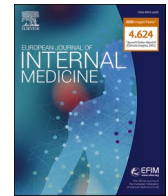




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Review Article

From mid-range to mildly reduced ejection fraction heart failure: A call to treat

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ABSTRACT

The historical classification of heart failure (HF) has considered two distinct subgroups, HF with reduced ejection fraction (HFrEF), generally classified as EF below 40%, and HF with preserved ejection fraction (HFpEF) variably classified as EF above 40%, 45% or 50%. One of the principal reasons behind this distinction was related to presence of effective therapy in HFrEF, but not in HFpEF.

Recently the expanding knowledge in the specific subgroup of patient with a LVEF between 41% and 49% and the potential benefit of new therapies and of those used in patients with LVEF below 40%, has led to rename this group as HF with mildly reduced EF (HFmrEF).

In this review we discuss the reasons behind this modification, we summarize the main characteristics of HFmrEF the similarities and differences with the two other EF categories, and finally we provide a comprehensive overview of the current available evidence supporting the treatment of patients with HFmrEF.

Heart failure (HF) is a global pandemic that affects more than 64 million people worldwide and its prevalence is steadily growing [1–4]. The overall aging of the worldwide population leads to increasing burden of HF-related hospital admissions and higher demand of HF specific therapies with increasing impact on health-care costs [5,6]. In the United States the health expenditures for the yearly 1.1 million hospital stays for chronic HF corresponds to 10% of the total health expenditures [7]. Health care-related costs associated with an increasing HF prevalence are projected to increase three-fold between 2010 and 2030 [8].

Despite therapeutic advances with impact on morbidity and survival, the prognosis of HF remains poor. HF is one of the most common causes of hospitalization and the mortality rate is paradoxically growing [9].

Despite the high complexity of HF, one single parameter endures as the primary classification tool in clinic and in research. Left ventricular ejection fraction (EF), indeed, remains the milestone of HF management as it is essential for diagnosis, prognostic stratification, eligibility for therapies and it is the first criteria for inclusion in randomized clinical trials (RCTs) [10].

The historical classification of HF has considered two distinct subgroups, HF with reduced ejection fraction (HFrEF - formerly “systolic”

HF, generally classified as EF below 40%) and HF with preserved ejection fraction (HFpEF - formerly “diastolic” HF, generally classified as EF above 50%) [10], and the principal reason behind this distinction was related to the fact that there was effective therapy in HFrEF but not in HFpEF. The remaining gap between the two categories created the premise for a novel HF category which was introduced by the European Society of Cardiology (ESC) guidelines in 2016 and denominated HF with mid(dle) range EF. The main aim was to explore the “underlying characteristics, pathophysiology and treatment of this group of patients” [11]. After 5 years, the expanding knowledge in this specific subgroup led the writing committee of the last HF ESC guidelines, published in 2021, to rename it as HF with mildly reduced EF (HFmrEF) [10]. In this review we discuss the reasons behind this modification, we summarize the main characteristics of HFmrEF, the similarities and differences with the two other EF categories, and finally we provide a comprehensive overview of the current available evidence supporting the treatment of patients with HFmrEF.

1. The genesis of mildly reduced ejection fraction heart failure

Since the 1980s, EF is the main tool for diagnosis, classification and

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risk stratification of HF [12,13]. For a long period, the classification of HF based on EF differentiated two distinct subgroups, HF with reduced ejection fraction (HFrEF - formerly “systolic” HF) and HF with preserved ejection fraction (HFpEF - formerly “diastolic” HF) [14]. The rationale of this dichotomization was the proof of evidence from large randomized clinical trials (RCT) that antineurohormonal drugs, and later HF devices, were able to improve survival in patients with reduced EF, and 40% was the “critical” threshold identifying patients with proven benefit from therapies.

