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Review Article

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Precision Cardiology: Phenotype-targeted Therapies for HFmrEF and HFpEF

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ABSTRACT

Heart failure with mid-range ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) represent over half of heart failure cases but lack proven effective therapies beyond sodium-glucose cotransporter 2 inhibitor and diuretics. HFmrEF and HFpEF are heterogeneous conditions requiring precision phenotyping to enable tailored therapies. This review covers concepts on precision medicine approaches for HFmrEF and HFpEF. Areas discussed include HFmrEF mechanisms, anti-inflammatory and antifibrotic treatments for obesity-related HFpEF, If inhibition for HFpEF with atrial fibrillation, and mineralocorticoid receptor antagonism for chronic kidney disease-HFpEF. Incorporating precision phenotyping and matched interventions in HFmrEF and HFpEF trials will further advance therapy compared to blanket approaches.

Keywords: Heart failure with mid-range ejection fraction (HFmrEF); Heart failure with preserved ejection fraction (HFpEF); Precision cardiology; Phenotypes

INTRODUCTION

Heart failure (HF) has been traditionally categorized according to left ventricular ejection fraction (LVEF) into HF with reduced EF (HFrEF, LVEF <40%), HF with mid-range EF (HFmrEF, LVEF 40–49%), and HF with preserved EF (HFpEF, LVEF ≥50%) (**Figure 1**). However, this taxonomy is affected by the inaccurate measurement of EF, with overlaps between the different categories of patients, and fails to capture the marked heterogeneity in mechanisms driving HF progression across the EF spectrum.[1)]

Specific treatment recommendations for each HF phenotype according to the European Society of Cardiology (ESC) guidelines[2)] are summarized in **Table 1**. While evidence-based therapies have significantly improved prognosis in HFrEF, mortality and morbidity remain high in HFmrEF and HFpEF even after the introduction of sodium-glucose cotransporter 2 inhibitor (SGLT2i).[3)] However, HFmrEF and HFpEF are increasingly recognized as distinct syndromes with diverse pathological phenotypes based on predisposing risk factors, genetics, and comorbidities.[4)] Therefore, developing targeted therapies directed at specific HFmrEF and HFpEF subtypes represents the future of precision cardiology to improve outcomes for these deadly and disabling

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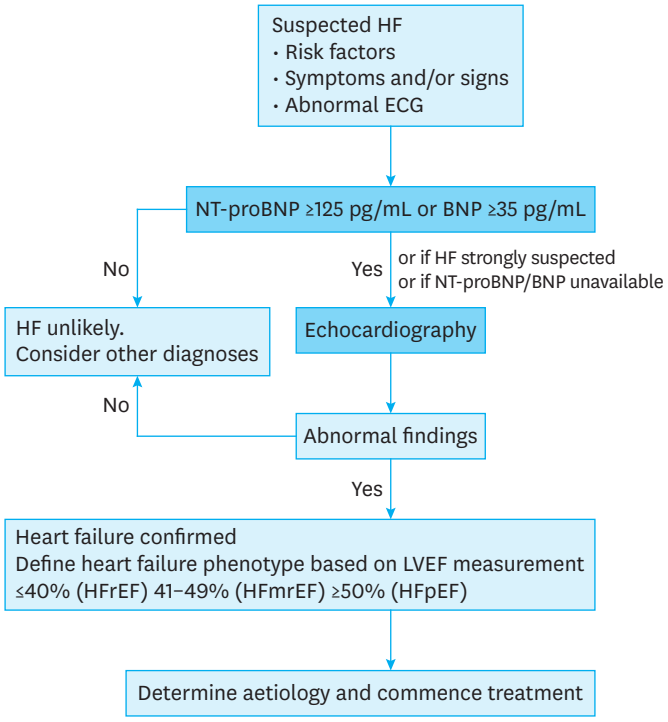

Figure 1. Diagnostic algorithms for HF according to European Society of Cardiology guidelines.[2]
HF = heart failure; ECG = electrocardiogram; NT-proBNP = N-terminal pro-B-type natriuretic peptide; BNP = B-type natriuretic peptide; LVEF = left ventricular ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

conditions.[5]

Taking into account these issues, this review discusses main concepts of precision medicine in HFmrEF and HFpEF.

