Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management

Andreas B Gevaert, Rachna Kataria, Faiez Zannad, Andrew J Sauer, Kevin Damman, Kavita Sharma, Sanjiv Shah, Harriette G C van Spall

Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management

Andreas B. Gevaert, MD PhD[1,2,3,*]; Rachna Kataria, MD[4,*]; Faiez Zannad, MD PhD[5,6]; Andrew J. Sauer, MD[7]; Kevin Damman, MD PhD[3]; Kavita Sharma, MD[8]; Sanjiv J. Shah[9]; Harriette G.C. Van Spall, MD MPH[10,11,12,#]

1 Research group Cardiovascular Diseases, GENCOR Department, University of Antwerp, Antwerp, Belgium

2 Department of Cardiology, Antwerp University Hospital (UZA), Edegem, Belgium

3 University of Groningen, Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands

4 Corrigan Minehan Heart Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

5 Universite de Lorraine, Inserm, Centre d'Investigations Cliniques-1433 and Inserm U1116, Centre Hospitalier Régional Universitaire Nancy, Nancy, France

6 French Clinical Research Infrastructure Network, Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists, Nancy, France

7 Center for Advanced Heart Failure and Heart Transplantation, The University of Kansas Health System, Kansas City, Kansas, USA

8 Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

9 Division of Cardiology, Department of Medicine and Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine, Chicago, USA

10 Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada.

11 Population Health Research Institute, Hamilton, Ontario, Canada.

12 Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

* Denotes shared first authorship

Corresponding author: Harriette G.C. Van Spall, Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton Health Sciences, 20 Copeland Avenue, David Braley Research Bldg, Suite C3-117, Hamilton ON L8L 0A3, Canada. Email: harriette.vanspall@phri.ca

Word count: 2984 (limit up to 3000 words).

Abstract: 249 (limit up to 250 words).

Tables/illustrations: 4 + 4 (limit up to 8).

Abstract

It is estimated that one-half of all patients with heart failure (HF) have heart failure with preserved ejection fraction (HFpEF). Yet, this form of HF remains a diagnostic and therapeutic challenge. Differentiating HFpEF from other causes of dyspnea can be challenging and may require advanced diagnostic methods such as exercise echocardiography, invasive haemodynamics, and investigations for "HFpEF mimickers". While the classification of HF has relied heavily on cut-points in left ventricular ejection fraction (LVEF), recent evidence points towards a gradual shift in underlying mechanisms, phenotypes, and response to therapies as LVEF increases. Among patients with HF, the proportion of hospitalizations and deaths due to cardiac causes decreases as LVEF increases. Medication classes that have been efficacious in HFrEF have been less so at higher LVEF ranges, decreasing the risk of HF hospitalization but not cardiovascular or all-cause death in HFpEF. These observations reflect the burden of non-cardiac comorbidities as LVEF increases and highlights the complex pathophysiologic mechanisms, both cardiac and noncardiac, underpinning HFpEF. Treatment with sodium-glucose cotransporter 2 inhibitors reduces the risk of composite cardiovascular events, driven by a reduction in HF hospitalizations; renin-angiotensin-aldosterone blockers and angiotensin-neprilysin inhibitors result in a smaller reduction in HF hospitalizations. Comprehensive management of HFpEF includes exercise and treatment of risk factors and comorbidities. Classification based on phenotypes may facilitate a more targeted approach to treatment than LVEF categorization, which sets arbitrary cut-points when LVEF is a continuum. This narrative review summarizes the pathophysiology, diagnosis, classification, and management of patients with HFpEF.

Recent concepts in diagnosis of HFpEF

The evolving definition of HFpEF

Almost two decades ago, it was demonstrated that patients heart failure (HF) and mild or no reduction in left ventricular ejection fraction (LVEF) had better outcomes when compared with patients with severe systolic dysfunction.[1] Mechanistic studies revealed that some of these patients even had normal filling pressures at rest and a complex interplay existed between pathophysiologic cardiac and noncardiac processes.[2] Heart failure with preserved ejection fraction (HFpEF) was first defined as patients with an LVEF >40%.[3] Since then, different definitions and thresholds have been proposed by major societies, also introducing heart failure with mid-range ejection fraction (HFmrEF), recently re-labelled as 'mildly reduced' for LVEF 40-50%.[3,4] HFpEF is now defined by normal LVEF (> 50%) along with signs and symptoms of heart failure, after exclusion of prior reduced LVEF and treatable underlying conditions.[4] However, these classifications of HF defined by arbitrary cut-points in LVEF do not appear consistent with recent evidence, which points to a gradual shift in underlying mechanisms, phenotypes, and response to therapy as LVEF increases, with considerable overlap (Figure 1).[5–8] HF therapies have generally not been effective at reducing cardiovascular (CV) death beyond LVEF 40-50% or HF hospitalization beyond 55-60%, reflecting the contribution of non-cardiac comorbidities as LVEF increases.[7,8] Meta-analyses and mechanistic studies demonstrated that pathophysiology and response to therapies are overlapping between HFrEF and HFmrEF.[7,8] Thus, the definition of HFpEF will continue to evolve as new information regarding phenotypes emerges.

