denotes higher than average among adults; + denotes strength of benefit; ± denotes insufficient evidence. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter–defibrillator; RAS, renin–angiotensin system.

definition and classification of HF published in 2021, HFrEF was defined as EF ≤40%, HFpEF as EF ≥50% and HFmrEF, renamed as HF with mildly reduced EF, as EF 41–49%[19]. The trials of HFrEF conducted in the past 5 years included patients with EF ≤40%, and given the 5% interval digit preference, we agree that HFrEF is most reasonably defined as ≤40%. However, the 2016 ESC HF guidelines put an EF of 40% in the HFmrEF category and, therefore, most research since then, including most of the studies discussed in this Review, have considered an EF of 40% to be part of the HFmrEF range of EF[6].

Epidemiology

The incidence of HF in Western countries is 1–9 cases per 1,000 person-years, with a prevalence of ~2%[62,63]. The prevalence of HFmrEF within the overall population of patients with HF is 10–25%[48,64–70]. However, HFpEF might be underdiagnosed because the EF is normal and might be missed in routine clinical care; therefore, the prevalence of HFmrEF might be proportionally lower than that of HFpEF. However, HFmrEF might also be underdiagnosed, considering the error and variability in EF measurement and the presence of milder symptoms in these patients compared with patients with HFrEF, leading clinicians to miss the HF diagnosis in patients with mild or diffuse symptoms and a low-normal or minimally reduced EF[48,64,65,67–71]. However, if HFmrEF was defined as an EF of 41–49% instead of 40–49%, the number of patients diagnosed with HFmrEF would be smaller. In a large, community-based, longitudinal cohort of individuals free from HF at baseline and followed up for >10 years, the incidence of HFmrEF was only 6.7 cases per 10,000 person-years versus an incidence of 26.9 and 34.9 cases per 10,000 person-years for HFpEF and HFrEF, respectively, with predictors of incident HF being consistent across the EF spectrum[64]. In the ESC-HF-LT registry, 24% of the enrolled patients had HFmrEF, whereas the proportion of patients with HFmrEF in the Swedish SwedeHF registry was 21%[48,65]. A slightly lower prevalence of HFmrEF was reported in Asian[68,70], New Zeland[68] and North American[67] registries. Finally, in the CHARM programme[72], which enrolled patients with HF regardless of EF, 17% of the patients had HFmrEF.

Clinical characteristics of HFmrEF

Proper characterization and phenotyping of HFmrEF is important because it might support treatment recommendations based on available data and inform the design of future interventional trials in HFmrEF by facilitating appropriate trial selection criteria. HFmrEF is often defined as 'intermediate' (favouring the use of the term 'mid-range') because this classification makes intuitive sense, or as a milder form of HFrEF (favouring the use of the term 'mildly reduced') because of some distinct clinical and treatment response similarities to HFrEF[73]. Both of these approaches are overly simplistic and ignore the extensive emerging research that characterizes HFmrEF in detail in relation to HFrEF and HFpEF. FIGURE 1 provides a conceptual representation of HFmrEF in relation to HFrEF and HFpEF, and FIGS 2,3 provide detailed characteristics from specific data sets.

In US cohorts of patients with HF, patients with an EF of 40–50% had similar characteristics to patients with HFpEF in terms of higher age, BMI and prevalence of hypertension and atrial fibrillation compared with patients with HFrEF[74–76]. However, this patient group was more similar to the HFrEF group in terms of sex distribution (more likely to be men) and a higher prevalence of ischaemic heart disease (IHD) than the HFpEF group[74–76]. In the ESC-HF-LT registry, the HFmrEF group shared several characteristics with the HFrEF group, including younger age, male sex, ischaemic aetiology and lower prevalence of atrial fibrillation compared with the HFpEF group[65]. Notably, patients with HFmrEF were less symptomatic (lower NYHA class), less likely to receive diuretics and with overall fewer comorbidities than either patients with HFpEF or patients with HFrEF. A potential explanation for these findings might be that HFmrEF represented a mild form of HFrEF or, in some patients,

Study	EF type (%)[a]	Number of patients	Setting	Age (years)	Women (%)	SBP (mmHg)	CCS (%)	AF (%)	CKD (%)	eGFR (ml/min/ 1.73 m²)	BMI (kg/m²)	Diabetes mellitus (%)	NT-proBNP (pg/ml)
HFrEF													
ESC-HF-LT[65]	60	5,460	Outpatient	64	22	122	49[c]	18	20	–	28	32	–
SwedeHF[48]	56	23,402	Both	72	29	124	54	51	45	63	26	27	3,071
GWTG-HF[75]	46	18,398	Inpatient	79	41	132	57	35	19	1.4[b]	26	38	8,845
OPTIMIZE-HF[74]	49	20,118	Inpatient	70	38	135	54[c]	28	–	1.4[b]	–	39	1,170[d]
ADHERE[76,e]	54	40,796	Inpatient	68/72	34/44	129/ 143	61/ 65	28/ 30	31	1.4[b]	28/29	39/45	–
TIME-CHF[69]	65	402	Outpatient	76	33	117	58[c]	30	54	54	25	34	4,242
CHART-2[70]	21	730	Outpatient	67	23	118	50[c]	38	–	58	23	38	216
BIOSTAT-CHF[86]	66	1,744	Outpatient	69	25	123	43[f]	43	48	–	–	31	3,054
HFmrEF													
ESC-HF-LT[65]	24	2,212	Outpatient	64	32	127	42[c]	22	17	–	29	31	–
SwedeHF[48]	21	9,019	Both	74	39	131	53	58	48	62	27	27	2,160
GWTG-HF[75]	8	3,285	Inpatient	81	52	141	55	37	19	1.3[b]	27	42	5,054
OPTIMIZE-HF[74]	20	7,321	Inpatient	74	52	147	49[c]	33	–	1.3[b]	–	44	757[d]
ADHERE[76,e]	23	17,045	Inpatient	74	54	150	60	33	31	1.3[b]	30	48	–
TIME-CHF[69]	17	108	Outpatient	79	46	127	57[c]	40	64	49	26	40	3,941
CHART-2[70]	17	596	Outpatient	69	28	125	53[c]	44	–	59	23	36	165[d]
BIOSTAT-CHF[86]	18	416	Outpatient	75	34	129	48[f]	49	53	–	–	35	1,839
HFpEF													
ESC-HF-LT[65]	16	1,462	Outpatient	69	48	131	24[c]	32	20	–	28	29	–
SwedeHF[48]	23	9,640	Both	77	55	133	42	63	56	59	28	28	2,018
GWTG-HF[75]	46	18,299	Inpatient	82	68	143	44	39	18	1.3[b]	27	39	4,104
OPTIMIZE-HF[74]	31	10,072	Inpatient	76	68	150	32[c]	32	–	1.2[b]	–	41	537[d]
ADHERE[76,e]	23	17,022	Inpatient	74	69	152	47	32	27	1.2[b]	31	44	–
TIME-CHF[69]	18	112	Outpatient	80	64	136	31[c]	43	62	54	27	39	2,142
CHART-2[70]	62	2,154	Outpatient	72	39	128	44[c]	52	–	59	23	34	127[d]
BIOSTAT-CHF[86]	16	300	Outpatient	78	46	130	33[f]	50	56	–	–	36	1,559

HFrEF characteristics | HFpEF characteristics | Intermediate characteristics

Fig. 2 | **HFmrEF clinical characteristics and similarities to HFrEF and HFpEF in major HF registries.** Summary of data from major registries of heart failure (HF) across the ejection fraction (EF) spectrum[48,65,69,70,74–76,86]. Data from the HF with mildly reduced EF (HFmrEF) category is shown with a blue background when resembling data from the HF with reduced EF (HFrEF) category, in red when resembling data from the HF with preserved EF (HFpEF) category and blue/red when intermediate. Values are mean (median for N-terminal pro-B-type natriuretic peptide (NT-proBNP)) and percentages. AF, atrial fibrillation; CCS, chronic coronary syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure. [a]Percentage of patients in each cohort or trial who were in the respective EF category. [b]Serum creatinine level (mg/dl); eGFR not provided. [c]Ischaemic heart disease as HF aetiology. [d]BNP provided instead of NT-proBNP. [e]Two HFrEF categories (EF <25% and 25–40%), HFmrEF defined as EF 40–55% and HFpEF defined as EF ≥55%. [f]History of myocardial infarction.