On the other side, before the publication of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial, there were no therapeutic strategies that demonstrated to reduce morbidity and mortality in patients with HFpEF [15,16]. The initial definition of HFpEF derived from the The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program that encompassed patients with HF regardless of EF [17]. The CHARM-Preserved enrolled patients with EF >40% that were defined as with HFpEF [18]. This strategy aimed to include patients excluded from RCT on HFrEF, acknowledging that “subclinical” LV dysfunction was amenable to be compared with the “true normal” EF. In the following years various thresholds were adopted to enroll patients in HFpEF RCT; the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOP-CAT) study, the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) and more recently the Angiotensin-Nephrilysin Inhibition in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) included patients with EF ≥45% [19–21]. The absence of univocal agreement in the definition of preserved EF created the first premise to the introduction of an alternative entity. Moreover, in guidelines the accepted lower range of normal EF is 52% in males and 54% in females [22]. Thus, in a rigorous interpretation, values of EF below 50% cannot be considered as normal. This originates a gap between the two entities that corresponds to the classification of mildly reduced EF in the guidelines for echocardiographic quantification of LV function [22]. The first attempt to fill this gap was made by the last ACCF/AHA (American College of Cardiology Foundation/American Heart Association) guidelines on HF in 2013 that classified patients with EF within 40 and 49% as having borderline HFpEF in order to differentiate them from patients with HFrEF [23]. In 2016 the European Society of Cardiology (ESC) guidelines first introduced the term “middle range” by creating a category of HF in between the two classical entities that was named HF with mid-range EF (HFmrEF) [11]. The aim of the guidelines committee was not to suddenly introduce a new clinical entity with a distinct pathophysiological background and specific therapy, but rather to stimulate dedicated research into the “underlying characteristics, pathophysiology and treatment of this group of patients” [11]. Although a certain confusion was generated among clinicians, in the years following its origin greater attention has been dedicated to HFmrEF and several studies have explored different aspects of this subgroup. Data collected during the first years following the publication of 2016 ESC guidelines allowed to better define the characteristics of HFmrEF and, in addition to the data from retrospective analyses of RCTs suggesting that HFmrEF may potentially benefit from the treatments for HFrEF, led to rename this entity from ‘heart failure with mid-range ejection fraction’ to ‘heart failure with mildly reduced ejection fraction’ [10]. The revised category has also changed for two additional aspects: following the criteria, and the demonstration of treatment benefit, from RCTs in HFrEF that included patients with EF ≤40%, patients with EF=40% are now included in the HFrEF group, and HFmrEF, thus, includes now the EF in the range 41-49%; the presence of symptoms and/or signs of HF (i.e. elevated BNP or NT-proBNP and other evidence of structural heart disease) are not considered mandatory anymore for the diagnosis of HFmrEF if the measurement of EF is considered reliable(10).

2. Epidemiology

The proportion of HFmrEF within the overall HF population ranges between 10 and 25% [24–30]. In a large community-based longitudinal cohort free from HF and followed for > 10 years, the incidence rate of HFmrEF was 6.7 cases per 10,000 person-years, vs 26.9 and 34.9 in HFpEF and HFrEF, respectively [28]. With few exceptions, predictors of incident HF were similar across the spectrum of EF [28]. In European registries the rate of prevalent HFmrEF was >20% of the entire HF cohort, and precisely 24% in the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) Registry and 21% in the Swedish HF (SwedeHF) Registry [26,27]. Slightly lower rates were reported in Asian, Australian and American registries [24,25,29]. Finally, in the world of RCTs, and specifically in the CHARM population, 17% had HFmrEF [31].