Current diagnostic approach and its limitations

HFpEF can be defined theoretically as presence of elevated left ventricular (LV) filling pressure at rest or during exercise, with normal LVEF.[9] However it is not feasible to subject all HFpEF patients to an invasive exercise hemodynamic study. Most guidelines define HFpEF clinically as (i) the presence of symptoms and signs of HF; (ii) an LVEF ≥ 50%, (iii) careful exclusion of "HFpEF mimickers" and (iv) evidence of elevated left ventricular (LV) filling pressure or non-invasive correlates (elevated E/e' ratio, increased left atrial volume, elevated natriuretic peptides [NP]).[4,9]

The diagnostic criteria of HFpEF are not without limitations. First, the optimal LVEF threshold to define HFpEF is still debated. Several "HFpEF" randomized clinical trials (RCTs) have used lower LVEF cut-offs (40-45%) to maximize event rates and thus attain statistical power. Additionally, patients with HFmrEF have similar pathophysiology and treatment response as those with HFrEF, so their inclusion in trials of HFpEF favours treatments effective in HFrEF.[7,8] Second, NP levels may not always guide diagnosis as they tend to be lower in HFpEF than HFrEF, likely due to lower diastolic wall stress and higher prevalence of obesity.[9] Third, while these criteria rely on measurements at rest, left-sided filling pressures increase only with exercise in many patients with HFpEF;[9] patients who do not experience dyspnea and demonstrate signs of elevated LV filling pressure at rest, require advanced testing such as exercise echocardiography or invasive exercise haemodynamics to unmask abnormal diastolic reserve (Figure 2).[9] E/e' during exercise has been shown to correlate reasonably well with invasively measured pulmonary capillary wedge pressure (PCWP) (Figure 2).[10] However, imaging studies during exercise are subject to limitations posed by body habitus and operator experience. Invasive haemodynamics provide a direct measurement of PCPW during exercise, although even the diagnostic threshold is still debated (exercise PCWP≥25 mmHg or ΔPCWP/Δcardiac output slope>2.0 mmHg/L/min).[11]

Two HFpEF diagnostic algorithms -the H_2FPEF score [12] and the European Society of Cardiology HFA-PEFF algorithm [9]- combine clinical characteristics and diagnostic parameters to distinguish HFpEF from non-cardiac dyspnea (Tables 1-2). Implementation of these scores in different populations has demonstrated little overlap between patients with high H_2FPEF and HFA-PEFF scores; however, both scores identify patients at high risk of HF events.[13] Validation of these scores against invasive haemodynamics demonstrated reasonable performance: area under the receiver operating characteristic curve was 0.73-0.74.[13] Still, up to 23% of patients were misclassified in both scores, typically occurring in patients with low scores who met invasive HFpEF criteria. Thus, low scores may not exclude HFpEF.[13] Furthermore, a substantial proportion of patients have an intermediate probability for HFpEF using this classification system, and require further testing.[4]

HFpEF mimickers and specific cardiac aetiologies of HFpEF

While most cases of HFpEF are associated with known risk factors and comorbidities, "HFpEF mimickers" such as lung disease, pulmonary embolism, right-sided heart failure secondary to pulmonary hypertension, and renal failure can present with similar symptoms and signs.[9] Also, several specific cardiac disorders can present with HFpEF. These can be classified into diseases that affect the myocardium and those that alter cardiac loading conditions (Table 3).[9] Cardiac amyloidosis, for example, is present in up to 13% of HFpEF patients on routine biopsy, even when not clinically suspected.[14] Targeted therapies exist for most of these conditions, and it is important that they are excluded when a clinical diagnosis of HFpEF is made.[9]

Recent insights in HFpEF pathophysiology

HFpEF results from a complex interplay between risk factors, comorbidities, and cardiac pathology that impact on LV structure, haemodynamics, and systemic organ function (Figure 3). In a normal LV, volume increases during diastole are accompanied by minimal pressure increases due to enhanced diastolic suction; LV end-diastolic pressure (LVEDP) remains normal with exercise. In HFpEF, due to increased chamber stiffness, the diastolic pressure-volume relationship is shifted upwards and left compared to a normal LV (Figure 2).[11] Volume changes thus lead to larger increases in LVEDP. Additionally, in most HFpEF patients the exercise-induced increase in cardiac output is blunted, due to poor contractile reserve and chronotropic incompetence.[10,11] In overt HFpEF, the elevated LVEDP persists at rest, resulting in poor exercise tolerance (Figure 2).

Cardiac and non-cardiac mechanisms

The importance of non-cardiac mechanisms in HFpEF is highlighted by the decreasing proportion of HF hospitalizations and CV deaths as LVEF increases.[1] Non-cardiac abnormalities in HFpEF can be grouped by organ systems.[2] Chronic obstructive *pulmonary* disease, sleep disordered breathing, and lung parenchymal disease can result in pulmonary hypertension, eventually leading to RV failure.[2,5] *Anaemia* is a common comorbidity, contributing to exercise intolerance and increased mortality.[2] *Peripheral vascular* dysfunction is frequent and is postulated to play a role in *skeletal muscle* dysfunction due to impaired oxygen delivery and extraction.[2] *Chronic kidney disease* is present in 50% of patients, and impaired fluid homeostasis in HFpEF is influenced by renal dysfunction. Finally, *obesity* is both a common comorbidity and risk factor for developing HFpEF. Regional variations in fat accumulation are associated with different HFpEF risk profiles, whereby

higher epicardial and visceral fat have the strongest association with HFpEF.[15] Plasma volume expansion can further dysregulate fluid homeostasis in obese HFpEF patients.[15] While the complex interaction of all the proposed non-cardiac mechanisms remain unclear, they appear to shift from mechanisms in HFrEF at higher ranges of LVEF, with a gradual change in phenotype and a gradual decrease in the proportion of CV causes of hospitalization and death as LVEF increases.[2,6] Nevertheless, sudden cardiac death accounts for 25% of mortality in HFpEF and may be a therapeutic target. A recently validated risk score can predict patients with HFpEF who are at risk of sudden cardiac death.[16]

HFpEF phenotypes

The identification of phenotypes -subgroups with similar clinical and pathophysiological characteristics that are distinct from other subgroups– may allow for the identification of specific HFpEF subgroups more amenable to therapy.[17] As LVEF increases, patients with HF are more commonly women; more commonly have hypertension and atrial fibrillation; less commonly have ischemic heart disease; and have lower NP levels.[1,5] Machine learning algorithms have separated patients into phenogroups based on presence of clinical characteristics, biomarker, and imaging profiles.[5,18] Although external validation is pending for most studies, the importance of this approach is demonstrated by robust stratification of clinical outcomes according to HFpEF phenotypes.[5,18] Different HFpEF phenotypes may reflect different underlying pathophysiology.[17] For example, cardiomyocyte calcium homeostasis was markedly abnormal in diabetic and hypertensive HFpEF but not in ischaemic HFpEF.[17] Obese HFpEF patients have markedly different clinical, hemodynamic and molecular changes compared to non-obese HFpEF patients.[17] However, current phenogroups are not mutually exclusive and a given patient can fit into different phenogroups, limiting the uptake of this approach.[18] Future research should focus

on external validation and on integrating phenotype-based classification schemes in clinical practice and in RCT recruitment (Figure 4).