an improved or partially recovered form of HFrEF[65,77]. In the CHARM programme, most patient characteristics in the HFmrEF group, including age, blood pressure, sex distribution and history of myocardial infarction or atrial fibrillation, resembled those of the HFrEF group[72]. In the SwedeHF registry, the HFmrEF category was more similar to HFpEF for the prevalence of atrial fibrillation and blood pressure levels, but more similar to HFrEF for many other important patient characteristics, such as age and history of chronic kidney disease, diabetes mellitus and IHD[48]. Notably, beyond the crude prevalence of IHD, the adjusted prevalence of IHD was also similar in the HFmrEF and HFrEF groups, and the risk of new ischaemic events was higher in patients with HFmrEF or HFrEF than in those with HFpEF[78]. The proportion of women was higher in the HFpEF group than in the HFrEF group, with the proportion in the HFmrEF group being more similar to that in the HFrEF group[79]. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were similar in the HFmrEF and HFpEF groups and lower than in the HFrEF group[48], but in the HFmrEF category, the NT-proBNP level was more affected by the presence of confounders such as atrial fibrillation and showed a higher prognostic and discriminatory power than in the HFpEF group[80]. However, in a more extensive and dedicated analysis of

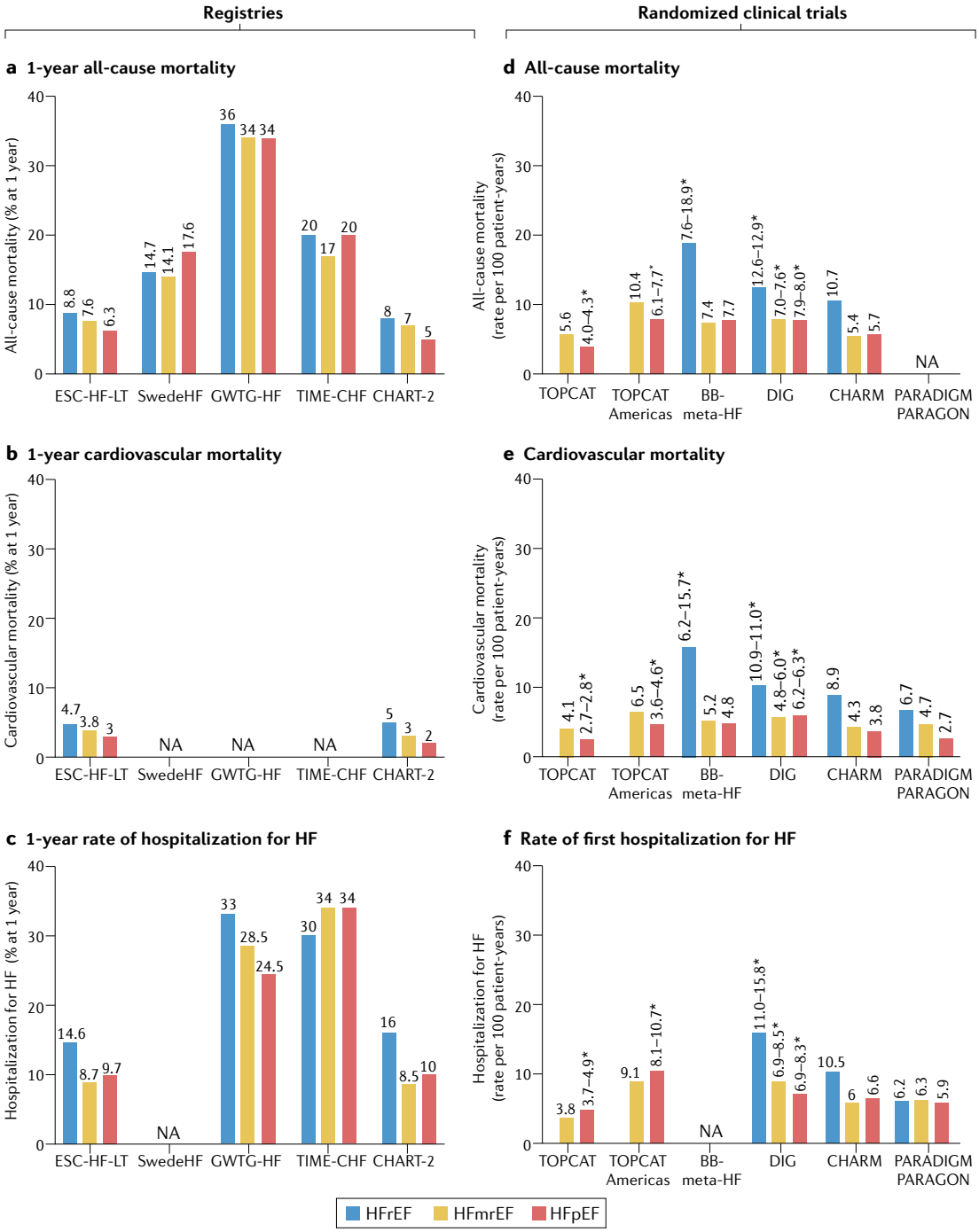
biomarkers in patients with acute HF, the HFmrEF phenotype was intermediate between the HFpEF and HFrEF phenotypes, with the biomarkers showing differential changes in HFmrEF mostly relating to cardiac stretch and inflammation[81].

Further studies from SwedeHF have provided additional characterization of HFmrEF versus HFpEF and HFrEF with regard to important comorbidities. Although the prevalence of atrial fibrillation decreased with decreasing EF, the clinical characteristics of patients with atrial fibrillation versus those in sinus rhythm were consistent across the EF spectrum, as was the unfavourable prognostic effect of the presence of atrial fibrillation[82]. Chronic kidney disease and the risk of worsening renal function were more likely to be present in patients with HFpEF but were more strongly associated with mortality in patients with HFmrEF or HFrEF[83,84]. This finding potentially suggests that kidney disease develops from the same underlying pathophysiology and in parallel with HFpEF and, therefore, has less prognostic importance than in HFrEF and HFpEF[83,84]. By contrast, in HFmrEF and HFrEF, the presence of kidney disease reflects more severe backward and forward haemodynamic changes in HF and, therefore, has a greater prognostic role[83,84]. Anaemia was more prevalent in patients with HFpEF than in those with HFmrEF or HFrEF, but the presence of anaemia was associated with a similar higher risk of death across the EF spectrum and had a greater association with the risk of death or hospitalization for HF in patients with HFmrEF or HFpEF than in those with HFrEF[85]. In the BIOSTAT-CHF study[86], the prevalence of other non-cardiac comorbidities in the HFmrEF category was intermediate between the HFrEF and HFpEF categories.