3. Clinical characteristics of HFmrEF – one reason behind the ‘mildly reduced ejection fraction’

After the introduction of HFmrEF within the spectrum of HF phenotypes, the debate about which was the most appropriate matching for the newborn category became essential. The obvious approach might be defining HFmrEF as the intermediate phenotype, but this is not supported by available evidences that rather highlight the difficulty to set HFmrEF in a precise scenario [32]. Earlier studies suggested that HFmrEF was closer to HFpEF in terms of clinical characteristics [33,34]. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study, patients with borderline EF presented features similar to the HFpEF population in particular in terms of age, systemic hypertension and atrial arrhythmias, and intermediate in terms of sex and ischemic etiology [33]. Similarly, in the Acute Decompensated Heart Failure Registry (ADHERE), that extended the limit of “borderline” EF to 55%, age, arterial blood pressure, atrial fibrillation, diabetes and chronic obstructive pulmonary disease (COPD) were comparable to HFpEF, while again gender and ischemic etiology were intermediate [34]. Although the Get With The Guidelines–Heart Failure (GWTG-HF) Registry recently reported characteristics of borderline EF that were more similar to HFpEF [35], the trend changed in later studies and HFmrEF appeared to be more close to HFrEF [26,27]. The ESC-HF-LT provided an extensive assessment of characteristics of the HF population in Europe. HFmrEF shared with HFrEF several aspects, including younger age, male sex, ischemic etiology, lower prevalence of atrial fibrillation. Of note, patients with HFmrEF were less symptomatic, less likely to receive diuretics and with less comorbidities compared to the other phenotypes. The proposed explanation was that HFmrEF represented early-stage or rather recovered, and therefore milder, HFrEF [26,36]. In the CHARM programme 1, 322 patients with HFmrEF were recruited and most of their characteristics, including age, systolic blood pressure, prevalence of females, history of myocardial infarction and atrial fibrillation were similar to HFrEF [31]. In the SwedeHF Registry, the > 9,000 of patients with HFmrEF were more similar to HFpEF for the prevalence of atrial fibrillation and for the values of systemic blood pressure, but more similar to HFrEF for many other characteristics including age, chronic kidney disease, diabetes mellitus and ischemic etiology [27]. Regarding the gender distribution, the proportion of females in HFmrEF was intermediate between HFrEF and HFpEF, but more similar to HFrEF [37].

3.1. Ischemic etiology

Ischemic etiology is important in the interpretation of HFmrEF as a mild form of HFrEF. Prevalence of ischemic heart disease has been systematically reported as similar in HFrEF and HFmrEF [25,30,38]. Not only the crude, but also the adjusted prevalence of ischemic heart disease appears comparable between the two phenotypes and HFmrEF patients were exposed to a risk of new ischemic events that was similar

to HF_rEF and higher compared to HF_pEF [39]. Additional insights into comorbidities within the spectrum of EF provided interesting observations related to the HF_mrEF subgroup.

3.2. Atrial fibrillation and Comorbidities

Although the prevalence of atrial fibrillation decreases with declining EF, characteristics of patients with and the prognostic implications of atrial fibrillation are consistent across EF categories [40]. Other non-cardiovascular comorbidities are typically more prevalent in HF_pEF than in HF_mrEF and HF_rEF, but their impact on prognosis may be different. Both chronic kidney disease and anemia similarly demonstrated higher prevalence in HF_pEF vs HF_rEF and HF_mrEF, but a stronger association with, respectively, mortality and mortality/HF hospitalizations in HF_rEF and HF_mrEF than in HF_pEF [41,42]. Obesity showed different profiles according to type of study report (i.e. observational studies vs RCTs). European registries described intermediate values of BMI in HF_mrEF [26,27,30], whereas at least two important RCTs on HF_pEF, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study and the Angiotensin-Nephrilysin Inhibition in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) study, reported high BMI in HF_mrEF, more similar to the HF_pEF cohort [43,44].

3.3. Biomarkers profiles

The biomarkers' profiles also demonstrated peculiarities in HF_mrEF. Data from the SwedeHF reported lower values of NT-proBNP in HF_mrEF compared to HF_rEF, that were more similar to HF_pEF [27]. Interestingly, in HF_mrEF NT-proBNP suffered more of the confounding effect of other variables such as atrial fibrillation and showed higher prognostic and discriminatory power compared to HF_pEF [45]. Finally, a dedicated analysis on patients with acute HF explored the patterns of distribution of different biomarkers across the EF spectrum and demonstrated an intermediate profile in the HF_mrEF category, with enhanced expression of both markers of cardiac stretch and of inflammation, and this suggested potential pathophysiological implications in the classification of HF_mrEF [46].