Recent developments in HFpEF management

Lifestyle-based therapy

Up to 80% of patients with HFpEF are overweight, and weight loss has beneficial effects on cardiac relaxation and metabolic profile in older patients without HF. In a small RCT in obese patients with HFpEF, a calorie restricted diet alone or in combination with exercise training (ET) was associated with significant weight loss and an increase in absolute peak oxygen consumption (VO_2peak).[19] Together, diet and exercise had additive effects.[19] A low sodium diet has been associated with favourable hemodynamic changes in HFpEF.[20]

ET has beneficial effects in HFpEF and associated comorbidities such as atrial fibrillation and coronary artery disease. A meta-analysis of 8 RCTs with 463 HFpEF patients found that ET improved VO_2peak, 6-minute walk distance and quality of life scores.[21] A recent RCT compared standard moderate continuous training to high intensity interval training. A significant improvement in the primary outcome of VO_2peak after 3 months in-person ET was shown, regardless of training modality.[22] However, the benefit in VO_2peak was not sustained during a 9-month home-based supervised extension of training, highlighting the importance of supervised ET.[22] Supervised cardiac rehabilitation remains underused in HF overall and is not reimbursed for HFpEF patients in many countries.

Atrial fibrillation is commonly associated with HFpEF, and may account for some of the symptoms. A 6-month exercise program combining supervised and home-based aerobic

exercise resulted in a significant decrease in the recurrence of atrial fibrillation and a reduction in symptom severity at 12 months.[23] Other studies have shown benefit of risk factor management, including weight loss and ET, on atrial fibrillation symptoms and severity.[24] Future studies should focus on how to successfully implement and sustain ET in these patents.

Medical therapy

Given the pathophysiologic complexity of HFpEF and the interplay with commonly associated comorbidities, the treatment of HFpEF should begin with evidence-informed management of risk factors and comorbidities.[4] To date, no medical therapy has demonstrated a reduction in CV death in trials of HFpEF, suggesting the relatively large burden of noncardiac mortality in this group. Despite a lack of robust evidence, diuretics have been the mainstay of HFpEF management and are recommended for relief of symptoms due to volume overload.[4]

Beta blockers are often prescribed in HFpEF to treat comorbidities such as coronary artery disease and atrial fibrillation. A meta-analysis of three medium-sized RCTs demonstrated a reduction in all-cause mortality, but a vast majority had LVEF <50%.[25] RCTs of beta-blockers in HFpEF are a major unmet need. It is likely that some patients with HFpEF benefit from beta-blockers while in others beta-blockers can worsen chronotropic incompetence. Additionally, beta-blocker type (vasodilating, such as carvedilol vs. primary rate controlling, such as metoprolol), may have differential effects across HFpEF phenotypes.

Renin angiotensin-aldosterone system inhibitors (RAASi) and mineralocorticoid receptor antagonists (MRAs) have an established role in HFrEF, but have been less effective in

HFpEF, likely because the RAAS plays a less prominent pathophysiologic role as LVEF increases.[7] Trials of angiotensin-converting enzyme receptor inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) have failed to show a significant reduction in all-cause or CV death in HFpEF (Table 4), but have decreased the risk of HF hospitalization.[7,26] The Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist (TOPCAT) trial of the MRA spironolactone in HFpEF, failed to show an overall benefit in the primary composite outcome of CV death or HF hospitalization. However, in an exploratory analysis including only patients from the Americas, a small benefit on the primary outcome was noticed.[27] In both TOPCAT and the TOPCAT-Americas subgroup, spironolactone was associated with a reduced risk of HF hospitalization. Machine learning analysis of the TOPCAT trial identified a phenotype characterized by obesity, diabetes, renal disease, and inflammation that exhibited higher CV risk and a better response to spironolactone treatment.[28] However, these results have not been validated externally, and only an RCT enriched for certain phenotypes will provide evidence for phenotype-based treatment (Figure 4).

The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril-valsartan did not reduce the composite of CV death or total HF hospitalizations in patients with HF and LVEF ≥45% relative to valsartan in the Prospective Comparison of ARNI With ARB on Global Outcomes in HFpEF (PARAGON-HF) trial, but significantly reduced HF hospitalizations.[29] Of note, patients with elevated troponin or recent HF hospitalization were at higher CV risk and were more likely to benefit from ARNI.[30,31] Also, benefits were higher in patients previously using MRA.[7,32] We can speculate that these HFpEF phenotypes –more likely to be associated with structural heart disease and volume overload- may be more responsive to ARNI treatment.

In the EMPEROR-Preserved trial, sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin reduced the risk of composite CV death or total HF hospitalization in HF with LVEF >40%.[33] The benefit was again driven by a reduction in HF hospitalizations. There was no statistically significant interaction between LVEF and the primary outcome in the trial, but benefit did not extend beyond LVEF of 60% in subgroup analysis.[6] Furthermore, in the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, the dual SGLT2 and SGLT1 inhibitor sotagliflozin reduced the primary outcome of CV death and HF hospitalizations in patients with diabetes and worsening HF (both HFrEF and HFpEF), driven by reduced HF hospitalizations.[34] It is likely that future updates of HF treatment guidelines will include a recommendation to use SGLT2i in HFpEF.