Study	EF type (%)[a]	Number of patients	Age (years)	Women (%)	SBP (mmHg)	CCS (%)	AF (%)	CKD (%)	eGFR (ml/min/ 1.73 m²)	BMI (kg/m²)	Diabetes mellitus (%)	NT-proBNP (pg/ml)
HFrEF												
TOPCAT[87]	0	–	–	–	–	–	–	–	–	–	–	–
BB-meta-HF[99,b,c]	93	13,443	61/63/ 63/64	20/23/ 25/27	114/120/ 127/130	58/66/ 69/81	0	–	62/61/ 66/65	27	25/26/ 24/22	–
DIG[159]	75	5,874	63	21	125	65[d]	0	–	1.3[e]	27	28	–
CHARM[72]	57	4,323	65	26	126	58[d]	26	–	1.2[e]	27	29	–
PARADIGM–PARAGON[26,f]	63	8,399	61/63/ 66	19/21/ 24	117/ 121/ 124	39/44/ 45[d]	28/33/ 45	–	68/68/ 67	27/28/ 29	34/34/ 35	2,183/ 1,645/ 1,406
HFmrEF												
TOPCAT[87]	15	520	66	37	128	44[d]	–	–	70	31	29	–
BB-meta-HF[99,b]	5	575	71	34	131	91	0	–	66	27	24	–
DIG[159]	15	1,195	64	29	133	63[d]	0	–	1.2[e]	28	30	–
CHARM[72]	17	1,322	65	30	130	58[d]	26	–	1.2[e]	28	29	–
PARADIGM–PARAGON[26,f]	11	1,427	71	40	131	32[d]	34	–	65	30	44	1,070
HFpEF												
TOPCAT[87,g]	85	2,924	68/68/ 70	49/51/ 59	129/ 129/ 130	28/22/ 20[d]	–	–	68/68/ 67	31/32/ 33	27/33/ 37	–
BB-meta-HF[99,b]	2	244	75	53	147	86	0	–	69	27	29	–
DIG[159]	9	719	67	47	139	45[d]	0	–	1.2[e]	29	29	–
CHARM[72]	26	1,953	67	45	140	37[d]	31	–	1.1[e]	29	28	–
PARADIGM–PARAGON[26,f]	26	3,368	73/74	54/63	131/130	20/16[d]	34/29	–	62/61	30	44/41	894/ 714

HFrEF characteristics | HFpEF characteristics | Intermediate characteristics

Fig. 3 | **HFmrEF clinical characteristics and similarities to HFrEF and HFpEF in major RCTs of HF.** Summary of data from randomized clinical trials (RCTs) of heart failure (HF) across the ejection fraction (EF) spectrum[26,72,87,99,159]. Data from the HF with mildly reduced EF (HFmrEF) category is shown in blue when resembling the HF with reduced EF (HFrEF) category, in red when resembling the HF with preserved EF (HFpEF) category and blue/red when intermediate. Values are mean, median or percentage, as reported in the original trial publications. AF, atrial fibrillation; CCS, chronic coronary syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure. [a]Percentage of patients in each cohort or trial who were in the respective EF category. [b]Patients in sinus rhythm. [c]Four HFrEF categories (EF <20%, 20–25%, 26–34% and 35–39%). [d]History of myocardial infarction. [e]Serum creatinine level (mg/dl); eGFR not provided. [f]EF range ≤42.5% for HFrEF, >42.5–52.5% for HFmrEF and >52.5% for HFpEF (chosen to avoid bias towards EF values ending in 0 or 5); three HFrEF categories (EF ≤22.5%, 22.5–32.5% and >32.5–42.5%) and two HFpEF categories (EF >52.5–62.5% and >62.5%). [g]Three HFpEF categories (EF 50.00–54.99%, 55.00–59.99% and ≥60.00%).



The BMI in the HFmrEF group was intermediate between that of the HFrEF and HFpEF groups in European registries as well as in the CHARM programme[48,65,72]. By contrast, in the TOPCAT and PARAGON-HF trials, the BMI of the group of patients with HFmrEF resembled more the BMI of the HFpEF group and was consistently ≥30 kg/m^2 as a mean or median[26,87]. In a US community study and in few dedicated RCTs of HFpEF, obesity was predominant among patients with HFpEF, and the mean BMI was >35 kg/m^2 (REFS[88–90]). The complex interaction between obesity and HF remains only partially understood. Obesity is a risk factor for HF but potentially more strongly so for HFpEF than for HFrEF[90–93], whereas obesity has not been investigated specifically as a risk factor for HFrEF[86]. Secondary mitral regurgitation and right ventricular dysfunction have been reported to be less prevalent in HFmrEF and HFpEF than in HFrEF, whereas data on the epidemiology of secondary tricuspid regurgitation by EF phenotype are currently lacking[94,95]. Differences in HFmrEF characteristics according to race or ethnicity are also poorly studied. In a US cohort of patients with HFmrEF, Black patients had a lower prevalence of previous myocardial infarction and Hispanic patients had more comorbidities but better survival compared with the other ethnicities[96].

◀ Fig. 4 | **Outcomes according to EF in patients with HF in major registries and RCTs.** All-cause mortality (panels **a**,**d**), cardiovascular mortality (panels **b**,**e**) and hospitalization for heart failure (HF) (panels **c**,**f**) according to left ventricular ejection fraction (EF) in patients with HF in major registries and randomized clinical trials (RCTs). Data from REFS[26,48,65,69,70,72,75,87,99,159]. ESC-HF-LT[65] included prevalent and incident HF; 1-year rates are shown for all outcomes. SwedeHF[48] included prevalent and incident HF; 1-year rates of all-cause death are shown; no data on cardiovascular mortality or hospitalization for HF were available. GWTG-HF[75] included in-hospital new-onset and worsening HF; 1-year all-cause mortality and 1-year hospitalization for HF estimated from the 1-year time point on the *x*-axis and percentage on the *y*-axis of Kaplan–Meier curves in REF.[75]; data on 5-year all-cause mortality and 5-year rate of hospitalization for HF shown in table 3 of the original article; no data on cardiovascular mortality were available. TIME-CHF[69] included prevalent HF; rate of 1-year hospitalization for HF or death is shown; rates estimated from the 1-year time point on the *x*-axis and percentage on the *y*-axis of Kaplan–Meier curves in REF.[69]; data on all-cause mortality and rate of hospitalization for HF during the overall follow-up reported in the main text of the original article; no data on cardiovascular mortality were available. CHART-2 (REF.[70]) included prevalent and incident HF; 1-year rates for all outcomes estimated from the 1-year time point on the *x*-axis and percentage on the *y*-axis of Kaplan–Meier curves in REF.[70]. TOPCAT and TOPCAT Americas trials[87]: 1-year rates are shown for all outcomes, patients with EF ≥50% were divided into subcategories (50.00–54.99%, 55.00–59.99% and ≥60.00%); we reported the ranges of event rates if different across subcategories (asterisks); event rates for patients with EF <50% are provided in table 3 of REF.[87]. BB-meta-HF[99]: rates at a median follow-up of 1.3 years are shown for all outcomes in patients in sinus rhythm; patients with EF <40% were divided into subcategories (<20%, 20–25%, 26–34% and 35–39%); we reported the ranges of event rates if different across subcategories (asterisks); event rates in the 40–49% and ≥50% categories were directly provided in the trial publication, and we converted them into an estimated event rate per 100 patient-years by dividing by 1.3; data on the rate of first hospitalization for HF were not provided. DIG[159]: 1-year rates shown for all outcomes; we reported the ranges of event rates if different between the treatment and placebo groups (asterisks). CHARM[72]: 1-year rates provided for all outcomes. PARADIGM-HF–PARAGON-HF[26]: no global follow-up duration was provided in the trial publication; therefore, we estimated rates per 100 patient-years by dividing by 2.25 (the median follow-up duration of PARADIGM-HF) for the EF <40% category and by dividing by 2.9 (the median follow-up duration of PARAGON-HF) for the EF 40–49% and EF ≥50% categories; data on all-cause mortality were not provided. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available.

Previous research has also assessed the degree of neurohormonal activation across the EF spectrum, showing higher circulating neurohormone levels in patients with HFrEF than in those with HFmrEF or HFpEF[80,97,98]. The higher neurohormonal activation in HFrEF might reflect the greater HF severity and be a marker of higher rates of cardiovascular events in patients with HFrEF than in patients with HFmrEF or HFpEF, as well as the observed efficacy of neurohormonal inhibition in patients with HFrEF, and potentially in those with HFmrEF, but not in patients with HFpEF (as discussed below)[26,72,99].

Although HFmrEF is overall more similar to HFrEF than HFpEF for most clinical characteristics and for treatment response, and might therefore be interpreted as being a mild form of HFrEF (that is, as HF with mildly reduced EF)[19,20], some inconsistencies are found across different analyses. However, in all the studies reported above, one consistent observation is that IHD has a similar prevalence in HFmrEF and HFrEF, which is greater than in HFpEF. From the perspective of research and clinical trial design, considering all these nuances would be beneficial. From the perspective of routine clinical care, a more simplistic message might be most effective, namely that, taken together, most data suggest that HFmrEF more closely resembles the HFrEF phenotype than the HFpEF phenotype (FIGS 1–3).