4. Prognosis

Larger observational studies that have explored the prognosis of HF_mrEF reported in large part more benign outcomes in HF_mrEF compared to HF_pEF and HF_rEF [25-27,29].

In a prospective international multi-ethnic cohort study, two-year all-cause mortality in HF_mrEF was 12%, with adjusted hazard of mortality comparable to HF_pEF and lower than HF_rEF [29]. Similarly, one-year mortality was also observed to be closer to HF_pEF and better than HF_rEF in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study and in the SwedeHF Registry [25, 27]. In the ESC-LT-HF Registry, observed one-year all-cause mortality was 7.6%, vs 6.3% in HF_pEF and 8.8% in HF_rEF [26]. Interestingly, the proportion of non-cardiovascular mortality was numerically higher, while the incidence of hospitalization for HF was lower (8.7% and 9.7% vs 14.6%), in HF_mrEF and HF_pEF vs HF_rEF [26].

On the other hand, the retrospective analysis of 39,982 patients enrolled in the GWTG-HF have reported similar 5-years mortality across the spectrum of EF, whereas cardiovascular and HF readmission rates were higher in HF_rEF and HF_mrEF compared with HF_pEF [35], and in the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) both mortality and rate of hospitalizations did not differ across the range of EF [30].

Differences in outcome between real-world studies and RCTs are also evident for HF_mrEF patients. In RCTs the divergence in risk across the EF spectrum is larger than in observational studies, with HF_pEF and HF_mrEF at lower risk of events compared to HF_rEF. In the CHARM-

Programme, the incidence of all-cause mortality at ~3 years was 12.6% in HF_mrEF, remarkably lower compared to the data from registries, and HF_mrEF and HF_pEF were at lower risk compared to HF_rEF for all the study outcomes [31]. When EF was assessed as a continuous variable, the adjusted relationship between EF and outcomes was characterized by a steep decrease in incidence rate with increasing EF up to 50% for all-cause and cardiovascular mortality, and up to 40% for the risk of HF hospitalization, than flattened attesting the similarity between HF_mrEF and HF_rEF [31].

In incident HF the relationship between HF phenotype and outcome appears to have different features. Data collected from a prospective, observational community-based cohorts free from HF reported an all-cause mortality rate after the onset of HF that was 497 events per 10,000 person years in HF_mrEF, 394 events per 10,000 person years in HF_pEF and 459 per 10,000 person years in HF_rEF. The survival in HF_mrEF was lower than HF_pEF ($p=0.02$) and similar to HF_rEF ($p=0.78$). The inclusion of patients limited to incident HF and the exclusion of patients with a documented transition of EF from HF_rEF to HF_mrEF, provided a reliable picture of the prognosis of HF_mrEF, supporting the same treatment approach for HF_mrEF and HF_rEF [28].

The risk of sudden cardiac death (SCD) in HF_mrEF has not been explored in depth and remains an unsolved issue. EF is key in the risk estimation of SCD in HF [47], and among HF_pEF and HF_mrEF SCD is not considered one of the leading causes of death. However, possible underestimation in observational studies and in RCTs should be accounted due to imprecise reporting or events adjudication, especially considering the potential confounding effect of non-cardiovascular causes of deaths. In a previous report specifically focusing on the modalities of death in HF_pEF, SCD accounted for the 30-40% of the cardiovascular causes of death and, thus, deserves future dedicated attention [48].

4.1. Treatment of HF_mrEF (Summary Figure)

Neurohormonal antagonists have been the cornerstone of pharmacological therapy for HF for the last decades [10]. However, these agents have demonstrated to be effective in HF_rEF, whereas until the recent release of studies on SGLT2i [16], no therapies demonstrated proven benefit in the two other categories of HF. Specifically, no dedicated studies have been designed to address the specific question of whether there is any pharmacological strategy active in improving outcomes in HF_mrEF. Observational data from registries are relatively scarce and suffers of obvious limitations due to confounding. The rate of GDMT use in registries is high among the HF_mrEF population, suggesting that in clinical practice these patients are frequently assimilated to the HF_rEF, have alternative indications to these treatments (i.e. systemic hypertension, atrial fibrillation) or alternatively, are "in transition" from HF_rEF [25-27,30,35,38]. These data may apparently support the use of GDMT in HF_mrEF, although in a former study there was a lacking association between GDMT and outcomes in HF_mrEF [33].