Sex and Racial differences

Epidemiological studies and randomized trials demonstrate a female predominance in HFpEF (50-84%) due to differences in age and risk factors; adjusting for these differences males and females are at equal risk of developing HFpEF.[35] In the TOPCAT-Americas trial, a post hoc analysis showed no sex differences in the primary composite outcome, but females had a greater reduction in all-cause mortality relative to males with spironolactone (interaction p=0.02).[36] In a prespecified subanalysis of the PARAGON-HF trial, benefits of sacubitril-valsartan on the primary composite outcome (total HF hospitalizations and CV death) were sustained up to a higher LVEF in females (up to 60%) than in males (up to 45%).[37] A meta-analysis of trials of RAAS inhibitors was consistent with this finding; the benefits of candesartan, spironolactone and sacubitril-valsartan were sustained to a higher LVEF in females than in males.[7] This may be partially explained by differences in LV remodelling

due to ageing, with more concentric remodelling in women, leading to a comparatively higher LVEF in females for any given LV volume.[38]

Analyses of racial differences in HFpEF have been limited by under-enrolment of Black, Indigenous, and People of Color (BIPOC) in clinical trials relative to disease prevalence, and inadequate reporting of treatment effect by racial or ethnic subgroups.[39] In the United States of America, Black patients have a lower health care utilization and risk of in-hospital mortality from HF, including HFpEF, but may be faced with higher rate of readmissions due to disparities in access to subspecialty and ambulatory care.[40] There is no evidence from TOPCAT or EMPEROR-PRESERVED that there are racial differences in treatment effect of MRAs and SGLT2i's, respectively.[27,33]

Integration of Remote Monitoring and Multidisciplinary Technology Deployment

With recent expansion of telemedical encounters, clinician-patient interactions are increasingly supported by digital and device innovations.[41] Virtual visits have been associated with better adherence to clinic follow-up.[41] Implantable remote pulmonary artery (PA) pressure guided monitoring for patients with HFpEF, NYHA Class III symptoms and a prior hospitalization was associated with a 46% reduction in HF hospitalizations compared to routine care.[41] The Haemodynamic-Guided Management of HF (GUIDE-HF) trial, testing whether this benefit extended to patients with NYHA class II- IV symptoms and without a prior history hospitalization found that PA pressure guided management did not reduce the composite endpoint of all-cause mortality and total HF events; recruitment / management of patients during the coronavirus disease 2019 (COVID-19) pandemic may have attenuated the

estimated treatment effect.[42] More RCTs are warranted in this field, including novel approaches such as patient-activated therapy and multisensory device algorithms.

Multidisciplinary care integration and health services in HFpEF

HFpEF remains a diagnostic challenge and is often poorly managed, but clinical pathways and multidisciplinary teams can facilitate better care.[43] Dedicated HFpEF clinical programs, nurse visiting programs or "dyspnea clinics" have been proposed to streamline diagnosis, management and follow-up of patients, but most admissions in patients with HFpEF are secondary to non-cardiac causes.[1] A multidisciplinary approach to treatment targeted at common cardiac and non-cardiac comorbidities may help improve outcomes.[17] Additionally, transitional care services after hospital discharge improve patient-reported outcomes and may decrease emergency department visits, particularly in women.[44–46]

Conclusions

Invasive exercise hemodynamics remain the gold standard to diagnose HFpEF, but are not feasible for all patients. Clinical scores as well as exercise echocardiography aid the clinician in discerning HFpEF from its mimickers and from non-cardiac causes of dyspnea. The three-category classification of HF by LVEF must be reconsidered in light of emerging evidence showing considerable overlap between HFmrEF and HFrEF regarding pathophysiology and response to treatment. LVEF is a continuous variable, and response to HF therapies appears to be graded such that HF therapies – including beta-blockers, RAAS inhibitors, ARNI, and SGLT2i - that reduce both CV death and HF hospitalization at lower LVEFs are less effective at reducing death but continue to reduce HF hospitalization at higher LVEFs beyond 50%. This points to the noncardiac mechanisms that underpin or accompany HF as the LVEF increases, as well as differences in underlying pathophysiology. Care of the patient who

presents with HF and higher ranges of LVEF should entail investigations to underlying specific cardiac causes and management of concomitant cardiac and non-cardiac comorbidities to decrease all-cause death and all-cause hospitalizations. Novel insights into HFpEF pathophysiology, including the discovery of phenotypes with specific traits and sex-based differences, may help us narrow down subgroups of HFpEF patients amenable to further personalized treatment.

Acknowledgements

Parts of Figure 1 by Servier Medical Art (http://smart.servier.com) used under CC-BY-3.0 license.

Conflicts of interest

KS is an advisory board member and consultant for Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Cytokinetics, Janssen, Novartis, and NovoNordisk and receives honoraria. SJS has received research grants from Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiora, CVRx, Cytokinetics, Edwards Lifesciences, Eidos, Eisai, Imara, Impulse Dynamics, Intellia, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Shifamed, Tenax, Tenaya, and United Therapeutics.
The other authors report no conflicts of interest with regards to this manuscript.

Funding

ABG acknowledges funding from the European Society of Cardiology in form of an ESC Training Grant. SJS has received research grants from the National Institutes of Health (R01 HL107577, R01 HL127028, R01 HL140731, R01 HL149423). HGCV is funded by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Canada.