Prognosis

Accurate prognostication in HFmrEF is important on a population level for proper resource allocation and for power and sample size assessments for trials. At the individual level, accurate prognosis is important for patients, families and providers to have reasonable expectations and make treatment decisions and prioritizations accordingly.

In observational and large registry studies, the risk of adverse cardiovascular outcomes seems to be lower in patients with HFmrEF or HFpEF than in patients with HFrEF[46,65]. By contrast, consistent with the higher age and the presence of comorbidities, the risk of non-cardiovascular events seems to be greater in patients with HFpEF, and possibly those with HFmrEF, than in patients with HFrEF[46,65]. All-cause mortality is higher in HFrEF than in HFmrEF and HFpEF in some reports[48,49,65,68,70], lower in HFmrEF than in HFpEF and HFrEF in other reports[26,100], and similar across the EF spectrum in others[74,75,101]. An analysis reported in 2020 of a large data set with available echocardiography data suggested a U-shaped relationship between EF and mortality, with very high values of EF (EF >65%) also associated with increased mortality after adjustment for conditions such as HF, mitral regurgitation, increased wall thickness and anaemia[49]. This observation might build the ground for a further EF subtype that might be defined as HF with supra-normal EF (HFsnEF)[49]. The enrolment of exclusively, or of different proportions of, inpatients versus outpatients in these studies might partly explain the heterogeneous data.

Differences in outcomes across the EF spectrum have been observed in both real-world studies and RCTs. The differences are greater in RCTs, in which patients with HFpEF or HFmrEF had a considerably lower risk of cardiovascular events than patients with HFrEF (FIG. 4). RCTs are more selective than real-world studies; for example, in RCTs, patients have a younger age and fewer comorbidities but more severe HF as a result of an enrichment strategy. In the CHARM programme[72], the risk of all-cause death over approximately 3 years of follow-up was 15.8% in patients with HFmrEF, which is remarkably low compared with estimates from registries (7–34% at 1 year)[48,65,69,70,75]. Additionally, patients with HFmrEF or HFpEF had a lower risk of death or hospitalization for HF than patients with HFrEF[72]. When the associations with EF were analysed as a continuous spline variable, a steep decrease in rates was observed with increasing EF until an EF of 50% for all-cause and cardiovascular death and 40% for the risk of hospitalization for HF, after which the incidence rate curves flattened[72]. The risk of non-cardiovascular adverse outcomes was overall higher in the HFpEF population[72]. By contrast, in the TIME-CHF trial[69], similar hospital admission rates and mortality were observed regardless of EF.

Prognostic data also differ in incident versus prevalent HF. In one study, the rates of all-cause death were 497 per 10,000 person-years for incident HFmrEF versus 394 per 10,000 person-years for incident HFpEF and 459 per 10,000 person-years for incident HFrEF, suggesting worse survival in patients with incident HFmrEF

or HFrEF than in those with incident HFpEF[64]. These data are important because they more closely represent a 'pure' HFmrEF, that is, new onset of HFmrEF, whereas in most of the cross-sectional analyses of HF cohorts, the proportion of patients with HFmrEF with transitioning EF might be relevant and confound the true prognostic influence of HFmrEF. Notably, in this study, the similar all-cause mortality in HFmrEF and HFrEF, which was higher than in HFpEF, which was reported after adjustment for several patient characteristics, including history of myocardial infarction and coronary heart disease, suggests that in terms of pathophysiology, HFmrEF might be closer to HFrEF than to HFpEF. Another explanation might be that in most of the studies, the observation that patients with HFpEF have a similar or worse prognosis than patients with HFmrEF or HFrEF might be due to HFpEF having a more gradual onset and longer disease duration, which leads to later diagnosis and worse prognosis at enrolment[64].

Composite prognostic models and scores are supporting tools in the risk stratification of patients with HF. The most-used risk scores, such as the MAGGIC score[102], the Seattle HF model (SHFM)[103] and the more contemporary PREDICT-HF[104], have been validated. However, these scores have been derived predominantly (MAGGIC score) or exclusively (SHFM and PREDICT-HF scores) in patients with HFrEF. The peak VO_2, an integrated parameter from the cardiopulmonary exercise test, and the Heart Failure Survival Score (HFSS) were both developed primarily for transplantation and mechanical circulatory support selection in patients with advanced (generally reduced EF) HF, but also seem to predict prognosis in patients with EF >40%[105]. No specific risk models for prognostication in HFmrEF are currently available, although reports from the SwedeHF registry supported the use of MAGGIC and SHFM in the general population of patients with HF, regardless of EF[106,107].

Secondary mitral regurgitation is related to the degree of left ventricular dilatation and EF, but seems to be associated with poor outcome regardless of EF and has a potentially greater prognostic role in HFmrEF than in HFrEF[94,108]. By contrast, the prognostic role of secondary tricuspid regurgitation in HFmrEF is currently unexplored. Right ventricular dysfunction was shown to be a prognostic predictor of poor outcomes in HF regardless of EF[95].

One of the less explored aspects of HFmrEF is the risk of life-threatening ventricular arrhythmias. Sudden cardiac death (SCD) is a feared yet often preventable mode of death in patients with HFrEF. The risk stratification for SCD in HF is based on the degree of reduced EF[109]. The risk of SCD is not considered to be high in patients with EF >40%. In HFmrEF and HFpEF, the mode of death, and in particular, SCD, has been poorly reported or imprecisely adjudicated in observational studies and RCTs, frequently confounded by the competing risk of non-cardiovascular deaths. However, when the mode of death was available, SCD accounted for 30–40% of the cardiovascular modes of death and should not be neglected[110]. Therefore, risk stratification for SCD might be as relevant in HFpEF and HFmrEF as in HFrEF. However, available prediction models for SCD, such as the Seattle proportional risk model and others, have been derived from cohorts that included almost exclusively patients with EF <40% and are therefore not applicable to patients with HFmrEF or HFpEF[111–113]. Alternative emerging methods, such as cardiac MRI, might provide further information for risk quantification[114].

Incident comorbidities in patients with HF and factors precipitating worsening HF can have a strong effect on disease progression and the risk of hospitalization and death. The precipitants of incident and worsening HFmrEF resemble those of HFpEF, with a single, essential exception: IHD[67,115]. In SwedeHF[78], IHD was more common in HFmrEF and HFrEF and also had a greater adverse prognostic influence in HFmrEF and HFrEF than in HFpEF. However, other analyses reported similar detrimental effects of IHD on survival in HFpEF to those in the other EF phenotypes of HF[116–119].

Prognostication in HF relies on multiple factors. Circulating levels of natriuretic peptides were shown to be associated with morbidity and mortality in both HFpEF and HFrEF[80,120–122]. Studies from the SwedeHF registry also support the prognostic role of natriuretic peptides in HFmrEF[68,69,80,120], even suggesting a greater prognostic and discriminatory role for NT-proBNP in HFmrEF, by showing a greater association between continuous NT-proBNP levels and outcomes as well as higher areas under the receiver operating characteristic curve for death and death or hospitalization for HF in HFmrEF than in the other EF categories[80]. In the heterogeneous setting of HFmrEF, which includes patients who had incident HFmrEF and those with transitioning EF (deteriorating or improving), natriuretic peptide levels might be a more reliable marker of severity than the EF itself. Indeed, in a prospective cohort study, the difference in mortality across the three HF phenotypes vanished after adjustment for NT-proBNP levels, which might imply that although natriuretic peptide levels and cardiovascular risk are lower in patients with HFpEF or HFmrEF than in patients with HFrEF, at a given value of NT-proBNP, the risk of death might be similar regardless of EF[68,80]. In TIME-CHF[69], a significant potential benefit of NT-proBNP-guided therapy was similarly observed in HFrEF and HFmrEF but not in HFpEF.