HFmrEF MECHANISMS AND TREATMENTS

HFmrEF accounts for 10–20% of HF cases and shares poor prognosis with HFrEF.[2] This condition, however, is ill-defined as it includes patients that have the features of HFrEF and others that have distinct trajectories of their EF.[6] In these latter patients, pathogenetic mechanisms include myocardial fibrosis, hypertrophy, inflammation, impaired relaxation and contraction, and chronotropic incompetence.[6]

Current guidelines recommend the use of SGLT2i as first line treatment for patients with HFmrEF with a class of evidence IA in the ESC guideline,[2] class IIA in the American College of Cardiology and American Heart Association guidelines,[7] and class Ib in the Korean Society of Heart Failure Guidelines[8] for patients with HFmrEF and HFpEF. The guidelines also recommend uptitration of guideline-directed medical therapies proven efficacious in HFrEF, such as renin-angiotensin system inhibitors/angiotensin receptor-neprilysin inhibitor (ARNI), beta blockers, and mineralocorticoid receptor antagonists with a low level of evidence (IIB). However, large dedicated randomized controlled trials in HFmrEF patients are lacking to confirm treatment efficacy and optimal dosing.

HFmrEF likely represents an overlap phenotype along the spectrum of HF that may benefit from precision application of therapies demonstrated effective in HFrEF in some patients but more tailored therapies in others.[5] However, confirmation of treatment benefit requires robust HFmrEF-specific outcomes trials like Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-preserved)[9] and Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER),[10] and not sub-analysis of trials conducted for HFrEF or phishing into subgroup analysis of negative trials.

HFpEF MECHANISMS AND TREATMENTS

HFpEF has long defied conventional treatment methods. Early trials primarily focused on managing fluid overload, hypertension, and comorbidities, yet their success was limited. Large-scale studies such as the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)[11] and Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction[12] trials showed marginal benefits at best, failing to establish definitive therapeutic interventions.

One of the primary obstacles in HFpEF research was the diverse patient population and the lack of simple definition of the syndrome. HFpEF encompasses a wide spectrum of underlying etiologies, ranging from hypertensive heart disease to diabetic cardiomyopathy.[13] This heterogeneity complicated the design of trials, making it challenging to identify a one-size-fits-all approach. Furthermore, the lack of biomarkers specific to HFpEF hindered the development of targeted therapies.[14] Unlike HFrEF, where neurohormonal activation and ventricular remodeling provide clear therapeutic targets, the pathophysiological mechanisms of HFpEF have remained elusive.

The emergence of SGLT2i marked a breakpoint moment in HFpEF research. Initially developed for the treatment of type 2 diabetes,

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Table 1. Treatment of HF phenotypes according to European Society of Cardiology guidelines

	Recommendation	Level of evidence
Treatment of HFrEF	ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	IA
	Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	IA
	MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	IA
	Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	IA
	Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	IB
	Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity and reduce HF hospitalizations.	IC
	An ARBc is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta-blocker and an MRA)	IB
	The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia.	IIIC
	An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 hours after an MI.	IA
	An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (II or III) of an ischemic etiology (unless they have had an MI in the prior 40 days—see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.	IA
	ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	IIIA
	ICD therapy is not recommended in patients in NYHA class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a VAD, or cardiac transplantation.	IIIC
	CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IA
	CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.	IA
	CRT is not recommended in patients with a QRS duration <130 ms who do not have an indication for pacing due to high degree AV block.	IIIA
Treatment of HFmrEF and HFpEF	Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.	IC
	Screening for, and treatment of, etiology, and CV and non-CV comorbidities is recommended in patients with HFpEF.	IC
	Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.	IC

HF = heart failure; ACE-I = angiotensin-converting enzyme inhibitor; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; ARB = angiotensin-receptor blocker; CV = cardiovascular; ARNI = angiotensin receptor-neprilysin inhibitor; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; CRT = cardiac resynchronization therapy; VAD = ventricular assist device; SR = sinus rhythm; QRS = Q, R, and S waves (on an ECG); LBBB = left bundle branch block; AF = atrial fibrillation; AV = atrio-ventricular; HFpEF = heart failure with preserved ejection fraction; RV = right ventricular; HFmrEF = heart failure with mildly reduced ejection fraction.