In previous RCTs on HF_pEF, the heterogeneity in the inclusion criteria permits deriving partial considerations on the potential of GDMT in HF_mrEF. In most of this RCTs the lower threshold of EF was set to include completely, or partially, the HF_mrEF spectrum [18-21]. Pooled data and post-hoc analysis of these studies can be helpful to formulate some recommendations on the most appropriate approach (Table 1). In CHARM, candesartan reduced the primary outcome and the risk of recurrent HF hospitalizations in HF_mrEF [31]. In the TOPCAT study, a significant interaction between EF and outcome was observed both for the primary composite endpoint of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest and for the secondary endpoint of HF hospitalizations, with potential efficacy in the lower EF range in the trial [43]. Noteworthy, the interaction between EF and outcome was more evident in males than in females [43]. An individual patient data meta-analysis of 11 RCT on betablockers demonstrated a treatment benefit for patients in sinus rhythm across the entire spectrum of EF. The hazard ratio for cardiovascular mortality in HF_mrEF patients was 0.48

Table 1

Summary of randomized controlled trials with subgroups/post-hoc analyses providing evidence on treatment effect in HFmrEF.

Study	Year	Size	Drug	Class	Range EF	Primary Outcome	Follow-up (months)
CHARM-Preserved	2003	3023	Candesartan	ARB	>40%	CV death/first HF hospitalization	37
DIG (ancillary)	2006	988	Digoxin	-	>45%	HF mortality/HF hospitalization	37
TOPCAT	2014	3445	Spironolactone	MRA	≥45%	CV death/aborted cardiac arrest/first HF hospitalization	40
BB-metanalysis	2017	17312	-	BB	Overall	All cause mortality and CV death	16
PARAGON-HF	2019	4822	Sacubitril/Valsartan	ARNI	≥45%	CV death/total HF hospitalizations	35
SOLOIST-WHF	2021	1222	Sotagliflozin	SGLT2i	<50%	CV death/total HF hospitalizations/urgent HF visits	9
EMPEROR-PRESERVED	2021	5988	Empagliflozin	SGLT2i	>40%	CV death/first HF hospitalization	26
EMPULSE	2022	530	Empagliflozin	SGLT2i	Overall	Clinical benefit	90 days

(95% CI 0.24–0.97) [49]. More recently, the PARAGON-HF assessed the effect of sacubitril/valsartan in the largest cohort of HFpEF to date. EF threshold for inclusion was ≥45%. Although the overall study was inconclusive, subgroup analysis demonstrated a benefit in patients with EF below the median (i.e. <57%) [21]. In a pre-specified analysis of the pooled data from this study and from the Prospective Comparison of ARNI [Angiotensin Receptor–Nepriylsin Inhibitor] with ACEI [Angiotensin-Converting– Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) [50], the effect of sacubitril/valsartan varied by EF and was greatest in patients with EF below normal [44]. Due to the post-hoc design of the analysis and the gap in EF with values >40% and <45% excluded from both the RCTs, these observations should be considered as hypotheses generating and claim for specifically designed studies. When pooled

together on a continuous scale, data from these studies suggest treatments might provide benefit in the mildly reduced range of EF, as also contemplated by the recently published European guidelines on HF (Figure 1) [10,51].