Phenotyping HFmrEF beyond EF

Owing to the limitations of the EF construct and measurement, numerous alternative methods are advocated for and are emerging to phenotype HF. Myocardial tissue characterization by cardiac MRI is part of the routine diagnostic work-up in patients with HF of unknown aetiology[123]. Emerging studies also highlight the importance of cardiac MRI in patients with EF >40%[114,124,125]. Late gadolinium enhancement (LGE) is known to be a major prognostic marker and a validated predictor of SCD and life-threatening arrhythmias in HFrEF[126]. However, LGE also correctly classifies the risk of death and SCD in patients with mild-to-moderate reduction in EF[114,127], and therefore could be considered to identify patients at increased risk of SCD who are suitable for trials that test strategies for primary prevention of SCD regardless of the EF[114].

The assessment of myocardial strain and in particular global longitudinal strain (GLS) from speckle-tracking analysis of 2D echocardiography is an emerging technique complementary to EF for the quantification of systolic and diastolic ventricular and atrial function[128,129]. Measurement of GLS has revealed how systolic dysfunction (reduced GLS) can be present even if the EF is preserved or normal[130,131]. Large observational studies and meta-analyses also support an incremental and independent role for GLS beyond EF in terms of mortality prediction in patients with EF >35%[132,133].

In the era of precision medicine, deep aetiological characterization of HF becomes both possible and meaningful to maximize the understanding of the underlying disease, predict its natural progression, individualize treatment strategies, and identify and design trials for novel treatment targets. Biomarkers and proteomic signatures might further help to highlight differences across the EF categories. A multiple biomarker approach in acute HF demonstrated that patients with HFmrEF have an intermediate profile between HFrEF (cardiac stretch) and HFpEF (inflammation)[81]. Proteomic variability was high across the EF phenotypes, and the mid-range category was heterogeneous and resembled HFpEF more than HFrEF[134].

Cardiac amyloidosis and hypertrophic cardiomyopathy are two important examples of how rigorous diagnostics and disease characterization have helped in both identifying patients for disease-targeted therapies and excluding patients from trials in which the target of therapy is different, such as HFpEF trials. Prevalent IHD modified the exposure to further ischaemic events but also non-ischaemic events in patients with HFmrEF enrolled in the SwedeHF registry[78]. Among non-ischaemic aetiologies of HF, specific phenotypes such as sarcoidosis might portend increased risks of poor outcomes irrespective of the severity of left ventricular dysfunction[135]. The genetic background of non-severely reduced EF in some cases can lead to alternative strategies to protect patients with a high risk of SCD even in the absence of reduced EF. Patients with specific genotypes of dilated cardiomyopathy, including variants in the gene encoding lamin A/C and variants in genes encoding desmosomal proteins, had a lower survival free from potentially fatal ventricular arrhythmias despite having EF >35%, which is the guideline-based threshold for receiving an implantable cardioverter–defibrillator (ICD)[136,137].

Transitioning through HFmrEF

A major limitation of registry, cohort and trial data sets is the relative paucity of longitudinal data. In studies of prevalent HF, a single assessment of EF provides a static snapshot of something that entails measurement error and often shifts over time. However, EF is subject to change owing to effects of therapy or the natural progression of HF[138,139]. Some patients with HFmrEF might be in transition from preserved to reduced EF as a result of an acute event (such as an ischaemic event) and, conversely, other patients with HFmrEF might be recovering from reduced to preserved EF after medical or device therapy for HF or invasive anti-ischaemic treatments[78,115,117,118,122].

In one prospective study of 126 patients with HFpEF with baseline EF of 63 ± 8% who were followed up for >11 years, 9.5% of patients progressed to HFmrEF and only 1.6% to HFrEF, suggesting that in patients with HFpEF, the EF is likely to remain stable over time (that is, EF ≥50%)[118]. Similarly, of 100 patients hospitalized with HFpEF (baseline EF of 67 ± 9%) who underwent EF assessment ≥1 year after hospital discharge, 11% had a decline to HFmrEF over a mean follow-up of 31.5 months[140]. In both studies, most patients transitioning to HFmrEF from HFpEF had an EF of 50–55% at the baseline. This finding might explain the efficacy of sacubitril–valsartan in patients with an EF within the lower range of HFpEF shown in the PARAGON-HF trial[26,59], and might also call into question whether the EF range 50–55% most appropriately applies to HFmrEF or to HFpEF. In a retrospective analysis of 4,942 patients in SwedeHF, roughly 33% of patients with HFmrEF or HFpEF transitioned to a lower EF category and 25% of those with HFmrEF or HFrEF transitioned to a higher EF category over a median follow-up of 1.4 years (interquartile range 0.5–3.0 years)[122] (FIG. 5). Among patients with HFmrEF, 37% and 25% switched to HFrEF and HFpEF, respectively, whereas among patients with HFrEF or HFpEF, 16% and 21%, respectively, switched to HFmrEF[122]. Several factors were associated with increasing EF (female sex, atrial fibrillation and less severe HF) or decreasing EF (diabetes, IHD and more severe HF)[122]. This registry-based analysis reflects EF assessment as performed in daily clinical care, with a bias towards obtaining repeat EF measurements in patients who reported a clinical deterioration or were judged to be sicker. Therefore, the risk of EF declining over time might have been overestimated. In the Olmsted County (Minnesota, USA) cohort, 39% of patients crossed from HFpEF (EF ≥50%) to HFrEF (EF <50%) and 39% of patients crossed from HFrEF to HFpEF over a 5-year observation period[23].

In HFrEF, evidence-based drugs seem to improve EF only by a few percentage points on average[139,141,142]. Growing evidence suggests that HF with recovered EF, or HF with improved EF, is frequent and might represent a further phenotype characterized by less myocardial damage and associated with a better outcome than HF with persistently reduced EF, although with a risk of EF reduction recurrence[122,138]. The recovery of EF from reduced to preserved EF has been shown to be associated with a 45% reduced risk of all-cause death or hospitalization for HF in a study from the SwedeHF registry[122]. Among 1,057 consecutive patients with HF with available baseline and 1-year measurements of EF, patients with recovered EF had better outcomes in terms of cardiovascular death and hospitalization for HF than those in either the HFpEF or the HFrEF subgroup[143]. Similar findings were observed in a retrospective analysis of >2,000 outpatients with HF[77]. In an analysis from the SwedeHF registry, increasing EF was associated with a lower risk of all-cause death or hospitalization for HF, whereas decreasing EF was associated with a higher risk[122] (FIG. 5). Partial or complete recovery of HFrEF was associated with significantly better outcomes than stable EF in HFrEF and, conversely, deterioration from

