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CONSENSUS STATEMENT

Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientific statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology, and the European Society of Hypertension

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Heart failure with preserved ejection fraction (HFpEF) represents a highly heterogeneous clinical syndrome affected in its development and progression by many comorbidities. The left ventricular diastolic dysfunction may be a manifestation of various combinations of cardiovascular, metabolic, pulmonary, renal, and geriatric conditions. Thus, in addition to treatment with sodium–glucose cotransporter 2 inhibitors in all patients, the most effective method of improving clinical outcomes may be therapy tailored to each patient's clinical profile. To better outline a phenotype-based approach for the treatment of HFpEF, in this joint position paper, the Heart Failure Association of the European Society of Cardiology, the European Heart Rhythm Association and the European Hypertension Society, have developed an algorithm to identify the most common HFpEF phenotypes and identify the evidence-based treatment strategy for each, while taking into account the complexities of multiple comorbidities and polypharmacy.

Keywords Heart failure • Heart failure with preserved ejection fraction • Phenotype

Introduction

Globally, more than 60 million people suffer from heart failure, and the prevalence is expected to continue rising.[1,2] Patients with heart failure have traditionally been classified into two groups based on their left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The exact LVEF cut-off used to demarcate HFrEF and HFpEF has varied but is usually between 40% and 50%. More recently, heart failure with mildly reduced ejection fraction (HFmrEF) has been introduced as a 'gray zone' with left ventricular function between 41% and 49%, and HFpEF has been defined as heart failure with a LVEF ≥50%. Epidemiological data show that the prevalence of HFpEF relative to HFrEF is increasing at a rate of 1% per year.[3]

Heart failure with preserved ejection fraction is characterized by myocardial dysfunction that results in disproportionate increases in left-sided filling pressures to maintain cardiac output. In the last three decades, several therapeutic options have emerged for the management of HFrEF, which have resulted in improved health-related quality of life and clinical outcomes.[4] In contrast, development of effective drugs for the treatment of HFpEF has been notoriously challenging, with phase III clinical trials of several drugs failing to convincingly demonstrate benefit.[5] Sodium–glucose cotransporter 2 (SGLT2) inhibitors are the only drugs that have demonstrated an improvement in clinical outcomes in an overall population with HFmrEF and HFpEF. In recent trials, the SGLT2 inhibitors empagliflozin and dapagliflozin were found to significantly reduce the composite of hospitalization for heart failure (HHF) or cardiovascular (CV) death, compared with placebo.[6,7]

Amongst the issues that may explain the slow therapeutic progress in HFpEF, one appears to be particularly important, that is, that HFpEF represents a highly heterogeneous clinical syndrome affected in its development and progression by many comorbidities. In a patient with HFpEF, the myocardial dysfunction may be a manifestation of various combinations of CV, metabolic, pulmonary, renal, and geriatric conditions that are estimated to be present in 5–80% of all HFpEF patients (*Figure 1*). In addition to treatment with SGLT2 inhibitors in all patients, the most effective method of improving clinical outcomes in HFpEF may be therapy tailored to each patient's clinical profile.

To better outline a phenotype-based approach for the treatment of HFpEF, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has developed an algorithm to identify the most common HFpEF phenotypes and identify an evidence-based treatment strategy for each, while taking into account the complexities of multiple comorbidities and polypharmacy.

Treatment considerations for all patients with heart failure with preserved ejection fraction

Sodium–glucose cotransporter 2 inhibitors

To date, SGLT2 inhibitors are the only pharmacotherapy that has convincingly demonstrated an improvement in clinical outcomes in patients with an LVEF >40%. The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial evaluated the efficacy of sotagliflozin (a combined SGLT2/SGLT1 inhibitor) versus placebo in 1222 patients who were recently hospitalized for worsening heart failure and had concomitant type 2 diabetes.[8] Sotagliflozin demonstrated a significant reduction in total HHF/CV death, and upon subgroup analysis, the effect was consistent in both HFrEF and HFpEF. However, the results of this trial should be viewed with caution as it was underpowered to study patients with HFpEF and only included patients with diabetes.

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial randomized 5988 patients with chronic HFpEF (LVEF >40%) to either the SGLT2 inhibitor empagliflozin

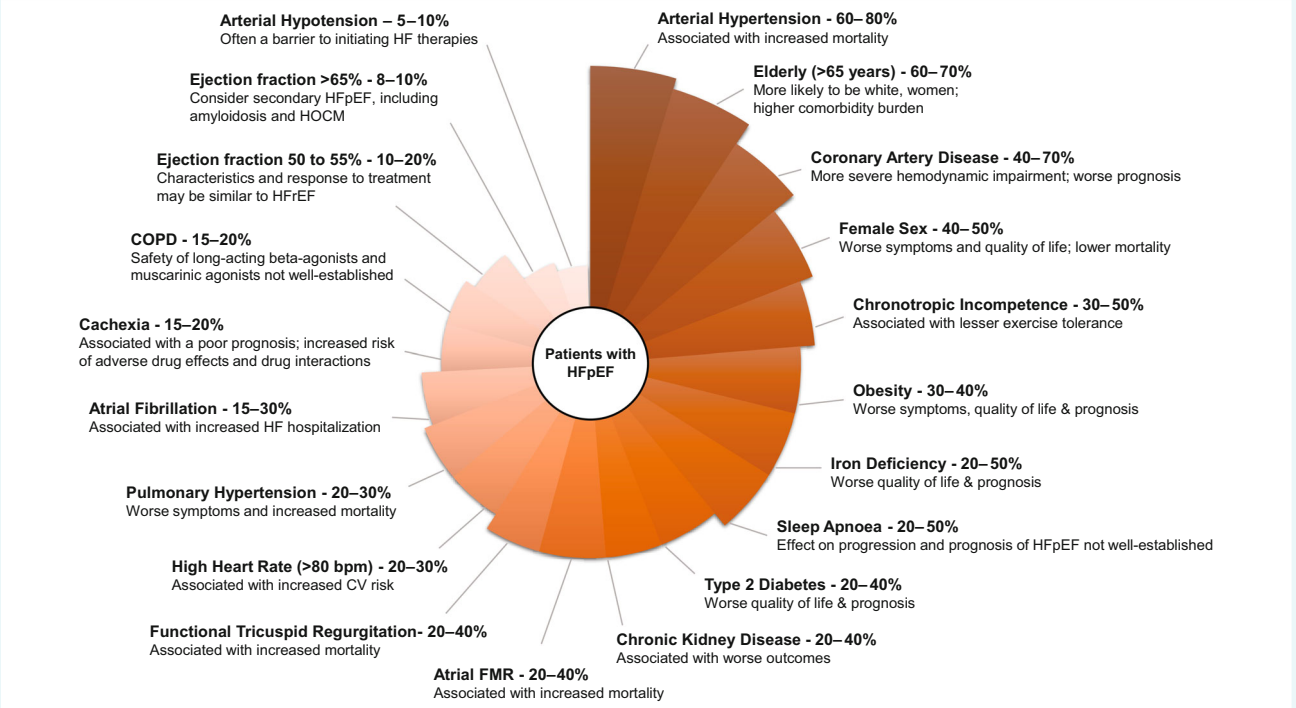

Figure 1 The estimated prevalence of important phenotypes of primary heart failure with preserved ejection fraction (HFpEF). COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FMR, functional mitral regurgitation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy.

or placebo. Empagliflozin, when compared with placebo, demonstrated a 21% reduction in the composite endpoint of first HHF/CV death.[6] This finding was primarily driven by a reduction in first HHF events. Empagliflozin also reduced the incidence of total HHF, slowed the decline of estimated glomerular filtration rate (eGFR), and improved health-related quality of life. These findings were consistent in the group of patients with LVEF >50%, in both males and females, and in patients with and without type 2 diabetes.[9] The DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial enrolled 6263 patients with chronic or recently worsening HFpEF and demonstrated a significant reduction in first HHF/CV death with the SGLT2 inhibitor when compared with placebo.[10] The study demonstrated a significant reduction of the primary composite endpoint of HHF and CV death with no effect attenuation throughout the LVEF range. Dapagliflozin also significantly improved quality of life measures. A meta-analysis of the DELIVER and EMPEROR-Preserved trials confirmed the benefits demonstrated by the two trials reinforcing the significant and consistent benefit of this class of drugs in HFpEF.[11]

Adverse effects associated with SGLT2 inhibitors are infrequent and include urinary and genital tract infections. In extremely rare cases, SGLT2 inhibitors may cause euglycaemic ketoacidosis – thus, SGLT2 inhibitors should be avoided in HFpEF patients with precipitating factors of euglycaemic ketoacidosis such as acute gastroenteritis or insulin pump failure or a history of ketoacidosis. Starting SGLT2 inhibitors should generally be avoided in HFpEF patients with an eGFR <20 ml/min/1.73 m^2. Overall, SGLT2 inhibitors are a safe and effective treatment for HFpEF and are advised for all patients who do not have contraindications.