The astonishing results from the two major RCTs on SGLT2 inhibitors for the treatment of HFrEF have generated great expectations for the potential of this class of drugs for the treatment of HFmrEF and HFpEF [52,53]. In the SOLOIST-WHF trial, 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 [54]. 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%. However, the premature conclusion of the study due to the loss of

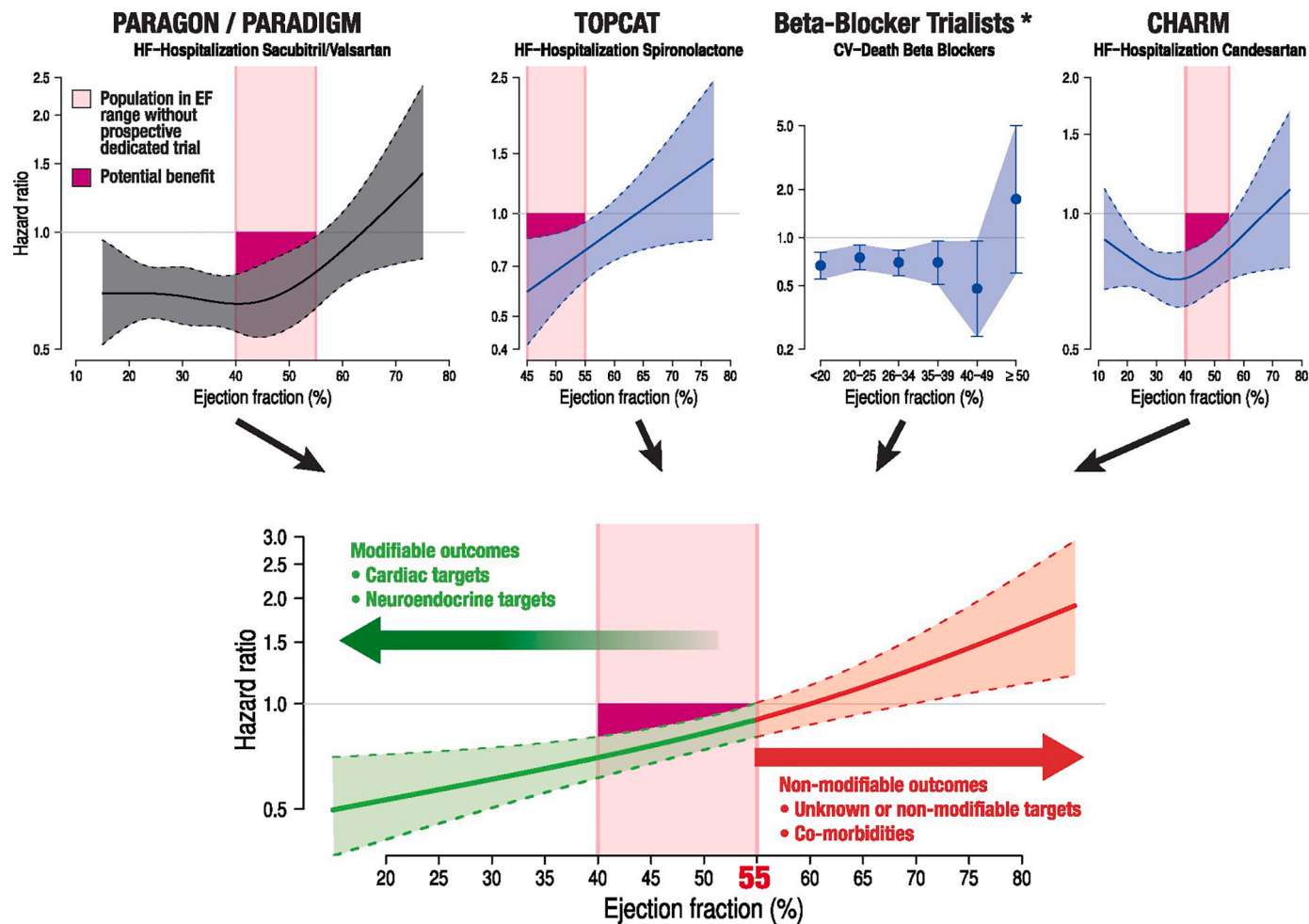


Figure 1. Treatment effects over a broad range of EF from major RCTs including the overall EF spectrum. The EF threshold for treatment effect appears to be around 55%. Dark red areas depict ejection fractions which are not covered by dedicated RCTs, but where evidence exists from exploratory analyses. *Reproduced from Böhm et al. Eur Heart J 2020 Jul 1;41(25):2363-2365.*