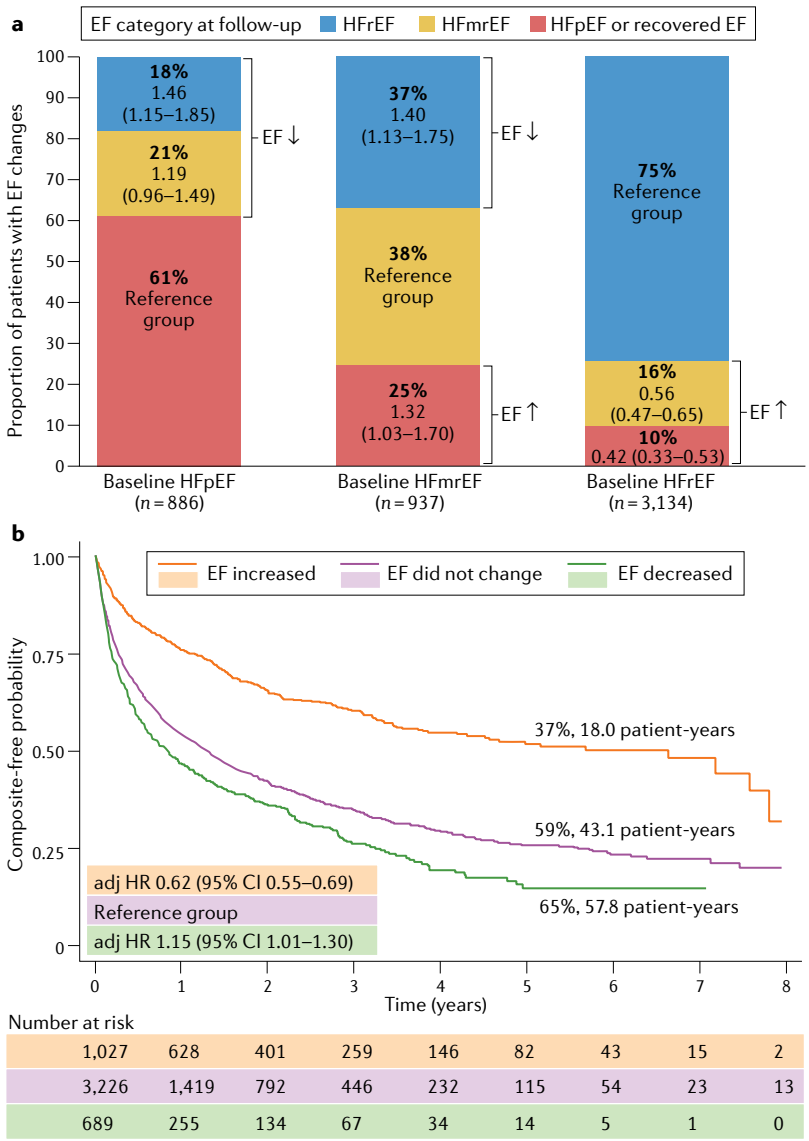


Fig. 5 | **Trajectories and changes in EF and outcomes over time in patients with HF.** Data from a retrospective, nationwide, registry study of patients with heart failure (HF)[122]. **a** | Each bar segment shows the proportion of patients with changes in left ventricular ejection fraction (EF) at follow-up and the associated hazard ratio (HR) and 95% confidence interval (CI) of all-cause death or hospitalization for HF by EF category at baseline. In each category, the group of patients with a stable EF over time was used as reference. **b** | The risk of all-cause death or hospitalization for HF relative to EF changes. adj, adjusted; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. Parts **c** and **d** adapted with permission from REF.[122], Elsevier.

HFpEF or HFmrEF to HFrEF was associated with worse prognosis than stable EF in HFrEF[122]. In a retrospective cohort study focusing on HFmrEF, only 15% of patients had stable HFmrEF, as assessed by comparing with previous echocardiography exams[144]. The risk of all-cause death, cardiovascular death and hospitalization for HF was higher for those with EF decreasing from >50% than in those with EF improving from <40%, after adjustment for confounding factors. Interestingly, the prognosis of patients with improving EF was not better but similar to that in patients with stable mid-range EF, suggesting that stable HFmrEF might represent a relatively low-risk phenotype[144]. Changes in EF in patients with HF have been observed to be more likely to occur in the early stages of the disease, following diagnosis and treatment initiation, and are less pronounced in patients with HFmrEF than in those with HFrEF[145]. However, EF trajectories in patients with diagnosed HFmrEF or HFrEF showed an inverse U shape, with EF tending to decline over time in both groups and finally overlap at 10 years of follow-up[145].

Treatment of HFmrEF

Historically, neurohormonal antagonist drugs (renin–angiotensin system (RAS) inhibitors, β-blockers and mineralocorticoid-receptor antagonists (MRAs)) have been the cornerstone of pharmacological therapy for patients with HFrEF. In 2014, angiotensin-receptor blocker–neprilysin inhibitors (ARNIs), and in 2019, sodium–glucose cotransporter 2 (SGLT2) inhibitors, both neurohormonal modulators, were also shown to be effective in HFrEF[6]. However, in subsequent trials, RAS inhibitors, β-blockers, MRAs and ARNIs were overall not effective in patients with HFpEF, generally defined as EF ≥40% or ≥45%[51,57–59,146,147]. Sotagliflozin, an SGLT2–SGLT1 inhibitor, was effective in patients with type 2 diabetes mellitus and HF across the EF spectrum[60], and dedicated trials of empagliflozin[148,149] and dapagliflozin[53,150] in HFmrEF and HFpEF are ongoing. No dedicated interventional trial has addressed HFmrEF specifically. Observational data are scarce and do not prove efficacy, but can provide hints regarding interventions that might potentially be beneficial in HFpEF and HFmrEF. With the known limitations of observational studies, large, registry-based studies suggest that angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists and β-blockers might potentially provide benefit in patients with HFmrEF[10,151]. The rate of HFrEF medication use in registries is high in the population of patients with HFmrEF, which might be explained by the role of these therapies in treating risk factors and comorbidities that are frequent in HF regardless of EF, such as hypertension, diabetes, chronic kidney disease, IHD and atrial fibrillation[48,152]. Diuretic use is also high in patients with HFmrEF, presumably for symptom relief, which is indicated regardless of EF[6,48]. These findings might also suggest that in clinical practice, patients with HFmrEF are frequently treated like those with HFrEF or, alternatively, that a large proportion of these patients have improved from HFrEF, in which case therapy should, and generally does, continue[48,65,69,70,75,153,154].

Most RCTs in HFpEF had EF cut-off values of 40% or 45% and therefore included, either completely or partially, the HFmrEF category[51,57–59] (TABLE 1; FIG. 6). In the CHARM programme[72], therapy with candesartan reduced the risk of the composite of cardiovascular death and hospitalization for HF in patients with HFrEF or HFmrEF but not in patients with HFpEF. Spline analyses, in which EF was analysed as a continuous variable, clearly showed that candesartan efficacy was constant with lower EF but started to decline when the EF increased above 50%[72]. However, even in the HFpEF

Table 1 | **Major phase III randomized, controlled trials including patients with HF with EF of 40–49%**

Study	Year	Number of patients	Drug	Class	EF range (%)	Main HF category focus	Primary outcome	Follow-up (months)	Refs
ANZ	1997	415	Carvedilol	β-Blocker	<45	HFrEF	Death, hospitalization for HF or worsening HF	19	165
CHARM-Preserved	2003	3,023	Candesartan	ARB	>40	HFpEF	Cardiovascular death or first hospitalization for HF	37	51
SENIORS	2005	2,135	Nebivolol	β-Blocker	All	HFrEF	All-cause mortality, hospitalization for cardiovascular causes	21	147
PEACE	2004	8,290	Perindopril	ACEi	>40	HFpEF	Cardiovascular mortality, MI or revascularization	58	166
PEP-CHF	2006	850	Perindopril	ACEi	LVWMI 1.4–1.6	HFmrEF and HFpEF	All-cause mortality, hospitalization for HF	26	146
DIG (ancillary)	2006	988	Digoxin	–	>45	HFpEF	HF mortality, hospitalization for HF	37	167
I-PRESERVED	2008	4,128	Irbesartan	ARB	≥45	HFpEF	All-cause mortality or hospitalization for cardiovascular causes	49	58
MIRACLE-EF	2012	44	CRT pacemaker	Devices	36–50	HFmrEF	Death or first hospitalization for HF	Stopped early	168
TOPCAT	2014	3,445	Spironolactone	MRA	≥45	HFpEF	Cardiovascular death, aborted cardiac arrest or first hospitalization for HF	40	57
J-DHF	2014	245	Carvedilol	β-Blocker	>40	HFpEF	Cardiovascular death or first hospitalization for HF	39	169
PARAGON-HF	2019	4,822	Sacubitril–valsartan	ARNI	≥45	HFpEF	Cardiovascular death or total hospitalizations for HF	35	59
VICTORIA	2020	5,050	Vericiguat	sGC stimulator	<45	HFrEF	Cardiovascular death or first hospitalization for HF	11	29
SOLOIST-WHF	2021	1,222	Sotagliflozin	SGLT2i	<50	HFrEF	Cardiovascular death, total hospitalizations for HF or urgent hospital visits for HF	9	60
SPIRRIT-HFpEF	2016–ongoing	3,200	Spironolactone	MRA	≥40	HFpEF	Cardiovascular death or first hospitalization for HF	Ongoing	55,56
SPIRIT-HF	2017–ongoing	1,300	Spironolactone	MRA	≥40	HFpEF	Cardiovascular death or total hospitalizations for HF	Ongoing	54
EMPEROR-Preserved	2017–ongoing	5,988	Empagliflozin	SGLT2i	>40	HFpEF	Cardiovascular death or first hospitalization for HF	Ongoing	148
EMPERIALPreserved	2018–ongoing	315	Empagliflozin	SGLT2i	>40	HFpEF	Changes in 6-min walking distance	Ongoing	149
DELIVER	2018–ongoing	6,100	Dapagliflozin	SGLT2i	>40	HFpEF	Cardiovascular death, first hospitalization for HF or urgent hospital visit for HF	Ongoing	53
DETERMINE-PRESERVED	2019–ongoing	504	Dapagliflozin	SGLT2i	>40	HFpEF	KCCQ-TSS changes	Ongoing	150
PARAGLIDE-HF	2019–ongoing	800	Sacubitril–valsartan	ARNI	>40	HFpEF	NT-proBNP changes	Ongoing	170
FINEARTS-HF	2020–ongoing	5,500	Finerenone	MRA	≥40	HFpEF	Cardiovascular death or total hospitalizations for HF	Ongoing	171