References

1 Solomon SD, Anavekar N, Skali H, *et al.* Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;**112**:3738–44. doi:10.1161/CIRCULATIONAHA.105.561423

2 Gevaert AB, Boen JRA, Segers VF, *et al.* Heart Failure With Preserved Ejection Fraction: A Review of Cardiac and Noncardiac Pathophysiology. *Front Physiol* 2019;**10**:638, 1–14. doi:10.3389/fphys.2019.00638

3 Hudson S, Pettit S. What is 'normal' left ventricular ejection fraction? *Heart* 2020;**106**:1445–6. doi:10.1136/heartjnl-2020-317604

4 McDonagh TA, Metra M, Adamo M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* Published Online First: 27 August 2021. doi:10.1093/eurheartj/ehab368

5 Gevaert AB, Tibebu S, Mamas MA, *et al.* Clinical phenogroups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes. *ESC Heart Fail* 2021;:ehf2.13344:1-14. doi:10.1002/ehf2.13344

6 Packer M, Zannad F, Anker SD. Heart Failure and a Preserved Ejection Fraction: A Side-by-Side Examination of the PARAGON-HF and EMPEROR-Preserved Trials. *Circulation* Published Online First: 2021. doi:10.1161/CIRCULATIONAHA.121.056657

7 Dewan P, Jackson A, Lam CSP, *et al.* Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail* 2020;**22**:898–901. doi:https://doi.org/10.1002/ejhf.1776

8 Cleland JGF, Bunting KV, Flather MD, *et al.* Beta-blockers for heart failure with

reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;**39**:26–35. doi:10.1093/eurheartj/ehx564

9 Pieske B, Tschöpe C, de Boer RA, *et al.* How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019;**40**:3297–317. doi:10.1093/eurheartj/ehz641

10 Prasad SB, Holland DJ, Atherton JJ. Diastolic stress echocardiography: from basic principles to clinical applications. *Heart* 2018;**104**:1739–48. doi:10.1136/heartjnl-2017-312323

11 Hsu S, Fang JC, Borlaug BA. Hemodynamics for the Heart Failure Clinician: A State-of-the-Art Review. *J Card Fail* 2021;**0**. doi:10.1016/j.cardfail.2021.07.012

12 Reddy YNV, Carter RE, Obokata M, *et al.* A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation* 2018;**138**:861–70. doi:10.1161/CIRCULATIONAHA.118.034646

13 Churchill TW, Li SX, Curreri L, *et al.* Evaluation of 2 Existing Diagnostic Scores for Heart Failure With Preserved Ejection Fraction Against a Comprehensively Phenotyped Cohort. *Circulation* 2021;**143**:289–91. doi:10.1161/CIRCULATIONAHA.120.050757

14 Hahn VS, Yanek LR, Vaishnav J, *et al.* Endomyocardial Biopsy Characterization of Heart Failure With Preserved Ejection Fraction and Prevalence of Cardiac Amyloidosis. *JACC Heart Fail* 2020;**8**:712–24. doi:10.1016/j.jchf.2020.04.007

15 Rao VN, Fudim M, Mentz RJ, *et al.* Regional adiposity and heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:1540–50. doi:10.1002/ejhf.1956

16 Adabag S, Langsetmo L. Sudden cardiac death risk prediction in heart failure with preserved ejection fraction. *Heart Rhythm* 2020;**17**:358–64.

doi:10.1016/j.hrthm.2019.12.009

17 Shah SJ, Kitzman DW, Borlaug BA, *et al.* Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction. *Circulation* 2016;**134**:73–90. doi:10.1161/CIRCULATIONAHA.116.021884

18 Fraser AG, Tschöpe C, de Boer RA. Diagnostic recommendations and phenotyping for heart failure with preserved ejection fraction: knowing more and understanding less? *Eur J Heart Fail* 2021;**n/a**. doi:10.1002/ejhf.2205

19 Kitzman DW, Brubaker P, Morgan T, *et al.* Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction. *JAMA* 2016;**315**:36–46. doi:10.1001/jama.2015.17346

20 Hummel SL, Seymour EM, Brook RD, *et al.* Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. *Circ Heart Fail* 2013;**6**:1165–71. doi:10.1161/CIRCHEARTFAILURE.113.000481

21 Fukuta H, Goto T, Wakami K, *et al.* Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019;**24**:535–47. doi:10.1007/s10741-019-09774-5

22 Mueller S, Winzer EB, Duvinage A, *et al.* Effect of high intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2021;**325**:542–51. doi:10.1001/jama.2020.26812

23 Elliot A, Verdicchio C, Mahajan R, *et al.* ACTIVE-AF: A Randomised Controlled Trial of an Exercise and Physical Activity Program in Patients with Atrial Fibrillation

(abstract). *Eur Soc Cardiol Congr 2021* Published Online First: 27 August 2021.https://esc2021-abstract.medicalcongress.online/mediatheque/share.aspx?channel=103467&mediaId=107307

24 Middeldorp ME, Ariyaratnam J, Lau D, *et al.* Lifestyle modifications for treatment of atrial fibrillation. *Heart Br Card Soc* 2020;**106**:325–32. doi:10.1136/heartjnl-2019-315327

25 Zheng SL, Chan FT, Nabeebaccus AA, *et al.* Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart* 2018;**104**:407–15. doi:10.1136/heartjnl-2017-311652

26 Cleland JGF, Tendera M, Adamus J, *et al.* The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–45. doi:10.1093/eurheartj/ehl250

27 Pfeffer MA, Claggett B, Assmann SF, *et al.* Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation* 2015;**131**:34–42. doi:10.1161/CIRCULATIONAHA.114.013255

28 Cohen JB, Schrauben SJ, Zhao L, *et al.* Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2020;**8**:172–84. doi:10.1016/j.jchf.2019.09.009

29 Solomon SD, McMurray JJV, Anand IS, *et al.* Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019;**381**:1609–20. doi:10.1056/NEJMoa1908655

30 Gori M, Senni M, Claggett B, *et al.* Integrating High-Sensitivity Troponin T and Sacubitril/Valsartan Treatment in HFpEF. *JACC Heart Fail* 2021;**9**:627–35.

doi:10.1016/j.jchf.2021.04.009

31 Vaduganathan M, Claggett BL, Desai AS, *et al.* Prior Heart Failure Hospitalization, Clinical Outcomes, and Response to Sacubitril/Valsartan Compared With Valsartan in HFpEF. *J Am Coll Cardiol* 2020;**75**:245–54. doi:10.1016/j.jacc.2019.11.003

32 Jering KS, Zannad F, Claggett B, *et al.* Cardiovascular and Renal Outcomes of Mineralocorticoid Receptor Antagonist Use in PARAGON-HF. *JACC Heart Fail* 2021;**9**:13–24. doi:10.1016/j.jchf.2020.08.014