funding, the larger predominance of HF_rEF in the study cohort and the exclusive inclusion of diabetic patients limit the applicability of results to the overall population of HF_mrEF/HF_pEF. In 2021, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) study has become the first RCT that provided solid evidence of benefit in the treatment of HF_pEF [16], with a 21% reduction in cardiovascular mortality/HF hospitalization in the treatment arm compared to the placebo group, although with not significant effect on mortality. With an EF threshold for inclusion of >40%, one-third of the trial population had HF_mrEF. The results were consistent across the entire EF spectrum.

More recently, the EMPULSE trial enrolled 530 patients hospitalized for HF within the overall spectrum of EF and demonstrated a significant clinical benefit in the treated arm, defined by a hierarchical composite of all-cause death, number of HF events and time to first HF event, or change in symptoms at 90 days. No interaction with EF was observed [55]. If the upcoming results of the second mortality trial in HF_pEF/HF_mrEF with a SGLT2 inhibitor, the Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) [56], will be confirmatory, SGLT2 inhibitors will be the first class of drugs with proven positive effect on the prognosis of patients with HF_pEF/HF_mrEF.

4.2. Additional strategies for phenotype characterization and longitudinal assessment of ejection fraction – implications for treatment

EF is a largely adopted and universally accepted parameter in clinical practice. It is widely available, easy to calculate and applicable to different imaging techniques [57]. It can rapidly be estimated visually in urgent settings and can be assessed by high as well low-quality equipment. There are also limitations, inter and intraobserver variability have been reported to be wide enough to generate potential misclassifications [58]. The thresholds of EF, as proposed by current recommendations, vary according to age and gender and a range of normality, rather than a single value, is defined [22]. This is in partial contrast with the arbitrary and fixed cut-off proposed by guidelines and adopted for inclusion in RCTs. In the rational approach to the single specific cases, further steps are required and alternative techniques are emerging to aid the clinicians. Myocardial tissue characterization by cardiac magnetic resonance imaging is part of the routine diagnostic work-up of patients with HF and can support the etiological characterization. Emerging studies suggest its importance in patients with EF>40% [59,60]. Late gadolinium enhancement (LGE) demonstrated to correctly classify the risk of mortality and SCD in patients with EF>40%, identifying patients that could be considered for primary prevention strategies regardless of their EF [61].

The assessment of global longitudinal strain (GLS) from speckle-tracking analysis of 2-dimensional echocardiography is an emerging technique complementary to EF for the quantification of myocardial function and with incremental prognostic performance [62–64].

In the era of precision medicine, deep etiological characterization of HF may maximize the understanding of the underlying disease, to predict its natural progression and to individualize the strategies of treatment. Specific aetiologies such as sarcoidosis may portend increased risks of poor outcome irrespective of the severity of LV dysfunction [65]. The genetic background of non-severe reduced EF in some cases can lead to alternative strategies in order to protect individuals with irretrievably high risk of dying suddenly regardless of EF. Specific genotypes of dilated cardiomyopathy, including Lamin A/C, Filamin C and desmosomal genes, demonstrated lower survival free-from potentially fatal ventricular arrhythmias despite EF values above the 35% “critical” threshold for ICD implantation [66,67].