Treatment effects for selected trials are shown in FIG. 6. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor blocker–neprilysin inhibitor; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptoms score; LVWMI, left ventricular wall motion index; MI, myocardial infarction; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sGC, soluble guanylate cyclase; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Study	Outcome	EF (%)	HR (95% CI)
CHARM programme	CV death or HHF	<40	0.82 (0.75–0.91)
		40–49	0.76 (0.61–0.96)
		≥50	0.95 (0.79–1.14)
	Recurrent HHF	<40	0.68 (0.58–0.80)
		40–49	0.48 (0.33–0.70)
		≥50	0.78 (0.59–1.03)
PEP-CHF	All-cause death or HHF	40–49	0.92 (0.70–1.21)
DIG (ancillary)	CV death or HHF	<40	0.83 (0.77–0.89)
		40–49	0.96 (0.79–1.17)
		≥50	0.92 (0.71–1.20)
	HF death or HHF	<40	0.74 (0.68–0.81)
		40–49	0.83 (0.66–1.05)
		≥50	0.88 (0.65–1.19)
PEACE	CV death	40–49	0.88 (0.72–1.09)
	HHF	40–49	0.96 (0.78–1.19)
TOPCAT	CV death, CA or HHF	<50	0.72 (0.50–1.05)
		50–54.99	0.85 (0.61–1.18)
		55–59.99	0.94 (0.68–1.29)
		≥60	0.97 (0.76–1.23)
	HHF	<50	0.76 (0.46–1.27)
		50–54.99	0.70 (0.47–1.04)
		55–59.99	0.73 (0.49–1.08)
		≥60	0.98 (0.74–1.30)
TOPCAT Americas	CV death, CA or HHF	<50	0.55 (0.33–0.91)
		50–54.99	0.83 (0.56–1.25)
		55–59.99	0.85 (0.60–1.21)
		≥60	0.89 (0.69–1.15)
	HHF	<50	0.60 (0.32–1.10)
		50–54.99	0.80 (0.51–1.25)
		55–59.99	0.70 (0.47–1.06)
		≥60	0.95 (0.71–1.26)
BB-meta-HF	CV death	<40	0.67–0.78 (0.52–0.65 to 0.80-0.99)
		40–49	0.48 (0.24–0.97)
		≥50	1.77 (0.61–5.14)
	CV death or CVH	<40	0.68–0.80 (0.60–0.72 to 0.77-0.88)
		40–49	0.83 (0.60–1.13)
		≥50	0.66 (0.38–1.15)
PARADIGM-HF–PARAGON-HF	CV death or HHF	≤42.5	0.77–0.81 (0.63–0.71 to 0.92–0.94)
		42.5–52.5	0.89 (0.73–1.10)
		≥52.5	0.89–1.03 (0.74–0.80 to 1.06–1.32)
	Total HHF	≤42.5	0.75–0.82 (0.60–0.63 to 0.90–1.11)
		42.5–52.5	0.77 (0.58–1.02)
		≥52.5	0.81–1.04 (0.63–0.76 to 1.04–1.44)

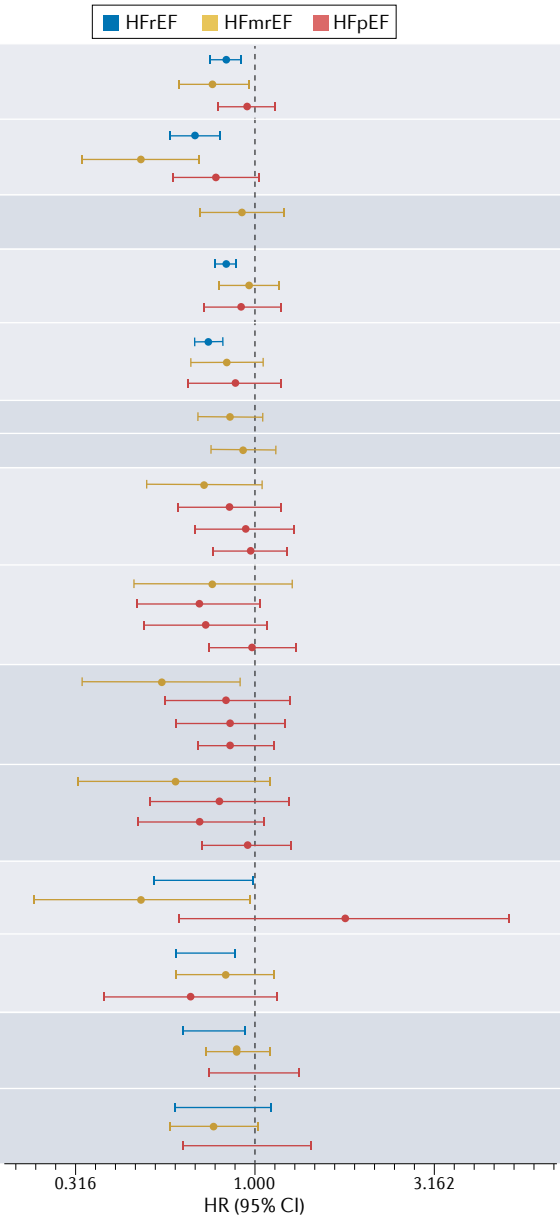


Fig. 6 | **Outcomes in patients with HF according to EF.** Forest plot depicting hazard ratio (HR) and 95% confidence interval (CI) for intervention versus control according to left ventricular ejection fraction (EF) in patients with heart failure (HF) with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF) and HF with preserved EF (HFpEF) for the specified trials and outcomes. In the CHARM programme[51,72], therapy with candesartan reduced the risk of cardiovascular (CV) death and hospitalization for HF (HHF) in patients with HFrEF or HFmrEF but not in those with HFpEF. In PEP-CHF[146], perindopril therapy was not effective in reducing the risk of all-cause death or HHF in elderly patients with mildly impaired systolic dysfunction. A retrospective analysis of the DIG trial[167] did not detect a benefit of digoxin therapy when the EF was >40%. The PEACE trial[156,166] did not show a reduction in the risk of CV death and HHF with angiotensin-converting enzyme inhibitors in patients with ischaemic HF with mildly reduced EF. In the TOPCAT Americas substudy[172], the risk of the primary composite end point of CV death, HHF or aborted cardiac arrest (CA) was reduced with spironolactone therapy in patients with EF at the lower end of the included EF spectrum (EF ≥45%). The BB-meta-HF study[99], a large meta-analysis of trials on β-blockers, demonstrated a lower all-cause and CV mortality in patients in sinus rhythm with HFrEF or HFmrEF but not in those with HFpEF. In a prespecified subgroup analysis of the PARAGON-HF trial[59], therapy with sacubitril–valsartan was effective in patients with EF lower than or the same as the median (EF 57%). For the HFrEF (EF <40%) category of the BB-meta-HF study, we report the ranges of HR and 95% CI across the subgroups of HFrEF considered in the study (EF <20%, 20–25%, 26–34% and 35–39%). For the HFrEF and HFpEF categories of the PARADIGM-HF–PARAGON-HF study, we report the ranges of HR and 95% CI across the subgroups of HFrEF (EF ≤22.5%, 22.5–32.5% and >32.5–42.5%) and HFpEF (EF >52.5–62.5% and >62.5%) considered in the study.