these agents were serendipitously found to have favorable cardiovascular outcomes. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes[15] trial demonstrated reduced cardiovascular mortality and hospitalization for HF in diabetic patients treated with empagliflozin, an SGLT2i. Building upon this success, subsequent trials such as Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure[16] and the aforementioned EMPEROR-preserved,[9] specifically investigated the efficacy of SGLT2i in patients with HFpEF. These trials, which included patients both with and without diabetes, revealed unprecedented positive results. They demonstrated a substantial reduction in HF hospitalizations and cardiovascular deaths, leading to the recommendation for SGLT2i as foundation therapy for HFpEF as well as for HFmrEF.[17]

Although most of the potential mechanisms remain to be elucidated, the success of SGLT2i in HFpEF can be attributed to their multifaceted mechanism of action.[18] Beyond their antidiabetic effects, these agents exert a favorable impact on cardiac and renal physiology. By inhibiting the reabsorption of glucose and sodium in the proximal tubule of the kidney, SGLT2i induces diuresis and natriuresis, thereby reducing blood pressure and extracellular fluid volume.[18] This effect is particularly beneficial in HFpEF, where fluid overload is a prominent feature. Moreover, SGLT2i have demonstrated anti-inflammatory and anti-fibrotic properties, which are crucial in addressing the underlying pathophysiological processes in HFpEF.[19] They improve endothelial function, decrease arterial stiffness, and mitigate cardiac remodeling, all of which contribute to improved cardiac function.[18]

The results of the EMPEROR-preserved[9] and DELIVER[10] studies have changed the paradigm of HF suggesting that other mechanisms beyond neuro-hormonal modulation are important in patients with LVEF ≥40%. The results of the SGLT2i trials suggest that we should move away from the silos definition of HF according to left ventricular function values but rather use the assessment of left ventricular function to tailor therapy, based on the individual trajectories in each patient.[20] This is of utmost importance for patients with HF and LVEF >40%.

COMORBIDITIES IN HFmrEF AND HFpEF

The complex underlying pathophysiology of HF with LVEF >40% involves left ventricular diastolic dysfunction, systemic and pulmonary vascular dysfunction, as well as numerous extracardiac comorbidities and abnormalities.[21] Comorbidities have an integral role in the pathogenesis, phenotypes, therapeutic responses, and clinical outcomes of patients with HFpEF.[22] Multiple highly prevalent comorbidities contribute to the development and progression of HFpEF.[21] Obesity and excess adiposity are present in 40–70% of HFpEF patients.[23] Increased inflammatory cytokines from visceral adipose tissue cause endothelial dysfunction and stiffness of the myocardium and vasculature. Adipokines such as leptin alter myocardial energetics and promote left ventricular hypertrophy independent of blood pressure elevation.[23] Hypertension affects 60–89% of HFpEF patients and leads to pressure overload, left ventricular remodeling, abnormal calcium handling, extracellular matrix accumulation, and impaired relaxation.[22] Diabetes, present in 20–45% of HFpEF patients, results in the formation of advanced glycation end products that crosslink extracellular matrix proteins.[24] This causes collagen accumulation, myocardial stiffness, and left ventricular hypertrophy. Microvascular endothelial dysfunction and rarefaction further contribute to diabetic cardiomyopathy.[24]

Chronic kidney disease, which complicates 20–50% of HFpEF cases, promotes vascular stiffness, endothelial dysfunction, vascular calcification, anemia, fluid overload, and electrolyte abnormalities.[25]

Chronic obstructive pulmonary disease occurs in over 30% of HFpEF patients and leads to pulmonary hypertension, right ventricular dysfunction and remodeling, left ventricular underfilling, and impaired left ventricular relaxation.[26]

Sleep disordered breathing and obstructive sleep apnea, present in over 50% of HFpEF patients, result in recurrent hypoxia and exaggerated swings in intrathoracic pressure, activating the sympathetic nervous system and inflammatory pathways.[27]

Anemia, affecting 15–20% of HFpEF patients, reduces oxygen delivery to tissues, increases cardiac output, and contributes to volume overload and left ventricular remodeling.[28]