Mineralocorticoid receptor antagonists

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial enrolled 3445 patients with HFpEF (LVEF >45%) and randomized them to the mineralocorticoid receptor antagonist (MRA) spironolactone or placebo.[12] Spironolactone did not reduce the primary endpoint (composite of CV death, aborted cardiac arrest or HHF) or CV death; however, it showed a significant reduction in the incidence of first HHF. In a post-hoc analysis by region, spironolactone was found to significantly reduce the primary outcome in the Americas, but not in Russia/Georgia.[13] The difference in effect sizes between the two regions was unusually large, and analysis of potassium, creatinine, and spironolactone metabolites suggested poor compliance to trial treatment in patients in Russia/Georgia.[13,14] However, findings from post-hoc analyses of negative trials should not guide evidence-based therapy. Therefore, the efficacy of MRAs in HFpEF remains in doubt. Two ongoing trials, SPIRIT-HF (Spironolactone In The Treatment of Heart Failure) and SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction) will further delineate the role of MRAs in HFpEF.[15,16] Currently, the ESC guidelines suggest that MRAs may be considered in patients with HFpEF, after weighing

the possible benefits against the risk of hyperkalaemia and side effects.[17]

Exercise

Reduced exercise tolerance, associated with a reduced quality of life, is the primary symptom of HFpEF. Left ventricular diastolic dysfunction plays a pivotal role in the pathophysiology of HFpEF and it is also an important contributor to exercise intolerance in these patients. Exercise training has been shown to be effective in improving maximal exercise capacity, assessed as peak oxygen consumption, in clinically stable patients with HFpEF. However, the trials performed to date have only involved smaller sample sizes (≤100 patients) and limited exercise intervention periods (≤24 weeks). Results of two subsequent meta-analyses have confirmed the beneficial effects of exercise training on cardiorespiratory fitness and quality of life in HFpEF.[18,19] It is not completely known through what mechanism exercise training improves exercise tolerance in HFpEF. Available data suggest that, similarly to what has been shown in patients with reduced LVEF, exercise training benefits HFpEF through peripheral mechanisms.

Peripheral adaptations in arterial and skeletal muscle function have been identified as the primary contributors to improvement in fitness after exercise training.[20] Data on central haemodynamic effects of exercise training in HFpEF are conflicting. In particular, it is not clear whether exercise training improves left ventricular diastolic dysfunction. While improvement of diastolic function has been described in some studies,[21] in the meta-analysis of Pandey *et al.*,[18] no changes in left ventricular systolic or diastolic function were observed. The same results were obtained by another meta-analysis in which the ratio of early diastolic mitral inflow to annular velocities and LVEF were unchanged after exercise training compared to controls.[22] Another point that needs to be clarified is which exercise modality is the most suitable and effective for patients with HFpEF. Recently, Mueller et al.[23] demonstrated that high-intensity interval training was no more effective than moderate-continuous training in improving exercise tolerance in HFpEF. Moreover, there are no data on concurrent (aerobic and resistance) exercise training in HFpEF. Overall, exercise appears to improve cardiorespiratory fitness and quality of life in patients with HFpEF, and according to the ESC guidelines regular exercise may be recommended in all patients with heart failure to the extent to which it can be tolerated.[17]

Important patient phenotypes in primary heart failure with preserved ejection fraction

Primary HFpEF refers to a condition in which a primary impairment in myocardial relaxation or compliance exists. It is typically not due to clearly identifiable specific conditions, but usually developing in a milieu of various risk factors. Thus, primary HFpEF is a very heterogeneous syndrome with multiple pathogenetic mechanisms that may span from arrhythmia to hypertension (*Table 1*). The management of patients with different clinical profiles may differ substantially as treatments that may benefit one phenotype may not be appropriate for another. To this end, it is important to profile patient phenotypes for a tailored therapeutic approach.

Table 1 List of primary and secondary heart failure with preserved ejection fraction phenotypes under consideration in this review

Primary HFpEF
Age
Sex
Type 2 diabetes mellitus
Obesity
Sleep apnoea
Arterial hypertension
Arterial hypotension
Pulmonary hypertension
Chronic obstructive pulmonary disease
Iron deficiency
Coronary artery disease
Atrial fibrillation
High heart rate
Chronotropic incompetence
Atrial functional mitral regurgitation
Functional tricuspid regurgitation
Cachexia and sarcopenia
Very high ejection fraction (>65%/>70%)
LVEF between 50% and 55%
HFpEF in patients with cancer
Secondary HFpEF
Restrictive cardiomyopathies
Hypertrophic cardiomyopathy
Constrictive pericarditis
Valvular heart disease

Age

Ageing is a critical element when assessing the phenotypes of patients with HFpEF. Although HFpEF is generally considered a disease of the elderly, in several studies a significant proportion of patients were younger than 65 years of age, accounting for 40% of all cases.[24] Two 'true' HFpEF phenotypes may be considered according to age. The younger patients are characterized by a high prevalence of male gender, diabetes and obesity, a predominance of Black and Asian race, a lower comorbidity burden, and worse quality of life compared with their older counterparts.[25] The older patients are more often white women with a higher comorbidity burden, who tend to present with a higher burden of arterial hypertension, atrial fibrillation, and chronic kidney dysfunction. Younger patients with HFpEF are more likely to die from CV causes, with sudden death being one of the most common causes of death, a finding with possible clinical and therapeutic implications.[24] Although overall mortality rates are higher in elderly patients, non-CV death is the more prevalent cause of death, likely due to a greater number of comorbidities. While no specific treatment modifications for HFpEF are required based on age, older patients with multiple comorbidities are often on polypharmacy and it is

advisable to carefully monitor them for adverse effects such as hyperkalaemia and volume depletion.[24] Nevertheless, it needs to be pointed out that the effect of SGLT2 inhibitors is similar across the age spectrum in HFpEF – not only on clinical outcomes, but also quality of life and preservation of kidney function. Moreover, increasing age was not associated with an increase in the rate of adverse events with SGLT2 inhibitors.[26]

Sex

Women are more prone to developing HFpEF, rather than HFrEF, as compared to men.[27] Several factors are likely responsible for this, including sex differences in genetics and epigenetics, oestrogen milieu, anthropometry, clustering of CV risk factors, and the burden of inflammation. For example, mitochondria express oestrogen receptors, and oestrogen promotes mitochondrial biogenesis, respiratory activity and signalling pathways for protection against oxidative stress. Women, therefore, demonstrate higher resistance to ischaemia/reperfusion injury (a common precursor to HFrEF).[27] Moreover, the following phenotypic features of the myocardium itself and of the CV system predispose women to HFpEF compared to men: smaller ventricular chambers and smaller vasculature; increased ventricular wall thickness and concentric myocardial remodelling; lower diastolic compliance and poorer diastolic reserve; increased myocardial blood flow and higher myocardial oxygen consumption with prominent lipid metabolism within the myocardium; greater arterial stiffness and pulse pressure leading to greater pulsatile afterload; and impaired pulmonary vascular reactivity with pulmonary vascular dysfunction and remodelling.[28]

Additionally, specific comorbidities and/or clinical conditions that are either highly prevalent or exclusively present in women predispose to the development of HFpEF, namely: metabolic risk factors (obesity, hypertension, diabetes, dyslipidaemia), iron deficiency, autoimmune diseases (related to increased inflammation and predisposing to pulmonary hypertension), preeclampsia, and breast cancer and its treatment.[28] Most of these factors are amplified by sex hormone deficiency after menopause.