4.3. Ejection fraction, a “dynamic” parameter

It should be considered that EF is a dynamic parameter inevitably

subject to variation with time. In observational registries collecting patients with prevalent HF, the value of EF provides a static snapshot of something that is shifting over time as the results of treatment or merely due to the natural progression of the underlying disease. In the Olmsted County, Minnesota, cohort, over a 5-years observation period \approx 40% crossed from HF_pEF to HF_rEF and viceversa [68]. In the SwedeHF Registry trends in EF across the spectrum of baseline EF were specifically explored in patients with available longitudinal data. Among individuals with HF_mrEF, 37% and 25% switched respectively to HF_rEF and HF_pEF, while among HF_rEF and HF_pEF 16% and 21%, respectively, switched to HF_mrEF [69]. The temporal trends of EF have also important implications on outcomes [36,69,70]. A recent retrospective cohort study focused specifically on patients with EF within the mid-range interval. The investigators collected all the patients examined in 2015 with EF between 40% and 50% and at least one previous echocardiographic examination. Of note only 15% of patients had stable HF_mrEF. The risk of all-cause mortality, cardiovascular mortality and HF hospitalization was higher for those with EF decreasing from >50% compared to those improving EF from <40%, even after adjustment for confounding factors. Interestingly, the outcome of patients improving EF was similar to patients with stable mid-range EF, suggesting that stable HF_mrEF might configure a relatively low risk entity [71].

The transition from the HF_rEF to the HF_mrEF category is in general the results of therapy. In this case the indefinite maintenance of GDMT is advocated and the withdrawal of neurohormonal antagonists after the improvement (or recovery) of EF should be strongly discouraged [72]. In the Withdrawal of Pharmacological Treatment for Heart Failure in Patients With Recovered Dilated Cardiomyopathy (TRED-HF) trial, therapy was 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 >10% to <50%, an increase in left ventricular end-diastolic volume >10% to greater than the normal range, a doubling of the NT-proBNP to >400 ng/l, or clinical evidence of HF, but no deaths were observed [73].

Further considerations in patients switching from HF_rEF to HF_mrEF concern the devices. With the progression of medical treatments for HF_rEF, the number of patients with primary prevention implantable-cardioverter defibrillator (ICD) that at the time of generator replacement have improved the EF not fulfilling anymore the criteria for ICD implantation, is growing(11). There is not univocal consensus on the most appropriate strategy to follow in this specific situation. In a previous retrospective study, patients with no longer guidelines indications to ICD at the time of replacement experienced a 3% annual rate of appropriate interventions, that was lower compared to patients with persisting indications [74]. A retrospective analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD HeFT) showed that the mortality benefit gained by ICD was similar between patients who improved EF>35% vs those with persisting EF \leq 35% [75]. Therefore, available evidences suggest that the arrhythmic risk persists despite the improvement in EF.

4.4. Remaining gaps and future perspectives

After the introduction of this new “intermediate” category in 2016 (11), a large amount of literature has been published that shed some light on this gray area and contribute to our understanding of the epidemiology, clinical characteristics and prognosis of HF_mrEF. The overall picture supports the notion that this category should be probably paired to the reduced rather than the preserved EF area and in this sense, it was reclassified as “mildly reduced” EF in the recent ESC guidelines. However, the broad heterogeneity in etiology, clinical presentation and natural progression requires a focused approach that overcomes the simple categorization by EF. In this era of precision medicine, the efforts should be directed to a more individualized work-up that involves alternative tools that can aid the diagnosis, characterization and risk stratification of patients. Emerging imaging techniques beyond the mere

assessment of EF are destined to integrate the clinical management and perhaps to provide further elements to improve the selection criteria for inclusion in RCT. Novel biomarkers and -omics studies might help to provide further insights into the pathophysiological knowledge of HFmrEF.

The absence of medical treatments with proven benefit has remained for long the most concerning aspect in the management of this category, but evidences from recent RCTs that included also patients in the HFmrEF category have probably determined the turning point in the treatment of HFpEF and HFmrEF. Low recruitment rate and limited number of events might interfere with the conduction of specific randomized studies on HFmrEF that will continue to be included in RCTs on HFpEF or, more appropriately, on HFrEF. Designing RCT that cover the whole spectrum of EF might represent a potential solution, although it might lead to underestimate the effect of interventions on the lower range of EF. Finally, novel strategies of intervention and novel emerging drugs acting through different targets might further implement in the future the options of treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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