33 Anker SD, Butler J, Filippatos G, *et al.* Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021;**0**:null. doi:10.1056/NEJMoa2107038

34 Bhatt DL, Szarek M, Steg PG, *et al.* Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021;**384**:117–28. doi:10.1056/NEJMoa2030183

35 Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;**14**:591–602. doi:10.1038/nrcardio.2017.65

36 Merrill M, Sweitzer NK, Lindenfeld J, *et al.* Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2019;**7**:228–38. doi:10.1016/j.jchf.2019.01.003

37 McMurray JJV, Jackson AM, Lam CSP, *et al.* Effects of Sacubitril-Valsartan, versus Valsartan, in Women Compared to Men with Heart Failure and Preserved Ejection Fraction: Insights from PARAGON-HF. *Circulation* 2020;**141**:338–51. doi:10.1161/CIRCULATIONAHA.119.044491

38 Hees PS, Fleg JL, Lakatta EG, *et al.* Left ventricular remodeling with age in normal men versus women: Novel insights using three-dimensional magnetic resonance imaging. *Am J Cardiol* 2002;**90**:1231–6. doi:10.1016/S0002-9149(02)02840-0

39 Wei S, Le N, Zhu JW, *et al.* Factors Associated with Racial and Ethnic Diversity among Heart Failure Trial Participants: A Systematic Bibliometric Review (in press). *Circ Heart*

Fail 2021.

40 Averbuch T, Mohamed M, Islam S, *et al.* The association between socioeconomic status, sex, race/ethnicity and in-hospital mortality among patients hospitalized for heart failure. *J Card Fail* Published Online First: 8 October 2021. doi:10.1016/j.cardfail.2021.09.012

41 Gensini GF, Alderighi C, Rasoini R, *et al.* Value of Telemonitoring and Telemedicine in Heart Failure Management. *Card Fail Rev* 2017;**3**:116–21. doi:10.15420/cfr.2017:6:2

42 Lindenfeld J, Zile MR, Desai AS, *et al.* Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *The Lancet* 2021;**0**. doi:10.1016/S0140-6736(21)01754-2

43 Shanbhag D, Graham ID, Harlos K, *et al.* Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure: a systematic review. *BMJ Open* 2018;**8**:e017765. doi:10.1136/bmjopen-2017-017765

44 Blumer V, Gayowsky A, Xie F, *et al.* Effect of patient-centered transitional care services on patient-reported outcomes in heart failure: sex-specific analysis of the PACT-HF randomized controlled trial. *Eur J Heart Fail* Published Online First: 2021. doi:10.1002/ejhf.2312

45 Van Spall HGC, Lee SF, Xie F, *et al.* Effect of Patient-Centered Transitional Care Services on Clinical Outcomes in Patients Hospitalized for Heart Failure. *JAMA* 2019;**321**:753. doi:10.1001/jama.2019.0710

46 Van Spall HG, DeFilippis EM, Lee SF, *et al.* Sex-specific outcomes of the Patient-Centered Care Transitions in Heart Failure (PACT-HF) randomized trial. *Circ Heart Fail* 2021;:In press.

47 Lam CSP, Carson PE, Anand IS, *et al.* Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ*

Heart Fail 2012;**5**:571–8. doi:10.1161/CIRCHEARTFAILURE.112.970061

48 Ahmed A, Rich MW, Fleg JL, *et al.* Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006;**114**:397–403. doi:10.1161/CIRCULATIONAHA.106.628347

49 Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). *Eur J Heart Fail* 2013;**15**:110–8. doi:10.1093/eurjhf/hfs141

Tables

Table 1. H2FPEF score. 1-2: low likelihood, 3-4: intermediate likelihood, ≥5: high likelihood of HFpEF.

Clinical Variable	Values	Points
Heavy	Body mass index > 30 kg/m^2	2
Hypertensive	2 or more hypertensive medicines	1
Atrial **F**ibrillation	Paroxysmal or Persistent	3
Pulmonary Hypertension	Doppler echocardiographic estimated PASP > 35 mm Hg	1
Elder	Age > 60 years	1
Filling pressure	Doppler echocardiographic E/e' > 9	1

PASP: pulmonary artery systolic pressure; E: mitral valve inflow E velocity; e': mitral annular tissue Doppler velocity.

Table 2. HFA-PEFF algorithm. Stepwise approach in diagnosing heart failure with preserved ejection fraction (P–F).

P	Initial work up (Step 1 (**P**): **P**re-test assessment)	• Symptoms and/or signs of HF • Co-morbidities/risk factors • ECG • Standard echocardiography • Natriuretic peptides • Ergometry/ 6MWT or CPET
E	Diagnostic work up (Step 2 (**E**): **E**chocardiographic and Natriuretic Peptide Score)	• Comprehensive echocardiography • Natriuretic peptides, if not measured in Step 1
F1	Advanced work up (Step 3 (**F1**): **F**unctional testing in case of uncertainty)	• Diastolic stress test: exercise stress echocardiography • Invasive hemodynamic measurements
F2	Etiological work up (Step 4 (**F2**): **F**inal Aetiology)	• Cardiovascular magnetic resonance imaging • Cardiac or non-cardiac biopsies • Scintigraphy/CT/PET • Genetic testing • Specific laboratory tests

HF: heart failure; ECG: electrocardiogram; 6MWT: 6 minute walk test; CPET: cardiopulmonary exercise testing; CT, computed tomography; PET, positron emission tomography.

Table 3: Specific cardiac aetiologies underlying HFpEF. Overview of specific etiological diagnoses presenting with signs and symptoms of HFpEF.