It has been demonstrated that women with HFpEF have more severe heart failure symptoms and a poorer quality of life as compared to men with HFpEF, even when adjusted for confounders.[29] On the other hand, in multivariate analyses and in registry studies, women as compared to men with HFpEF have lower all-cause, CV and non-CV mortality.[30]

In the EMPEROR-Preserved and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials, the benefit of empagliflozin on clinical outcomes was similar in both men and women, regardless of LVEF.[31,32] In contrast, post-hoc analyses of trials with other drugs have raised the possibility that sex may influence the response to treatment. In the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial, sacubitril/valsartan did not reduce the primary outcome (HHF/CV death); however, a significant treatment-by-sex interaction was seen, with women showing a greater decrease in the primary outcome than men with sacubitril/valsartan.[33] These data, however, come from a post-hoc analysis of a negative trial and the suggestion that sacubitril/valsartan may be effective in women should be tested in an ad-hoc study.

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a common comorbidity in patients with HFpEF.[34] In clinical trials of patients with HFpEF, the prevalence of known T2DM ranged between ~27% and ~43%,[12,35–37] whilst the prevalence of newly diagnosed T2DM was ~20%.[38] Observational, registry-based data suggest wide regional and global heterogeneity in the frequency of T2DM in HFpEF, with a prevalence of 29% in Europe,[39] 45% in the United States,[40] and 44–57% in the Asia-Pacific region.[41,42] Potential reasons for the observed heterogeneity include differences in demographic factors, socio-economic settings, lifestyle and dietary habits, and the prevalence of risk factors, but the more precise explanation awaits further studies. Over the past few decades, a trend towards an increase in the prevalence of comorbid T2DM has been observed, most significantly among patients with new-onset HFpEF.[40] T2DM increases the risk of HF hospitalization, all-cause and CV mortality independently of other clinical characteristics in patients with HFpEF.[12,35–37]

Despite intensive research, current understanding of the mechanisms involved in the development of HFpEF in T2DM remains limited.[43] Several interrelated mechanisms have been postulated to explain this association. Firstly, hyperglycaemia in the setting of T2DM results in excessive production of advanced glycated end-products, which have been implicated in increased interstitial fibrosis and stiffness of the myocardium and the vasculature.[44,45] Furthermore, there is an apparent shift away from glucose utilization towards increased use of free fatty acids for myocardial energy production.[46,47] This shift is driven by hyperinsulinaemia and insulin resistance, which hamper the uptake of glucose into the myocytes whilst flooding the heart with free fatty acids, triglycerides, and non-esterified fatty acids. Since the uptake of free fatty acids is not insulin-dependent, they become the preferred metabolic fuel at a price of increased oxygen consumption, greater production of free oxygen species and higher oxidative stress. Furthermore, non-esterified fatty acids, which are not the substrate for beta-oxidation, accumulate in the myocytes, resulting in a perturbation in several cellular signalling processes, which is defined as lipotoxicity.[48,49] In addition, free fatty acid oxidation is less energy-efficient than glucose oxidation and leads to a reduced production of high-energy phosphate that impairs the sarcoplasmic endoplasmic reticulum calcium pump and ultimately cardiac relaxation.[50] Consequently, there is an increased production of proinflammatory and profibrotic cytokines, excessive collagen deposition in the extracellular matrix, and myocyte apoptosis. Impaired insulin signalling plays a key part in promoting a switch between the two isoforms of titin protein, and favours the 'stiffer' isoform, which together with the maladaptive changes in cardiac metabolism lead to impaired relaxation and increased myocardial stiffness.[51] Moreover, hyperinsulinaemia, inflammation, and oxidative stress promote microvascular and systemic endothelial dysfunction.[52] Reduced nitric oxide bioavailability in the myocardium results in titin hypo-phosphorylation and activation

of signalling pathways responsible for cardiomyocyte hypertrophy. Collectively, these pathological changes promote the development of concentric left ventricular remodelling and diastolic dysfunction, which are the hallmarks of HFpEF in patients with T2DM. In addition, hyperglycaemia stimulates upregulation of the SGLT2 in the kidney, leading to increased proximal tubular sodium reabsorption, intravascular volume expansion (and congestion), and decreased diuretic response.[53]

An important step forward in preventing heart failure (including HFpEF) in T2DM has occurred with the development of SGLT2 inhibitors. Several, placebo-controlled CV outcome trials of patients with T2DM and known atherosclerotic CV disease or with multiple risk factors, demonstrated that SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) provide a consistent reduction in HHF, regardless of a previous history of heart failure or the presence of atherosclerotic CV disease.[54–57] SGLT2 inhibitors have also proven beneficial for the prevention of HHF in high-risk patients with diabetic nephropathy,[58] as well as in patients with chronic kidney disease (with and without T2DM).[59,60] Moreover, a recent meta-analysis of six CV and kidney outcome trials in patients with T2DM confirmed a significant 22% risk reduction in CV mortality or HHF with SGLT2 inhibitors, as well as a significant reduction in CV events and kidney outcomes.[61] Therefore, current guidelines and expert consensus documents recommend the use of SGLT2 inhibitors in individuals with T2DM to prevent HHF, major CV events, end-stage renal dysfunction, and CV death.[17,62] SGLT2 inhibitors are also an obvious choice for the treatment of patients with co-existing HFpEF and T2DM, as they have been shown to improve outcomes in trials of both T2DM as well as of HFpEF.

Obesity

Obesity is a major risk factor for HFpEF, and body mass index (BMI) adequately predicts development of HFpEF.[20] Moreover, cardiometabolic profiles and CV disease risk are worse for those with larger waist:hip ratio than for individuals with smaller waist circumferences for the same BMI.[63] Furthermore, left ventricular longitudinal strain and e' velocity have been observed to worsen with an increase in waist:hip ratio.[63] The follwing cardiac changes have been observed in patinets with obesity and HFpEF: raised pulmonary vascular resistance, a greater mean pulmonary arterial pressure, and indications of right ventricular dysfunction with a raised right atrial to pulmonary capillary wedge pressure ratio as well as a flattening of the left ventricular septum.[21,64] On average, patients with HFpEF who are obese are younger than those who are not.[65] Obesity in patients with HFpEF also leads to increased peripheral oedema, orthopnoea, worse New York Heart Association (NYHA) scores, poorer quality of life, and dramatically reduced 6-min walk distance.[65] Therefore, weight loss should be a specific target in patients with HFpEF.

Lifestyle modification, diet and exercise should be recommended in all heart failure patients.[17] In addition, pharmacotherapy is an option. Several therapeutic interventions in obese patients have failed or have shown a negative safety profile increasing CV death.[66] More recently, the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide (2.4 mg subcutaneously, once weekly) and the combined GLP-1/glucose-dependent insulinotropic polypeptide agonist tirzepatide (5–15 mg subcutaneously, once weekly) have demonstrated excellent weight-loss efficacy in patients with obesity, with or without diabetes.[67,68] It appears advisable to considered these therapies for the treatment of obesity in patients with HFpEF, as is done for obesity in general. Weight loss following bariatric surgery is also associated with reduced left ventricular mass and mass–volume ratio and improved diastolic function. However, currently surgery is not specifically recommended for heart failure patients as clinical trial results are lacking.

Sleep apnoea

Sleep apnoea is very frequent in heart failure. Common risk factors for both obstructive sleep apnoea and heart failure (such as smoking, obesity, excess alcohol intake and male sex) have been known for many years, but more recently it has been appreciated that heart failure itself is amongst the strongest risk factors for central sleep apnoea.[69] As a result, any patient profiling of HFpEF patients should consider this major comorbidity, which is itself associated with poor quality of life and reduced survival. Other than with some experimental agents, sleep apnoea is not typically treated with pharmacotherapy. Most current evidence on the safety and efficacy of conventional therapy for sleep apnoea – positive pressure airway mask therapy – is available only in patients with HFrEF.

The SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure) trial enrolled patients with HFrEF and sleep apnoea, and randomized them to either adaptive servo-ventilation in addition to guideline-directed medical therapy (GDMT) or GDMT alone.[70] This trial demonstrated an increase in the risk of all-cause and CV death in patients randomized to adaptive servo-ventilation. In contrast, the recently completed ADVENT-HF (Effect of Adaptive Servo Ventilation [ASV] on Survival and Hospital Admissions in Heart Failure) trial showed that adaptive servo-ventilation successfully controlled both central and obstructive sleep apnoea and did not influence the risk of all-cause mortality.[71] Thus, studies in patients with HFrEF have not yielded a clear answer on whether or not positive pressure airway mask therapy should be used for sleep apnoea. Currently, there is no large-scale trial evaluating the effects of positive pressure airway mask therapy in HFpEF. In a randomized controlled trial of 36 patients with HFpEF, adaptive servo-ventilation, when compared with usual care, did significantly improve diastolic function (as evaluated by echocardiography), and also reduced cardio-ankle vascular index and brain natriuretic peptide (BNP). In this small trial, patients in the adaptive servo-ventilation group had a significantly fewer CV events at 6 months.[72]

Arterial hypertension

Amongst the several CV risk factors associated with HFpEF, arterial hypertension is the most prevalent.[73–75] It is unclear whether arterial hypertension represents a risk factor or a

condition for the development of HFpEF, given that the underlying mechanisms of arterial hypertension and HFpEF may overlap. Renin–angiotensin–aldosterone and sympathetic nervous system over-activation and increased oxidative stress are causative factors in both conditions.[76] However, the most important mechanisms that link arterial hypertension and HFpEF are left ventricular hypertrophy (LVH), myocardial fibrosis, and diastolic dysfunction. These cardiac changes are likely secondary to frequent vascular alterations (increased arterial stiffness, microvascular alterations, and atherosclerosis). For instance, aortic stiffness is a key determinant of ventricular–arterial interaction and may be responsible for an increase in wave reflections, central blood pressure and late systolic load, thus participating in worsening of diastolic dysfunction. Therefore, it is plausible that the changes in cardiac structure and function typical of arterial hypertension may, in susceptible subjects, be responsible for the development of HFpEF in hypertensive patients. Furthermore, arterial hypertension frequently clusters with other risk factors for HFpEF, such as obesity and diabetes mellitus.

Registries and cohort studies have demonstrated that arterial hypertension is more prevalent in patients with HFmrEF and HFpEF than in those with HFrEF. The Swedish HF registry study that included 42 061 patients with heart failure (56% HFrEF, 44% HFmrEF or HFpEF) found that about 60–70% of patients were hypertensive (i.e. 56% in HFrEF, 64% in HFmrEF and 72% in HFpEF)[77] and also showed a relation between pulse pressure and mortality.[78] The association was U-shaped in patients with HFmrEF and HFpEF, but more linear in HFrEF, where only low pulse pressure was associated with increased mortality. It has been reported that serum uric acid may be related to the incidence of HFpEF and CV events in patients with arterial hypertension,[79] supporting the importance of metabolic abnormalities in the development of HFpEF in hypertensive patients.

Clinical trials support treatment of hypertension to prevent heart failure. In the HYVET (Hypertension in the Very Elderly Trial) study, the thiazide-like diuretic indapamide demonstrated a significant 64% reduction in the occurrence of heart failure in patients with arterial hypertension.[80] A meta-analysis of the comparison between indapamide and chlorthalidone demonstrated a greater reduction of heart failure with indapamide.[81] A systematic review and meta-analysis of 123 large-scale blood pressure-lowering trials published between 1966 and 2015 demonstrated that blood pressure reduction was associated with a 28% reduction in heart failure, thereby supporting the causative role of arterial hypertension in the development of HFpEF and the need for strict blood pressure control.[82] Similarly, another comprehensive meta-analysis by Thomopoulos and colleagues demonstrated a 43% reduction in the risk of heart failure – an effect which was related to improvements in systolic blood pressure (SBP), diastolic blood pressure, and pulse pressure.[83]

On the other hand, clinical trials targeting hypertension with neuro-hormonal inhibitors (targeting the renin–angiotensin–aldosterone system [RAAS] and sympathetic nervous system) in patients with existing HFpEF have been mostly negative. Prospective, randomized, placebo-controlled clinical trials using candesartan, perindopril, irbesartan, and spironolactone in patients with HFpEF failed to demonstrate increased efficacy of RAAS inhibition.[12,35,84,85] More recently, although sacubitril/valsartan showed a trend towards improvement in HHF or CV death in the PARAGON-HF trial, this failed to reach statistical significance.[86]

There have been no trials testing different blood pressure targets in the HFpEF population. Based on the findings of the SPRINT (Systolic Blood Pressure Intervention Trial) trial, the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines recommend an SBP target of <130 mmHg in HFpEF.[87] An SBP target of <130 mmHg was also found to be beneficial in secondary analyses of trials such as PARAGON-HF and TOPCAT.[88,89] The results of the recent OPTIMIZE-HF registry suggest that a SBP <120 mmHg may be associated with worse outcomes in older patients with HFpEF.[90] SGLT2 inhibition is beneficial for all HFpEF, and it could also have some therapeutic effect on hypertension. Other traditional antihypertensive drug classes, including angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), beta-blockers, and MRA, have been demonstrated to improve symptoms, exercise capacity, left ventricular remodelling, and reduction in HHF in HFpEF, though no mortality benefit has been shown. The treatment of arterial hypertension in HFpEF may follow the core treatment algorithm for drug therapy of the 2018 ESC/European Society of Hypertension (ESH) guidelines, possibly with an earlier use of MRA and/or replacement of ACEI/ARB with angiotensin receptor–neprilysin inhibitor (ARNI), due to a signal of possible clinical benefit in the TOPCAT and PARAGON-HF trials, especially in patients with LVEF <60%.[91] Moreover, comorbidities should be considered when selecting drugs. For example, ACEI/ARB and SGLT2 inhibitors for patients with diabetes and proteinuria, and beta-blockers for patients with atrial fibrillation. Finally, we should also emphasize the importance of lifestyle modifications, including moderate sodium restriction diets, weight control for obese patients, and regular moderate physical activity.

Arterial hypotension

Although hypertension is one of the most prevalent triggers of diastolic dysfunction,[75,92,93] low blood pressure might be a barrier to implement therapies for heart failure. Patients with low SBP in both HFrEF and HFpEF have a higher risk of death and hospitalization representing a U-shaped curve for the association of risk and blood pressure.[94,95] Although this curve might not necessarily reflect causality,[95] low blood pressure might represent a treatment initiation barrier among physicians for treatments such as SGLT2 inhibitors. Importantly, the effect of SLGT2 inhibitors on CV hospitalization and CV death but also preservation of kidney function remains stable across the entire blood pressure range studied in the pivotal studies.[26,95] These findings are important as HFpEF is sometimes termed ‘decapitated hypertension’, which means that there is a decline of blood pressure over time in HFpEF.[96]

Pulmonary hypertension

The prevalence of pulmonary hypertension in HFpEF is unclear due to the non-systematic assessment by right heart catheterization. In

the Olmsted County study, it was estimated to be 83%, whereas it was 31% in PARAGON-HF.[97,98] Patients with HFpEF who also have pulmonary hypertension are more likely to be older, hypertensive, have a higher E/e' ratio, left atrial volume, and show a worse prognosis.[97] Pulmonary hypertension in HFpEF is, in most cases, isolated post-capillary and reflects HFpEF severity. However, identifying patients with an additional or isolated pre-capillary involvement by right heart catheterization is important due to the therapeutic implications. Indeed, patients with post-capillary pulmonary hypertension have not been shown to respond to pulmonary vasodilators, although those with pre-capillary hypertension do.[99] Prevalence of combined pre- and post-capillary pulmonary hypertension in HFpEF has been shown to vary across different studies up to 55%,[100] with a few randomized studies showing potential benefits with phosphodiesterase inhibitors in terms of improved in haemodynamics, right ventricular function and exercise capacity.[101,102] However, these are short-term trials and long-term efficacy is not well-established. Due to lack of evidence, current guidelines do not specify any recommendation in patients with HFpEF and combined pre- and post-capillary pulmonary hypertension.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is associated with a two-fold increased risk of HFpEF.[39,103] The prevalence of COPD is around 14% in large population studies of patients with HFpEF.[41,104] Systemic inflammation, endothelial dysfunction, pulmonary hypertension due to vasoconstriction, remodelling of pulmonary arteries, and impaired left ventricular diastolic filling linked with airway obstruction and lung hyperinflation might be some of the mechanisms linking COPD to HFpEF. In HFpEF, COPD is associated with worse quality of life and with higher mortality and risk of HHF.[105] COPD versus non-COPD patients hospitalized for HFpEF are more likely to be males, have a history of hospitalizations, be smokers, and use diuretics.[104] They are also more likely to report more concentric left ventricular geometry, greater left ventricular mass and fibrosis, and greater thoracic aortic stiffness.[106]