category, when repeat events rather than time to first event were analysed, candesartan significantly reduced the risk of cardiovascular death or recurrent hospitalization for HF by 25%[155]. In a post hoc analysis of the PEACE trial[156], which enrolled patients with stable coronary artery disease and normal or slightly reduced EF, the angiotensin-converting enzyme inhibitor trandolapril improved survival and a composite of death, myocardial infarction and stroke compared with placebo in patients with HFmrEF but did not reduce cardiovascular

mortality and hospitalizations for HF. In TOPCAT[87], which enrolled patients with HF with EF ≥45%, a significant interaction between treatment and EF and outcomes was observed for both the primary end point (a composite of cardiovascular death, hospitalization for HF and aborted cardiac arrest) and the secondary end point of hospitalization for HF. Spline analyses highlighted a significant treatment effect with spironolactone in terms of reduced risk of the primary outcome or hospitalization for HF when the EF moved below 55%[87]. Additionally, spironolactone significantly reduced the primary outcome when data from North and South America were separately analysed, as well as in the subgroup of patients who were included in the trial based on their high natriuretic peptide levels, which would increase the likelihood of the true presence of HF[87,157]. Accordingly, in December 2020, the FDA advisory committee recommended with an 8/4 vote that existing evidence supported the use of spironolactone for the reduction of hospitalizations for HF in patients with HFpEF, specifying that the benefit might be expected in patients in the mildly reduced range of EF (with comments made about EF of 45–55% or up to 57%)[158].

An individual patient-data meta-analysis of 11 RCTs of β-blockers demonstrated the benefit of this therapy for the reduction of all-cause and cardiovascular mortality in patients in sinus rhythm with HFrEF or HFmrEF but not in those with HFpEF[99]. In a retrospective analysis of the DIG trial[159], therapy with digoxin significantly reduced cardiovascular death or hospitalizations for HF in patients with HFrEF but not in patients with HFpEF or HFmrEF. This finding was confirmed in a spline analysis in which the digoxin treatment effect became nonsignificant when the EF changed above 40%[159]. In 2020, in the PARAGON-HF trial involving patients with HF with EF ≥45%, treatment with sacubitril–valsartan was effective in patients with EF equal to or below the median (EF ≤57%), which was also shown when the relationship between continuous EF values and treatment effect was analysed by spline analyses[26,59]. An expanded indication for sacubitril–valsartan was granted in 2020 by the FDA, with the clarification that the most benefit is expected in patients with EF below normal values[160]. Altogether, these data suggest that the use of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, MRAs and sacubitril–valsartan can be considered in HFmrEF[161]. The ongoing, registry-based RCT SPIRRIT-HFpEF[53] enrolling patients with EF ≥40% (HFmrEF and HFpEF) will provide further important evidence regarding the potential benefit of MRAs in the entire HFmrEF and HFpEF spectrum.

Novel drugs that act on alternative pathways are emerging for the treatment of HF and have been demonstrated to be effective in the setting of HFrEF in the past few years. Three large RCTs have tested treatment with SGLT2 inhibitors in patients with HF. The risk of cardiovascular death or hospitalization for HF was significantly reduced by empagliflozin in the EMPEROR-Reduced trial[36] and by dapagliflozin in the DAPA-HF trial[35] (which enrolled patients with HFrEF with or without diabetes). These results have generated great expectations for the potential of SGLT2 inhibitors for the treatment of HFmrEF and HFpEF, which is currently being tested in the EMPEROR-Preserved and DELIVER trials[162]. The first data supporting the use of SGLT2 inhibitors in patients with HFmrEF or HFpEF come from the SOLOIST-WHF trial[17]. Patients with HF and type 2 diabetes who were stabilized after hospitalization for worsening HF or recently discharged from hospital were randomly assigned, regardless of EF, to the SGLT2–SGLT1 inhibitor sotagliflozin or placebo. The benefits of sotagliflozin for risk reduction of cardiovascular death or hospitalizations or urgent visits for HF was consistent in patients with EF <50% or ≥50%[17].

A proportion of patients with HFmrEF are those in whom the EF has improved from HFrEF owing to the successful use of HFrEF therapies[122]. In this setting, available data support the indefinite continuation of HFrEF treatments, and the withdrawal of neurohormonal antagonists after the improvement (or recovery) of EF should be strongly discouraged[138]. In the TRED-HF trial[154], HFrEF treatments were withdrawn in a small group of patients with dilated cardiomyopathy and recovered EF. After weaning, about 40% of patients experienced a recurrence of HF within 6 months, defined by a fall in EF of >10% to <50%, an increase in left ventricular end-diastolic volume of >10% to greater than the normal range, a doubling of the NT-proBNP level to >400 ng/l, or clinical evidence of HF, but no deaths were observed in this small, short-term trial[154]. However, whether patients with recovered EF who have not yet received HFrEF therapy should be started on this therapy after EF has already recovered remains unknown.

The use of device therapy in patients with HFmrEF has no supporting data. However, a growing subgroup of patients who receive an ICD for primary prevention have an improvement in EF to HFmrEF or HFpEF at the time of generator replacement and, therefore, no longer fulfil the criteria for an ICD for primary prevention[6]. In a retrospective study, albeit lower than in patients with

Box 2 | **Knowledge gaps and future directions**

- The advancing concept of precision medicine is based on deep phenotyping and individualization of treatments and might replace or complement the current left ventricular ejection fraction (EF)-based approach to diagnosis and categorization of heart failure. Integrating emerging imaging techniques, advanced analytics, multiple biomarkers and omics with EF assessment might provide more precise phenotyping and targeted treatment.
- Heart failure with mildly reduced EF (HFmrEF) is a heterogeneous category that is based on a snapshot EF measurement in the dynamic natural history that characterizes the heart failure syndrome. Current data provide an extensive but static characterization of HFmrEF. Therefore, there is a need for a comprehensive assessment of EF trajectories over time and their interaction with multiple patient characteristics that also change over time in complex, time-dependent models.
- Strategies for the prevention of sudden cardiac death in patients with EF ≥40% have not been tested. The potential role of device-based therapies, such as cardiac resynchronization therapy, is unknown.
- Future treatment of HFmrEF might rely on weak guideline recommendations that are based on post hoc and subgroup analyses of completed trials of heart failure that have included patients with HFmrEF. However, trials evaluating existing therapies for heart failure with reduced EF will also need to be assessed in dedicated HFmrEF trials, that is, trials on the new use of existing drugs or 'repurposing' trials. These studies are less likely to be sponsored by industry and are suitable for publicly funded, pragmatic trials.

persisting ICD indication, patients who did not fulfil the criteria for an ICD had an annual rate of appropriate ICD interventions of around 3%[163]. A retrospective analysis of the SCD-HeFT trial[164] investigated patients with available reassessment of EF at a median interval of 13 months after ICD implantation and showed that the subsequent benefit in reduced mortality that was gained by receiving an ICD was similar in patients who improved to EF >35% and those with persisting EF ≤35%. Therefore, the available evidence suggests that the risk of arrhythmia persists at least to some extent in patients with improved or recovered EF.

Conclusions

After the introduction of the mid-range EF category of HF in the 2016 ESC HF guidelines[6], many studies have contributed to improving our understanding of the epidemiology, clinical characteristics, prognosis and potential treatment effects in patients with HFmrEF. The overall picture supports the notion that HFmrEF is more similar to HFrEF than to HFpEF, especially in aetiology and treatment response, and therefore is more appropriately termed HF with mildly reduced EF[19,20]. Gaps in our knowledge need to be filled, and future dedicated research should encompass the whole scenario of HFmrEF, from pathogenesis to treatment (BOX 2).

A broad range of effective therapies for HFrEF is now available. HFpEF seems to be distinctly different from HFrEF and is likely to need more targeted treatments and dedicated clinical trials. Patients with HFmrEF seem to be responsive to HFrEF medications but the strength of recommendations and level of evidence for these drugs in patients with HFmrEF must be considered modest. Ongoing clinical trials in patients with HFmrEF or HFpEF, in particular of MRAs and SGLT2 inhibitors, will inform the future treatment landscape in HFmrEF.

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