These comorbidities interact to drive key mechanisms underlying HFpEF pathophysiology including left ventricular hypertrophy, myocardial fibrosis, inflammation, coronary microvascular dysfunction, vascular stiffness, and impaired ventricular-vascular coupling.[22] The additive effects of comorbidities on these pathways results in diastolic dysfunction, chronotropic incompetence, rely on preload, and diminished cardiac output reserve during stress, characteristic of HFpEF.[22]

Hypertension-predominant HF may benefit from medications directly lowering blood pressure and reducing fibrosis like indapamide, spironolactone and nebivolol.[20] In hypertension-predominant HFmrEF and HFpEF, blood pressure lowering is effective in reducing the occurrence of HF.[29] Therefore, ensuring optimal guideline-directed medical therapy for the treatment of arterial hypertension titrated to maximally tolerated doses and using fixed dose combinations to improve adherence is pivotal.

Phenotyping patients with HF based on underlying comorbidities may allow personalized management approaches. Several randomized controlled trials in HF patients with LVEF >40% using neurohormonal antagonists that showed efficacy in HFrEF have failed to improve mortality and morbidity, as reviewed elsewhere.[30] This highlights the different pathophysiology of HFpEF and HFmrEF compared to HFrEF and the overriding influence of comorbidities.[21] The aforementioned TOPCAT trial[31] showed significant regional variation in the efficacy of spironolactone in HFpEF, likely related to heterogeneity in patient characteristics and comorbidity prevalence between regions.[32] The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction trial[33] found no mortality or hospitalization benefit of sacubitril/valsartan over valsartan in HFpEF, but did show improvement in measures of cardiac structure and function like left atrial volume index and N-terminal pro-B-type natriuretic peptide (NT-proBNP). This suggests that intervening earlier before accumulation of irreversible comorbid disease pathology may be needed in HFmrEF and HFpEF.

Given the importance of comorbidities, management of HFmrEF and HFpEF requires a multi-dimensional approach. Lifestyle interventions including diet, exercise, and weight loss should be strongly recommended.[34] Guidelines-based pharmacotherapies

to optimize control of individual comorbidities are essential. Interdisciplinary care models engaging cardiologists, primary care, endocrinologists, nephrologists, and other specialists are beneficial to comprehensively manage this complex patient population. Moving forward, further research on phenotyping and trajectories of patients with HF and LVEF >40%, interactions between cardiac and extracardiac disease mechanisms, and therapies targeting comorbidities is imperative to improve outcomes in this common and difficult to treat syndrome.

Given the increasing prevalence of HF with LVEF >40%, better characterization of distinct phenotypes based on underlying comorbidities and development of therapies that target extracardiac as well as myocardial disease processes will be essential to making progress against this major public health problem.[20]

Targeting obesity in HF

Obesity is a major risk factor for HF development and portends a worse prognosis in patients with established HF.[35] Up to 70% of patients with HF have a body mass index over 30 kg/m^2, classifying them as obese. Excess adiposity contributes to HF pathogenesis through inflammation, insulin resistance, myocardial energetics dysregulation, lipotoxicity, ventricular-vascular stiffness, and functional limitations.[36] Given the high prevalence of obesity in HF, targeted therapies for obesity-related cardiomyopathy are needed.

Weight loss through diet, exercise, and bariatric surgery has demonstrated improvements in cardiovascular risk factors, cardiac structure and function, biomarkers, functional status, and mortality in obese HF patients.[37] However, achieving and maintaining significant weight reduction is challenging. Pharmacotherapies including glucagon-like peptide 1 agonists, SGLT2i, and other antidiabetic medications indirectly promote weight loss while also providing metabolic benefits.[38]

Emerging evidence supports using anti-inflammatory agents to target obesity-driven inflammation in HF. In the STEP-HFpEF study,[39] treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss in obese HFpEF patients, than placebo.