Chronic obstructive pulmonary disease might mimic HFpEF symptoms (e.g. dyspnoea, exercise limitation) and signs and therefore increase the chance of misdiagnosing HFpEF. Consistently, in the TOPCAT trial, patients with markers of COPD were more likely to cluster with those with normal left ventricular geometry, low arterial stiffness, low natriuretic peptides, lower event rates, and those enrolled in Russia/Georgia, leading to the question of a true diagnosis of HFpEF in this specific subpopulation.[107] Some specific HFpEF phenotypes might require use of beta-blockers, for example, patients with atrial fibrillation for rate control, which are chronically underused in patients with COPD. Use of cardioselective beta-blockers has been shown to be safe in patients with COPD and CV disease, and might even reduce COPD exacerbations.[108] Beta-adrenergic agonists, such as inhaled albuterol, which are used for COPD, have been shown to have haemodynamic effects, such as improving pulmonary vascular reserve without worsening left heart congestion in patients with HFpEF.[109] However, the long-term effects of COPD treatments, including muscarinic receptor agonists and beta-adrenergic agonists, are not well-established in patients with HFpEF.

Kidney disease

About half of patients with HFpEF have chronic kidney disease (CKD). In the PARAGON-HF trial in patients with HF and an LVEF ≥45%, eGFR at baseline was <60 ml/min/1.73 m^2 in 47% of cases and <45 ml/min/1.73 m^2 in 18%.[37] In the EMPEROR-Preserved trial in patients with HFpEF and an LVEF ≥40%, 50% of cases had a baseline eGFR <60 ml/min/1.73 m^2.[6] Of interest, in the RELAX-AHF-2 (Relaxin in Acute Heart Failure) trial, the incidence of worsening renal function during HHF increased with increasing LVEF, in parallel to increasing age and comorbidity burden, including CKD, while worsening renal failure was associated with higher risk of post-discharge events in the upper three LVEF quartiles.[110]

Chronic kidney disease is associated with an increased risk of incident HFpEF.[111] In terms of pathophysiology, CKD is associated with hypertension and is followed by metabolic abnormalities, activation of a systemic inflammatory reaction and endothelial dysfunction that are believed to hold a key role in the pathogenesis of HFpEF, through endothelium and cardiomyocyte cross-talking and activation of myocardial stiffening, hypertrophy, and interstitial fibrosis.[112] Accordingly, CKD seems to be associated with worse myocardial remodelling and/or function in HFpEF. In the PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) trial, renal dysfunction, defined as an eGFR >30 and <60 ml/min/1.73 m^2 and/or albuminuria, was associated with more frequent LVH and abnormal geometry (concentric hypertrophy, eccentric hypertrophy or concentric remodelling), lower mid-wall fractional shortening and higher N-terminal proBNP (NT-proBNP) levels.[113] Similarly, in an observational study in HFpEF, CKD was associated with worse left ventricular longitudinal strain, right ventricular free wall strain and left atrial reservoir strain.[114] On the other hand, the haemodynamic derangement induced by HFpEF, with increased filling pressures, pulmonary hypertension and peripheral congestion and the ensuing neurohormonal activation may impair renal function and contribute to the development of kidney disease. CKD is an independent predictor of adverse outcomes in HFpEF. The risk of mortality or HF hospitalization increases with decreasing eGFR, as shown in the TOPCAT trial,[115] as well as with worsening CKD stage.[114]

Traditional heart failure drugs may have an adverse effect on renal function in patients with HFpEF. In a meta-analysis of eight studies with a total of 28 961 patients with HFrEF or HFpEF, RAAS inhibitors were associated with increased risk of worsening renal failure in both HFrEF and HFpEF. Moreover, RAAS-related worsening renal failure had a greater impact on adverse outcomes, including mortality, in patients with HFpEF than in those with HFrEF.[116] Spironolactone also increased the risk of worsening renal failure, defined as a doubling of serum creatine concentration, in the TOPCAT trial.[117] In contrast, novel heart failure therapies seem to have a favourable effect on renal function. Empagliflozin reduced the rate of eGFR decline in the EMPEROR-Preserved trial.[6] Similarly, sacubitril/valsartan attenuated the eGFR decline

and reduced kidney events compared with valsartan in the PARAGON-HF trial.[118] In patients at risk for heart failure (stage A and B) with CKD and diabetes, the selective, non-steroidal MRA finerenone has been shown to improve CV outcomes, including HHF, in patients with or without a history of heart failure (mostly HFpEF).[119,120] The ongoing FINEARTS-HF (Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity & Mortality in Participants With Heart Failure and Left Ventricular Ejection Fraction Greater or Equal to 40%) trial (NCT04435626) is studying the effect of finerenone on HHF/CV death in patients with HFpEF and eGFR $\geq$25 ml/min/1.73 m^2.

Iron deficiency

Iron deficiency is observed in 50–75% of patients with HFpEF.[121,122] A recent study of 4422 heart failure patients found that iron deficiency was somewhat more prevalent in HFpEF patients (75%) than in HFmrEF (65%) or HFrEF patients (61%).[122] In a meta-analysis iron deficiency in HFpEF was found to be associated with lower maximal oxygen consumption, more dyspnoea, reduced 6-min walking distance, and reduced health-related quality of life.[121] While some studies have suggested that iron deficiency in HFpEF can lead to worse clinical outcomes, other studies did not find an association with hospitalization or death.[121] To investigate the potential benefits of intravenous iron supplementation in HFpEF, the FAIR-HFpEF trial (NCT03074591) and the PREFER-HF trial (NCT03833336) are both currently running and randomizing intravenous iron versus placebo in HFpEF patients with the primary endpoint being the change in exercise capacity as measured by 6-min walking test between baseline and 52 weeks or 24 weeks.

Coronary artery disease

Both obstructive epicardial coronary artery disease (CAD) and coronary microvascular dysfunction (CMD) are frequent in patients with HFpEF.[123–125] It is, therefore, difficult to state whether CAD may characterize a specific phenotype of HFpEF or be a common comorbidity and/or a mechanism of disease in most of these patients. Several factors predispose to both CAD, CMD and HFpEF, including aging, female sex, hypertension, diabetes, smoking, and chronic inflammatory diseases.[126]

The prevalence of epicardial CAD ranges from 35% to 76% in patients with HFpEF, and half of these patients may have no symptoms or history of CAD.[123,125] In a series of 376 consecutive patients hospitalized for HFpEF who underwent coronary angiography, CAD was observed in 68% of the cases.[123] Over a median follow-up of 4 years, patients with epicardial CAD were more likely to develop a deterioration of left ventricular function and had higher mortality, compared to those without. Those with CAD who underwent complete coronary revascularization had a better outcome.[123] Patients with HFpEF and epicardial obstructive CAD had reduced coronary perfusion pressure, more severe haemodynamic impairment during exercise, and increased troponin levels, suggesting that myocardial ischaemia may contribute to myocardial dysfunction and fibrosis.[127]

The prevalence of CMD in patients with HFpEF has been assessed in both retrospective and a few prospective observational studies.[124] PROMIS-HFpEF (Prevalence of Microvascular Dysfunction in HFpEF) was a prospective multicentre observational study enrolling 202 patients without epicardial CAD and fulfilling strict criteria for HFpEF, who underwent non-invasive coronary flow reserve measurement through adenosine stress transthoracic Doppler echocardiography.[124] Three quarters of subjects presented with a coronary flow reserve <2.5. The latter was associated with both systemic endothelial dysfunction and markers of heart failure severity (NT-proBNP and right ventricular dysfunction).[124]