Conditions affecting the myocardium	**Clinical clues**	**Diagnostic approach**	**Important considerations**
Coronary Artery Disease (CAD)			
Epicardial	-Chest pain -ECG changes -Abnormal stress testing -Abnormal LV GLS	- Coronary CT angiography - Invasive angiography	- CAD→ risk of HFpEF.[38] - Complete revascularization of epicardial stenosis →improved overall outcomes.[5] - Effect of therapies targeted towards microvascular dysfunction →under investigation.
Microvascular	-ECG evidence of ischemia in the absence of focal wall motion abnormalities or perfusion defects on stress testing -Can cause abnormal LV GLS	- Invasive angiography with pharmacological provocation - Stress perfusion CMR - Stress cardiac PET	
Infiltrative cardiomyopathies and storage disorders			
Amyloidosis	-Bilateral carpal tunnel syndrome -Biceps tendon rupture -Lumbar spinal stenosis -Autonomic dysfunction -Severely reduced tissue Doppler s', e', and a' -Relative apical sparing on LV GLS -LV, RV and atrial septal hypertrophy -Pericardial effusion	- CMR - Endomyocardial biopsy - $^{(99m)}$Tc-DPD or -PYP scintigraphy - Serum/urine immunofixation, free light chains - Genetic testing	- Storage diseases more common in younger patients; amyloidosis, sarcoidosis and hemochromatosis in older adults. - Often manifesting as restrictive cardiomyopathy - Elevated 5-year mortality in adults. - Endomyocardial biopsies may be limited by sampling bias, especially in cases of suspected cardiac sarcoidosis. - Targeted therapies exist or are under investigation.
Sarcoidosis	-Extracardiac manifestations of sarcoid -Conduction system disorders -Ventricular arrhythmias in preserved LVEF -Basal septal thinning	- CMR - Cardiac PET - Noncardiac biopsy	
Storage disorders incl. haemochromatosis	-Family history, young age of onset -Skin, hair, muscle, neurologic abnormalities -Elevated serum creatine kinase, liver enzymes -Diabetes	- CMR - Endomyocardial biopsy - Lab tests - Genetic testing	
Hypertrophic cardiomyopathies	-Family history, young age of onset -LV hypertrophy in absence of hypertension -Biventricular hypertrophy -LV GLS abnormal in the anteroseptum or apex	- Echocardiography - CMR - Genetic testing	- May progress to restrictive or dilated cardiomyopathy - Expression of myocardial hypertrophy is age-dependent [10]

Immune, inflammatory, metabolic and toxic cardiomyopathies	-History of specific exposure to immune, inflammatory, metabolic or toxic agent	- CMR - Endomyocardial biopsy - Lab tests	
Conditions that alter cardiac loading conditions	**Clinical clues**	**Diagnostic approach**	**Important considerations**
Hypertensive urgency	-LV GLS abnormal in the basal septum -Significant LV hypertrophy	- Clinical exam - Echocardiography	- Hypertension is an important risk factor for HFpEF
Acquired or congenital valvular heart disease, particularly left-sided valvular regurgitation or stenosis.	-Murmur -Echocardiography is generally diagnostic	- Echocardiography - CMR	- Volume overload (mitral or aortic regurgitation) - Increased afterload (aortic or mitral stenosis) - Treatment specific for valvular pathology
Pericardial diseases such as constrictive pericarditis.	-Respiratory variation in mitral inflow -Diastolic septal bounce -Hepatic vein diastolic flow reversal during expiration -Septal e' velocity ≥ lateral e' velocity	- Echocardiography - Cardiac CT - Simultaneous left and right heart catheterization	- Patients with constrictive pericarditis usually meet clinical and echocardiographic criteria for HFpEF.[10] - Risk factors: history of pericarditis, cardiac surgery, radiation to the chest wall, and tuberculosis.
Arrhythmias, ventricular and supraventricular.	-HF symptoms in conjunction with palpitations -Paroxysmal HF symptoms	- Holter monitor, - Exercise test	- Can cause hemodynamic compromise and symptoms mimicking HFpEF.
High output state: anaemia, sepsis, pregnancy, liver disease, thyroid disease, myeloproliferative disorders, arteriovenous fistula, beriberi disease, obesity	-Tachycardia -Wide pulse-pressure and warm extremities -High cardiac output calculated by echocardiography -Symptoms and signs specific to the underlying disorder	- Lab tests - Echocardiography	- High-output heart failure should always be considered in patients presenting with normal LVEF, shortness of breath and congestion. - The comorbidities listed here should be actively excluded before a diagnosis of HFpEF is made.
Fluid dysregulation in chronic renal disease	-Patient with end-stage renal disease	- Lab tests - Echocardiography	- Complex interactions between end-stage renal disease and HFpEF
Pulmonary hypertension	-Patient with sleep apnea or lung disease including chronic obstructive pulmonary disease -Echocardiography is generally diagnostic	- Echocardiography - Pulmonary function tests	- Altered right heart loading conditions due to pulmonary hypertension also cause LV diastolic dysfunction

$^{(99m)}$Tc-DPD: technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid; CMR: cardiac magnetic resonance imaging; CT: computed tomography; GLS: global longitudinal strain; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; PET: positron emission tomography.

Table 4: Primary results and sex differences in major phase III randomized cardiovascular outcome clinical trials in patients with HFpEF.

Study (publication year)	Drug	Number of patients	% women	LVEF (%)	Outcome	Overall treatment effect (hazard ratio, 95% confidence interval)	Sex-specific treatment effect	P value for treatment-sex interaction
ACEI/ARB								
CHARM-Preserved (2003) [7]	Candesartan vs. placebo	3023	40%	>40	Primary: composite of CV death or HF hospitalization	0.89 (0.77 – 1.03)	No difference in primary outcome or all-cause death	Not reported
PEP-CHF (2006)[26]	Perindopril vs. placebo	850	55%	≥40	Primary: composite of all-cause death or unplanned HF hospitalization	0.92 (0.70 – 1.21)	Not reported	Not reported
I-PRESERVE (2008) [47]	Irbesartan vs. placebo	4128	61%	≥45	Primary: composite of all-cause death or first CV hospitalization	0.95 (0.86 – 1.05)	Not reported, but lower rate of primary endpoint in women regardless of treatment	Not reported
Digitalis								
DIG-PEF (2006)[48]	Digoxin vs. placebo	988	41%	>45	Primary: composite of HF death or HF hospitalization	0.82 (0.63 – 1.07)	Not reported	Not reported
Beta blocker								
SENIORS subanalysis (2009)[8]	Nebivolol vs. placebo	752	50%	>35	Primary: all-cause mortality or HF hospitalization	0.81 (0.63 – 1.04)	Not reported	Not reported
J-DHF (2013) [49]	Carvedilol vs. placebo	245	42%	>40	Primary: composite of CV death or HF hospitalization	0.90 (0.54 – 1.49)	Women: 1.02 (0.47 – 2.21) Men: 0.82 (0.43 – 1.59)	p=.68
MRA								
TOPCAT (2014)	Spironolactone	3445	52%	≥45	Primary: composite of	0.89 (0.77 – 1.04)	Women: 0.89 (0.71 – 1.12)	p=.99