Obesity-related HF may respond better to therapies targeting myocardial energetics like SGLT2i.[23] Emerging therapies like drugs targeting the inflammation pathways, the elevated serum uric acid levels may also provide metabolic benefits in obesity-related HFpEF.[23]

Agents targeting myocardial energetics may also hold promise for treating obesity-related cardiomyopathy.[36] Obese HF is characterized by shifts in substrate metabolism and impaired energy utilization. Trimetazidine and parhexilline are metabolic modulators that inhibits free fatty acid oxidation, shifting myocardial metabolism from fatty acid to more efficient carbohydrate oxidation.[40] In obese patients with HFpEF, free fatty acid oxidation inhibition improved exercise capacity, diastolic function, and myocardial energetics.[23] The EMPEROR-preserved trial[41] showed another metabolic modulator, empagliflozin, to reduce HF hospitalizations in HFpEF patients, 40% of whom had a body mass index over 30 kg/m^2.

Finally, exercise training is an important intervention to counteract skeletal muscle abnormalities and impaired functional status common in obese HF patients.[23] Supervised exercise programs have demonstrated benefit on exercise capacity, symptoms, and quality of life in this population.[42]

Therefore, the increasing prevalence of obesity-related HF necessitates the development of targeted pharmacological and lifestyle therapies. Anti-inflammatory agents, metabolic modulators, lipotoxicity reducers, and exercise training hold promise for treating HF in the setting of obesity. Further research is needed to determine optimal patient selection, combination strategies, and impact on hard clinical outcomes. Given the complex intersecting pathways, employing a multi-pronged approach may be required to comprehensively address the numerous intricacies of obesity-related cardiomyopathy.

Treating atrial fibrillation (AF) in HF with LVEF >40%

AF is highly prevalent in patients with HF, occurring in up to 40% of those with HFpEF and HFmrEF.[43] AF and HFpEF share similar risk factors and pathogenic mechanisms including hypertension, diabetes, obesity, inflammation, atrial remodeling, and fibrosis.[44] AF contributes to worsening HF symptoms through loss of atrial contraction, rapid heart rates, and irregular rhythm.[45] Conversely, HF in patients with LVEF >40% promotes atrial fibrosis and dilatation that perpetuates AF.[46] Managing coexisting AF in patients with HFpEF provides unique challenges.

Strategies for rate control include beta blockers, nondihydropyridine calcium channel blockers like diltiazem, and digoxin.[47] Beta blockers are indicated for rate control in AF but may be insufficient alone, due to comorbidities limiting dose escalation. Calcium channel blockers can be added but must be used cautiously to avoid hypotension. Digoxin is not ideal when the LVEF is greater than 40% due to potential to exacerbate diastolic dysfunction.[48] Rhythm control is advisable in HFmrEF and HFpEF patients who remain symptomatic despite adequate rate control.[2] Amiodarone

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has the most favorable profile for maintaining sinus rhythm in HF given low proarrhythmic risk, but long-term use is limited by toxicity.[48] Catheter ablation has demonstrated improvement in symptoms, quality of life, and left ventricular function in AF and HF. However, AF recurrence after ablation is common in HF due to extensive atrial disease. Recent trials found catheter ablation reduced hospitalization in HFrEF, but there is less evidence for ablation benefit specific to HFpEF.[49]

Anticoagulation is imperative for stroke prevention in AF.[47] Warfarin has been the mainstay but requires monitoring and dose adjustments. Novel oral anticoagulants (NOACs) like apixaban, rivaroxaban and edoxaban are preferred alternatives to warfarin in AF given more predictable effects without need for monitoring.[47] NOACs showed similar efficacy and superior safety compared to warfarin for stroke prevention in AF. Small trials demonstrated benefit of NOACs in HFmrEF and HFrEF populations, but none focused specifically on these patient populations.[48] Careful assessment of renal function, drug interactions and side effects is crucial when using NOACs in complex HF patients with an LVEF >40%.[50]

Selecting optimal HF therapies in HFmrEF and HFpEF patients with AF requires weighing risks and benefits. Drugs like digoxin and non-dihydropyridine calcium channel blockers that slow AV nodal conduction could promote ventricular rate control but may worsen HF symptoms.[48] Beta blockers reduce mortality in HFrEF but demonstrated a neutral effect in patients with LVEF >40% and can potentially exacerbate bradycardia in AF.[51] Therefore, the optimal treatment of HFmrEF and HFpEF patients with AF requires integrated rate and rhythm control strategies along with appropriate anticoagulation.[48] Further studies are needed to determine the safety and efficacy of ablation techniques, novel anticoagulants, and HF pharmacotherapies in this complex patient population. A precision medicine approach tailored to individual AF and HFmrEF and HFpEF subtypes may help optimize outcomes in the future. Improving evidence-based treatment of AF in the setting of HF with LVEF >40% is an important priority given the rising prevalence of both conditions.