Other prospective observational studies performed with invasive assessment of coronary flow reserve have yielded consistent findings. In a series of consecutive patients hospitalized for HFpEF, 51% of the subjects had epicardial CAD, 66% had endothelium-independent CMD (defined as abnormal coronary flow reserve and high microvascular resistance during hyperaemia) and 24% had endothelium-dependent CMD (defined as abnormal response to acetylcholine administration). CMD had a similar prevalence in those with and without epicardial CAD, with a total of 91% of patients presenting with epicardial CAD, CMD, or both.[125] These data are consistent with two previous studies showing a prevalence of CMD of 71% and 72%, respectively.[128,129] Patients with endothelium-independent CMD showed more fibrosis at cardiac magnetic resonance, worse diastolic dysfunction, and worse outcomes.[129]

Mohammed *et al.*[130] compared autopsy reports from 124 patients with an ante-mortem diagnosis of HFpEF and 104 controls without a diagnosis of heart failure or cardiac death. Patients with HFpEF had more severe epicardial CAD, heavier hearts, more severe left ventricular fibrosis, and lower microvascular density, than controls. Microvascular density was inversely related to myocardial fibrosis in both HFpEF and control subjects, suggesting a pivotal role of CMD in HFpEF pathophysiology.[130]

In conclusion, epicardial obstructive CAD and/or CMD can be shown in most patients with HFpEF. They are related to more severe haemodynamic impairment and worse prognosis. They are therefore potential therapeutic targets for patients with HFpEF as supported by results from observational studies.[131,132] However, long-term randomized studies are required to definitively determine the safety and efficacy of revascularization in this population, and in whom exactly to apply such therapy (e.g. only those with anginal symptoms).

Atrial fibrillation

There is a strong association between HFpEF and atrial fibrillation. In large HFpEF studies, the prevalence of atrial fibrillation (including paroxysmal atrial fibrillation) is up to 50%. The underlying pathophysiology is incompletely understood, but increased left and right atrial pressures, cardiomyocyte and fibroblast remodelling, atrial fibrosis, and inflammatory processes are involved in atrial myopathy in the context of HFpEF. Atrial fibrillation may negatively impact on the clinical course of HFpEF, and many HHF in HFpEF may in fact result from episodes of atrial fibrillation. Therefore, treating atrial fibrillation in HFpEF has evolved as an attractive therapeutic target in recent years. The CASTLE-AF (Catheter Ablation versus

Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial, which enrolled patients with atrial fibrillation and HFrEF, showed that catheter ablation was superior to usual therapy in reducing the composite endpoint of death from any cause or hospitalization for worsening heart failure.[133] The EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) trial compared usual care with early rhythm control (with antiarrhythmic drugs or ablation) in patients with atrial fibrillation. This trial demonstrated that early rhythm control reduced the composite primary outcome of CV death, stroke, or hospitalization for worsening of heart failure or for acute coronary syndrome – a finding which was consistent in the subgroup of patients with heart failure (any LVEF).[134] However, these trials were not dedicated to patients with HFpEF, and their findings should be extrapolated to this population with caution. The German Center for Cardiovascular Research (DZHK) has launched an international multicenter Phase III outcome study (CABA-HFpEF [Catheter Ablation for Atrial Fibrillation in HFpEF], NCT05508256) to directly address potential clinical outcome benefits of rhythm control in HFpEF.

High heart rate

Resting heart rate (RHR) is regulated by the autonomic nervous system but is also influenced by single nucleotide polymorphisms influencing RHR and exercise heart rate.[135] A high RHR is associated with adverse outcomes in many CV diseases but also non-CV diseases, including cancer, pulmonary disease, and multiorgan dysfunction syndromes.[136–140] In patients with reduced ejection fraction, RHR predicts prognosis and is a marker of risk,[137] in particular in combination with low blood pressure.[141] However, as selective RHR reduction with ivabradine reduces heart failure events like CV death and HHF, it is considered a modifiable risk factor in HFrEF.[142]

In HFpEF, secondary analyses from CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)[138] and I-PRESERVE (Irbesartan in HFpEF Study)[139] have also shown an association between risk of all-cause death and increasing RHR in sinus rhythm, but not atrial fibrillation. Similar findings are reported in the CHART-2 (Chronic Heart Failure Analysis and Registry in the Tohoku District 2) study[143] and in the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) registry.[144] In this respect, it is noteworthy that many patients with HFpEF suffer from chronotropic incompetence[145] and that in an ageing population such as HFpEF patients, RHR tends to be lower than in younger individuals.[137–140]

Several treatment approaches to reduce a high RHR have been studied.[146] The effect of beta-blockers in patients with HFpEF remains unclear, due to relative under enrolment of these patients in beta-blocker trials. In the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial, the beta-blocker nebivolol reduced the composite of all-cause mortality or CV hospital admission in heart failure – an effect that appeared to be consistent in patients with an LVEF <35% and >35%.[147] An individual patient-level meta-analysis of beta-blocker trials also demonstrated a signal towards reduced CV hospitalization with beta-blockers, but also a statistically non-significant trend towards increased all-cause and CV mortality in patients with LVEF ≥50%.[148] The aforementioned analyses, however, were majorly limited by a small sample of patients with HFpEF. In the ELANDD (Effect of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity and left ventricular function in patients with Diastolic Dysfunction) trial, nebivolol failed to increase exercise capacity and left ventricular function.[149]

The EDIFY (The prEserveD left ventricular ejectIon fraction chronic heart Failure with ivabradine studY) study explored the effects of selective RHR reduction with ivabradine in patients with HFpEF, showing that there was neither an anti-hypertrophic or anti-remodelling effect, nor an effect on exercise tolerance or NT-proBNP.[140] The recent myPACE trial demonstrated that in patients with HFpEF and existing pacemakers, a moderately accelerated personalized heart rate setting improved NT-proBNP levels, physical activity and quality of life, when compared with the standard setting (60 bpm).[150] Therapeutical approaches addressing a high RHR are still lacking. Nevertheless, it is important to note that the treatment effect of SLGT2 inhibitors in HFpEF remains stable over the whole spectrum of heart rates including CV death and HHF.[151]

Chronotropic incompetence

Patients with heart failure have a significantly impaired exercise tolerance to which chronotropic incompetence significantly contributes.[152–154] Beta-blockers blunt chronotropic response to exercise; their effect on outcomes in HFpEF is not well-established.[145,155,156] A controlled trial has shown that in patients with HFpEF, beta-blocker withdrawal increased the functional capacity and oxygen uptake significantly.[157] This is in line with findings that selective heart rate reduction in HFpEF with the I_f-inhibitor ivabradine does not show any benefit on exercise tolerance or echocardiographic parameters in HFpEF.[140] Therefore, the role of beta-blockers in all-comers with HFpEF is questionable; however, they may be warranted in patients with certain phenotypes (such as hypertension and ischaemic heart disease – in which there is evidence for their use). In patients with HFpEF and chronotropic incompetence, the use of a rate-adaptive atrial pacing to enhance exercise heart rate did not improve exercise capacity in a randomized, double-blind cross-over trial.[158]

Atrial functional mitral regurgitation

Atrial mitral regurgitation (MR) is a form of functional MR (FMR) where left ventricular size and systolic function are typically normal and isolated mitral annular dilatation and inadequate leaflet coaptation result in MR. Its hallmarks are normal left ventricular systolic function, normal leaflet motion, central MR jet, and severe left atrial dilatation.[159] It is common in patients with atrial fibrillation and/or HFpEF.[160,161] In HFpEF patients, its prevalence is reported to be as high as 50% and it is associated with worse clinical outcomes,[161] making HFpEF with atrial FMR a unique but common and clinically important phenotype. In this regard, the coexistence of atrial fibrillation and atrial FMR in HFpEF patients may represent a particularly troublesome HFpEF phenotype, demonstrating very

large left atria and very high mortality.[162] Such patients may respond to mitral valve intervention, but this has not been well studied in a population of pure atrial FMR patients.

Functional tricuspid regurgitation

Heart failure with preserved ejection fraction can cause functional tricuspid regurgitation (FTR) – its prevalence in HFpEF patients is about 20%.[39] Mechanistically, post-capillary pulmonary hypertension leads to right ventricular remodelling resulting in tricuspid annular dilatation and leaflet tethering, while right atrial enlargement and dysfunction lead to tricuspid annular dilatation, with the latter being the most common mechanism.[163,164] Atrial FTR has recently emerged as a distinct pathophysiological entity typically occurring in patients with persistent/permanent atrial fibrillation and HFpEF.[164] It is associated with unfavourable outcomes[165,166] and residual congestion after a HHF.[167] Since surgery of isolated FTR is burdened by a high intraoperative risk, percutaneous techniques are emerging as possible treatment options for these patients. Patients with HFpEF may benefit from percutaneous treatment of FTR,[168] however evidence is limited and further research is needed to confirm such preliminary results.