[7]	vs. placebo				CV death or HF hospitalization		Men=: 0.89 (0.73 – 1.09)	
TOPCAT Americas (2014) [7]	Spironolactone vs. placebo	1767	50%	≥45	Primary: composite of CV death or HF hospitalization	0.82 (0.69 – 0.98)	Women: 0.81 (0.63 – 1.05) Men: 0.85 (0.67 – 1.08)	p=.84
ARNI								
PARAGON (2019) [7]	Sacubitril-valsartan vs. valsartan	4882	52%	≥45	Primary: composite of CV death and total HF hospitalizations	0.87 (0.75 – 1.01)	Women: 0.73 (0.59 – 0.90) Men: 1.03 (0.84 – 1.25)	p=.017
SGLT2i								
EMPEROR-PRESERVED (2021)[33]	Empagliflozin vs. placebo	5988	45%	>40%	Primary: composite of CV death and first HF hospitalization	0.79 (0.69 – 0.90)	Women: 0.75 (0.61 – 0.92) Men: 0.81 (0.69 – 0.96)	p=0.54
SOLOIST-WHF (2021)[34]	Sotagliflozin vs. placebo	1222	34%	all	Primary: composite of CV death, HF hospitalizations and urgent HF visits	0.67 (0.52 – 0.85)	Women: 0.80 (0.51 – 1.25) Men: 0.62 (0.47 – 0.82)	Not reported

CV: cardiovascular; HF: heart failure; LVEF: left ventricular ejection fraction; *Note: sex-specific treatment effects were not reported for HFpEF only, data refers to HFpEF and HFrEF patients combined

Figure Legends

Figure 1: Evolution of pathophysiologic understanding of HFpEF. *A:* Old concept of HFpEF as hypertrophic heart with diastolic heart failure, evolving into systolic heart failure over time. *B:* Prevailing concept of HFpEF and HFrEF as separate diseases, HFpEF caused by microvascular inflammation, HFrEF caused by cardiomyocyte loss. *C:* Emerging concept of heart failure as phenotypes overlapping across the spectrum of LV systolic function, with a gradual change in underlying pathophysiology, mode of death, and response to HF therapies with decreasing LVEF, influenced by sex, comorbidities, lifestyle, and genetics. GLS: global longitudinal strain; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LV: left ventricle; LVEF: left ventricular ejection fraction, NO: nitric oxide; ROS: reactive oxygen species; SV: stroke volume.

Figure 2: LV physiology in normal hearts, early HFpEF and advanced HFpEF. *Top panel:* Example tracings of LV pressure-volume loops at rest (red) and during exercise (blue) illustrating LVEDP (black dots) and EDPVR (black line). Dotted line represents high LVEDP, which causes symptoms of dyspnea. In a normal LV, during exercise EDV and ESV are increased, leading to increased stroke volume without increase in LVEDP. In early HFpEF, LV physiology is near normal at rest, but reduced diastolic reserve blunts the increase in stroke volume and increases LVEDP. In advanced HFpEF, the EDPVR is shifted upwards and to the left due to a stiffer ventricle, leading to increased LVEDP even at rest. *Bottom panel:* Example tracings of E/A (pulse wave Doppler) and e'/a' (tissue Doppler) waves at rest (red) and during exercise (blue). In a normal LV, during exercise E and e' both increase. In early HFpEF, E is normal or low with low e' at rest, which can also occur in the absence of HFpEF (e.g., with aging and due to comorbidities). However, during exercise e' does not appropriately increase, leading to a higher E/e' ratio. In advanced HFpEF, high left atrial

pressure and a stiff ventricle lead to elevated E/e' ratio at rest. A: mitral valve atrial inflow velocity; a' mitral annular atrial diastolic velocity; E: mitral valve early inflow velocity; e': mitral annular early diastolic velocity; EDPVR: end-diastolic pressure-volume relationship; EDV: end-diastolic volume; ESV: end-systolic volume; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle; LVEDP: left ventricular end-diastolic pressure.

Figure 3: Features of HFpEF. Phenotype is influenced by different risk factors, comorbidities, pathology, LV structure, haemodynamics, and organ dysfunction in each patient. LA: left atrium; LV: left ventricle; PA: pulmonary artery; RV: right ventricle.

Figure 4: Personalized medical treatment of HFpEF. Different phenotypes (based on clinical, imaging, biomarker, and/or transcriptomic data) represented by red, green and blue colours. *A:* Conventional approach to HFpEF medical therapy, treating all HFpEF patients with a one-size-fits-all treatment regardless of phenotype. As a whole, no clinical benefit is observed (less patients improved compared to patients without change or worsened). However, subgroups with benefit may be observed (Red phenotype). *B:* While a better overall treatment response to SGLT2i led to overall net clinical benefit, still subgroups of patients with better response (Blue phenotype) can be observed. *C:* Personalized treatment: considering the phenotype-specific response to medical therapy, a targeted approach using specific drugs in specific phenotypes could lead to net clinical benefit for all patients. ARNI: angiotensin receptor neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium glucose cotransporter 2 inhibitor.