TOWARDS A PRECISION MEDICINE IN HF: UPCOMING RESEARCH

ESC guidelines[2] recommended imaging tests in order to detect reversible/treatable causes of HF and to exclude the diagnosis of coronary artery disease. As for echocardiography, details about the quality standards to determine the presence of reduced left ventricular systolic function are addressed by the European Association of Cardiovascular Imaging position paper.[52] Briefly, LVEF remains a landmark functional classification marker for HF, to guide treatment in individual cases, although its well-known limitations. Recently, a new echocardiographic tool based on myocardial work analysis has been developed for the evaluation of LV global systolic function, to overcome EF and strain disadvantages.[53] Nevertheless, limitations of such a tool have been reported as well, especially at the individual, single-case, level.[53] There is evidence[54,55] that multi-parametric cardiovascular magnetic resonance may be helpful defining cardiac phenotypes of HF. However, further work is needed to confirm imaging peculiarities of HF phenotypes.

As for biomarkers, the ESC guidelines recommended measurement of NPs for HF diagnosis, if available.[2] A plasma concentration of B-type natriuretic peptide <35 pg/mL, NT-proBNP <125 pg/ mL, or mid-regional pro-atrial natriuretic peptide <40 pmol/L68 make a diagnosis of HF unlikely. Practical algorithms are deeply discussed in a recent ESC consensus document on biomarkers.[56] Upcoming studies are warranted to provide data on the evidence-based use of biomarkers in HF phenotypes.

Also, further phenotyping of HFmrEF and HFpEF patients using advanced imaging, biomarkers, and genomics is needed to better characterize comorbidity-driven subtypes.[20]

Given the importance of comorbidities, guidelines recommend lifestyle interventions, weight loss, and optimizing treatment of all coexisting conditions.[2] However, clinical trials in HFmrEF and HFpEF using drugs effective in HFrEF have led to mixed results, likely because they fail to address the specific comorbid drivers. Therapies targeting HFmrEF and HFpEF phenotypes defined by underlying comorbidity patterns may improve outcomes compared to blanket approaches. For example, in obesity-predominant HFpEF, weight loss with semaglutide and drugs improving myocardial energetics are warranted. In hypertension or diabetes-driven HFpEF, agents reducing fibrosis like spironolactone or targeting the renin-angiotensin-aldosterone system could help reverse remodeling.[57] Loop diuretics may provide greater relief of volume overload in HFmrEF and HFpEF patients and indapamide has the potential of reducing incident HF as demonstrated by the Hypertension in the Very Elderly Trial study.[58]

Tackling specific comorbidities provides symptomatic benefit.[59] Therefore, the heterogeneous nature of HFmrEF and HFpEF suggests that tailored therapy targeting specific comorbid disease profiles may be more successful than blanket approaches. Research into the interactions between cardiac and systemic pathologies will provide insights into disease mechanisms.[5] Precision medicine strategies selected based on individualized

assessment of relative contribution from each comorbidity hold promise for improving outcomes in this common syndrome that currently lacks effective treatments.

CONCLUSIONS

The marked heterogeneity underlying HFmrEF and HFpEFand HFmrEF pathophysiology mandates transitioning from oversimplified categorization based on EF alone to precision medicine approaches. HF with LVEF >40% requires deep phenotyping based on predisposing conditions to enable matching specific therapies to distinct disease mechanisms. Ongoing and future HFmrEF and HFpEFtrials are incorporating precision strategies including pre-specified subgroup analysis of treatment effects in particular phenotypes, selective enrollment based on HFmrEF and HFpEFsubtypes, and biomarker profiling for treatment selection and monitoring. Harnessing multidimensional data with machine learning also holds promise to optimize individualized HF therapy.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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