Cachexia and sarcopenia

Heart failure with preserved ejection fraction is associated with older age, multiple comorbidities and decreasing physical function. All of these make cachexia, sarcopenia and frailty more likely.[169,170] These three clinical features are also well known to be associated with an adverse prognosis irrespective of the presence or absence of other diseases, and so it is highly likely that differential profiling of HFpEF, by the presence or absence of either frailty or muscle wasting is likely to identify subgroups with much higher mortality than those without these complications. Whether HFpEF patients with frailty and wasting will be more or less likely to respond to particular drugs is not yet known, but there has been recent information that frailty does not prevent beneficial effects of drugs such as SGLT2 inhibitors, at least in HFrEF.[171] It would be highly worthwhile, therefore, to test frailty as a particular marker for differential response to potential new treatments in HFpEF. However, even the recommended doses of GDMT may be affected by substantial body wasting.[172]

As a statement of need for future research, we would like to highlight that cachexia may be traits of more progressive, advanced and/or end-stage disease in patients with HFpEF. More aggressive therapy for such patients may be warranted, but at this stage it is unclear what exactly should be done differently for such patients. No trials in this field exist, but clearly there is a need for gaining a better understanding. Equally, whether advanced therapies are suitable for some of these patients is not certain.

Very high ejection fraction (>65%/>70%)

A U-shaped relationship between mortality and LVEF has been noted in several studies.[173–177] Values of 60–65% show the lowest mortality, while both lower and higher LVEF have a higher mortality. These findings were found to be robust even after adjusting for several confounders, including age and sex, and included hyperdynamic left ventricular function in patients with HFpEF.[173] An LVEF >70% can have a similar prognosis to that of an LVEF of 35–40%, suggesting that it may be inappropriate to pool all patients with HFpEF into a single group.[174] According to the HFA-PEFF algorithm, it is therefore mandatory to clarify the underlying aetiologies of HFpEF, including those of symptomatic patients with supranormal LVEF, diastolic dysfunction, and increased BNP levels.[178] This can include non-cardiac and cardiac pathologies, such as anaemia, infections (including COVID-19[179]), hyperthyroidism, or MR, hypertension, tachycardia, or LVH, respectively. Cardiomyopathies with LVH, such as hypertrophic cardiomyopathy, Fabry disease, or cardiac amyloidosis can be associated with a HFpEF-like phenotype and sometimes an LVEF in the supranormal range.[180] They need an extended diagnostic phenotyping including a cardiac magnetic resonance imaging, bone Tc-scintigraphy, cardiac endomyocardial biopsy, or specific blood tests like measurements of galactosidase activity, Bence–Jones protein levels, and electrophoresis.[178]

In summary, HFpEF patients with a very high LVEF belong to a clinically underdiagnosed population with increased mortality. This group needs further clinical phenotyping and a search for aetiologies for which specific treatments are already established. This can include the treatment with a cardiac myosin inhibitor (mavacamten) in hypertrophic cardiomyopathy; enzyme substitution in Fabry disease, or tafamidis in cardiac transthyretin amyloidosis.

Left ventricular ejection fraction between 50% and 55%

An LVEF between 50% and 55% is borderline reduced[181] and below normal LVEF (normal ranges: male 52–72%; women 54–74%).[182] In the TOPCAT study, patients with LVEF 50% to <55% were a distinct group intermediate between mildly reduced LVEF and normal ejection fraction groups with worse outcomes compared to patients with normal LVEF.[183] This group of patients also had a beneficial treatment effect of spironolactone compared to those with normal LVEF. Similar findings emerged from the PARAGON-HF trial where sacubitril/valsartan had a more pronounced beneficial effect on reducing the composite primary endpoint of total HHF and CV death in patients with LVEF at or below the median of 57%.[37] This finding was evident across the range of LVEF, with the beneficial effect emerging as the LVEF decreased into the 50–55% range.[86] Finally, in the EMPEROR-Preserved trial,[6] the beneficial treatment effect of empagliflozin also began to emerge in patients with LVEF ≥50% to <64%,[184] suggesting that empagliflozin also provided a beneficial effect in patients with normal LVEF. Patients with borderline reduced LVEF (50–55%) are a group with different baseline characteristics, incidence rates of clinical outcomes, and responses to therapies compared to patients with normal LVEF.

Heart failure with preserved ejection fraction in patients with cancer

In cardio-oncology, research has traditionally focused on the association between certain cancer therapies and systolic dysfunction

(i.e. HFrEF). However, it is increasingly being recognized that many interventions in cancer have myocardial, vascular and metabolic effects that may increase the risk of HFpEF. For example, anthracyclines are a known cause of HFrEF, but recent studies have revealed significant diastolic dysfunction after anthracycline treatment – suggesting potentially increased risk of HFpEF.[185,186] In a study of 362 patients with breast cancer, doxorubicin treatment was associated with worsening diastolic dysfunction on echocardiography, which was evident in 60% of patients at 1 year, and 80% at 3 years.[185] Similarly, monoclonal antibodies and small molecule tyrosine kinase inhibitors directed against vascular endothelial growth factor commonly cause hypertension and increased vascular stiffness, which are associated with diastolic dysfunction. Whether these changes culminate in overt HFpEF in cancer survivors is yet to be studied. Prospective cohort studies have also shown an association between carfilzomib use and heart failure events – and studies with imaging data available show that most events are consistent with HFpEF, rather than HFrEF.[187,188] Similarly, other cancer therapies such as BCR-ABL fusion inhibitors, and immune checkpoint inhibitors may result in myocardial changes, which may increase HFpEF risk.[189,190] Moreover, radiation therapy is a known cause of HFpEF, which likely occurs secondary to microvascular endothelial damage, inflammation and fibrosis induced by radiation.

The link between cancer therapy and HFpEF is one that needs further study. As of now, careful CV workup and echocardiography should be considered in patients receiving interventions for cancers to allow early detection of diastolic dysfunction.[191] It is advisable that the diagnosis of cancer therapy-induced HFpEF is made after excluding reversible and treatable conditions (such as endocrinopathies and amyloidosis).[191] Treatment of HFpEF in patients with cancer should be generally similar to treatment of HFpEF in the non-cancer population – including SGLT2 inhibitors, diuretics as needed, and control of risk factors.

As a note of caution and as a statement of need for future research, we would like to highlight that patients with HFpEF and cancer (whether due to their treatment or pre-existing) were excluded from all large HFpEF trials including the SGLT2 inhibitor studies. Therefore there is no evidence specifically in cancer patients with HFpEF regarding either the efficacy or the safety of SGLT2 inhibitors. Of note, safety is important particularly in patients receiving cytotoxic chemotherapy where frequent infections are more likely. This should be an area of future research.

Secondary heart failure with preserved ejection fraction

In contrast to primary HFpEF, secondary HFpEF has a clearly identifiable condition which is responsible for diastolic dysfunction (*Table 1*). Secondary HFpEF is also referred to as 'HFpEF mimics'. Key conditions to be aware of include restrictive cardiomyopathies, hypertrophic cardiomyopathy, constrictive cardiomyopathy, and valvular heart disease.

Restrictive cardiomyopathies

Restrictive cardiomyopathy is defined as severely impaired myocardial compliance and diastolic dysfunction along with normal LVEF. Common causes include infiltrative diseases (amyloidosis or glycogen storage disease), endomyocardial fibrosis, chest radiation therapy, iron overload, and eosinophilic cardiomyopathy. In certain cases, restrictive cardiomyopathy may be idiopathic. Left ventricular wall thickness is often normal in infiltrative diseases, while it is increased in all other forms of restrictive cardiomyopathy.[192] Cardiac magnetic resonance is often useful for diagnosis; however, endomyocardial biopsy may be required for a definitive diagnosis. Treatment for all restrictive cardiomyopathies includes diuretics for symptomatic relief of congestion. It must be noted that beta-blockers are often tolerated poorly in this population.[191,192]

A particularly important and underrecognized cause of restrictive cardiomyopathy is transthyretin-derived amyloidosis (ATTR) with the wild type (wt) more frequent than the variant type. In patients with HFpEF and LVH, it has been found that ATTRwt amyloidosis was present in 13% of patients.[193] In a cohort of patients with HFpEF without LVH, the prevalence of cardiac ATTR amyloidosis was 5%.[194]

If non-hypertensive patients present with significant LVH and low voltage QRS on the electrocardiogram, clinicians should suspect cardiac ATTR amyloidosis and initiate the relevant clinical tests. Diphosphonate tracer scintigraphy is useful for the early detection of cardiac ATTR amyloidosis. Whether we should screen all the HFpEF population with unexplained LVH, especially those older than 60 years, for ATTR amyloidosis needs consideration.[195]

Recently, a new drug for ATTR amyloidosis, tafamidis, has shown a reduction in morbidity and mortality, especially if treatment is started in the early stage.[196] Other potential drugs, such as small interfering RNA or transthyretin degraders, need future evidence. It might also be promising to use a combination therapy of the above-mentioned drugs, especially for advanced stages. The ongoing APPOLLO-B (A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy [ATTR Amyloidosis With Cardiomyopathy]) trial (NCT03997383) will evaluate the safety and efficacy of patisiran (a double-stranded small interfering RNA that targets a sequence within the transthyretin messenger RNA) for the treatment of ATTR amyloidosis-related cardiomyopathy.

It is to be noted that some patients with a small left ventricle who also have a high (very high) ejection fraction, such as AL amyloidosis or a small proportion of patients with hypertrophic cardiomyopathy, have significant symptoms of heart failure. The use of diuretics can relieve the symptoms. However, they are prone to blood pressure intolerance, often accompanied by low blood pressure, and underweight. The patients often cannot tolerate ACEI/ARB/ARNI. This is a phenotype that needs further attention.

Hypertrophic cardiomyopathy

Obstructive hypertrophic cardiomyopathy causes HFpEF in most patients, and non-obstructive hypertrophic cardiomyopathy causes HFpEF in ~10% of patients.[180] Concomitant presence of both conditions is associated with a worse prognosis.[197] In patients

with concomitant disease, general HFpEF treatment is advisable, in addition to treatment for hypertrophic cardiomyopathy. Briefly, in symptomatic patients, pharmaceutical treatment options include non-vasodilating beta-blockers, verapamil, disopyramide, and mavacamten.[198] These agents increase cardiac filling and left ventricular outflow to relieve symptoms of shortness of breath or chest pain. If symptoms persist, or there is significant obstruction, a septal myectomy or alcohol ablation should be considered as per recent guidelines.[198] In addition, implantable cardioverter-defibrillator placement is recommended for patients at high risk for sudden cardiac death.[198]

Constrictive pericarditis

Constrictive pericarditis is a consequence of decreased pericardial compliance due to a thickened or calcified pericardium. Constrictive pericarditis should be suspected in patients with risk factors including a history of pericarditis, radiation to the chest, trauma, or cardiac surgery. Additionally, constrictive pericarditis may result from systemic diseases that may involve the pericardium, such as tuberculosis, malignancy or connective tissue disease. On echocardiography, findings indicating constrictive pericarditis include respiration-linked ventricular septal shift, increased or preserved medial mitral annular e' velocity and prominent hepatic vein expiratory diastolic flow reversals.[199] In addition to diuretics, anti-inflammatory drugs are advisable to use in severe cases with pericardiectomy.

Valvular heart disease

Valvular heart disease is the most commonly seen cause of secondary HFpEF. Stenosis or regurgitation of the left heart valves leads to acute or chronic loading of the left ventricle and/or atrium.[200,201] Imaging studies have shown an association between aortic stenosis and diffuse myocardial fibrosis. The low-gradient (transvalvular gradient <40 mmHg) variant of aortic stenosis is of particular interest. These variants may present with either reduced LVEF (classical low-gradient) or preserved ejection fraction (paradoxical low-gradient).[200,201] The paradoxical low-gradient variants present with a syndrome akin to HFpEF. Moreover, paradoxical low-gradient aortic stenosis is more common in elderly, females, and those with diabetes or hypertension – all characteristics of patients with HFpEF.[200,201] Thus, valvular disease, and particularly aortic stenosis, should be suspected in patients presenting with HFpEF. Early intervention and targeted therapy may reverse the heart failure and improve prognosis.

Conclusion

In this paper, we laid out a phenotype-based approach for the treatment of HFpEF (*Figure 2*). Patients with HFpEF have highly heterogeneous clinical profiles, and the efficacy of certain medications can vary within subgroups of patients with HFpEF. We consider SGLT2 inhibitors together with diuretics as foundational therapies for patients with HFpEF. To achieve optimal clinical outcomes, while

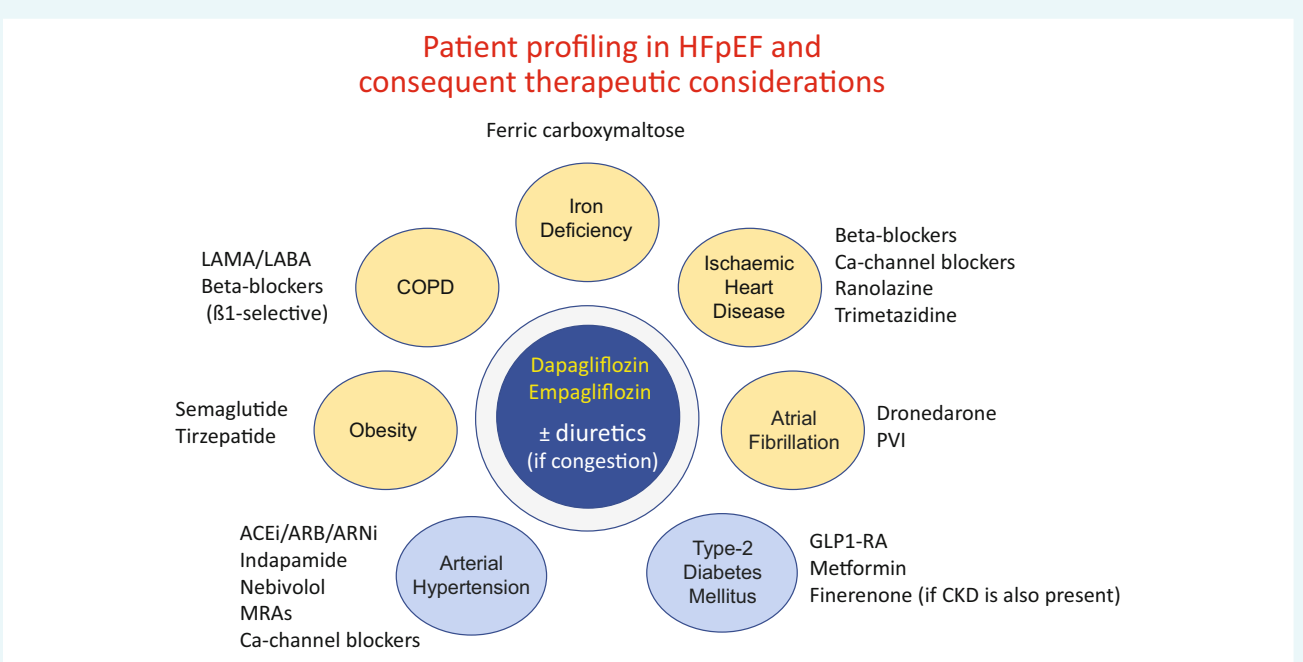

Figure 2 Patient profiling in heart failure with preserved ejection fraction (HFpEF) and its possible therapeutic consequences. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; Ca, calcium; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GLP1-RA, glucagon-line peptide-1 receptor agonist; LABA, long-acting β-agonist; LAMA, long-acting muscarinic receptor antagonist; MRA, mineralocorticoid receptor antagonist; PVI, pulmonary vein isolation.

minimizing futile use of medications, additional interventions are advisable based on sex, BMI, and the presence or absence of T2DM, hypertension, COPD, atrial fibrillation and CAD.

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