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

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1 **Abstract**

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

23

24

1 **Recent concepts in diagnosis of HFpEF**

2 **The evolving definition of HFpEF**

3 Almost two decades ago, it was demonstrated that patients heart failure (HF) and mild or no
4 reduction in left ventricular ejection fraction (LVEF) had better outcomes when compared
5 with patients with severe systolic dysfunction.[1] Mechanistic studies revealed that some of
6 these patients even had normal filling pressures at rest and a complex interplay existed
7 between pathophysiologic cardiac and noncardiac processes.[2] Heart failure with preserved
8 ejection fraction (HFpEF) was first defined as patients with an LVEF >40%.[3] Since then,
9 different definitions and thresholds have been proposed by major societies, also introducing
10 heart failure with mid-range ejection fraction (HFmrEF), recently re-labelled as ‘mildly
11 reduced’ for LVEF 40-50%.[3,4] HFpEF is now defined by normal LVEF (> 50%) along with
12 signs and symptoms of heart failure, after exclusion of prior reduced LVEF and treatable
13 underlying conditions.[4] However, these classifications of HF defined by arbitrary cut-points
14 in LVEF do not appear consistent with recent evidence, which points to a gradual shift in
15 underlying mechanisms, phenotypes, and response to therapy as LVEF increases, with
16 considerable overlap (Figure 1).[5–8] HF therapies have generally not been effective at
17 reducing cardiovascular (CV) death beyond LVEF 40-50% or HF hospitalization beyond 55-
18 60%, reflecting the contribution of non-cardiac comorbidities as LVEF increases.[7,8] Meta-
19 analyses and mechanistic studies demonstrated that pathophysiology and response to therapies
20 are overlapping between HFrEF and HFmrEF.[7,8] Thus, the definition of HFpEF will
21 continue to evolve as new information regarding phenotypes emerges.

22

23 **Current diagnostic approach and its limitations**

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

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

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Two HFpEF diagnostic algorithms -the H₂FPEF 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 H₂FPEF 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]

1 **Recent insights in HFpEF pathophysiology**

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

12

13 **Cardiac and non-cardiac mechanisms**

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

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

9

10 **HFpEF phenotypes**

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

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

3

4 **Recent developments in HFpEF management**

5 **Lifestyle-based therapy**

6 Up to 80% of patients with HFpEF are overweight, and weight loss has beneficial effects on
7 cardiac relaxation and metabolic profile in older patients without HF. In a small RCT in obese
8 patients with HFpEF, a calorie restricted diet alone or in combination with exercise training
9 (ET) was associated with significant weight loss and an increase in absolute peak oxygen
10 consumption (VO_{2peak}).[19] Together, diet and exercise had additive effects.[19] A low
11 sodium diet has been associated with favourable hemodynamic changes in HFpEF.[20]

12

13 ET has beneficial effects in HFpEF and associated comorbidities such as atrial fibrillation and
14 coronary artery disease. A meta-analysis of 8 RCTs with 463 HFpEF patients found that ET
15 improved VO_{2peak} , 6-minute walk distance and quality of life scores.[21] A recent RCT
16 compared standard moderate continuous training to high intensity interval training. A
17 significant improvement in the primary outcome of VO_{2peak} after 3 months in-person ET was
18 shown, regardless of training modality.[22] However, the benefit in VO_{2peak} was not
19 sustained during a 9-month home-based supervised extension of training, highlighting the
20 importance of supervised ET.[22] Supervised cardiac rehabilitation remains underused in HF
21 overall and is not reimbursed for HFpEF patients in many countries.

22

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

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

6

7 **Medical therapy**

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

15

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

23

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

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

16

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

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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

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

3

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

12

13 **Integration of Remote Monitoring and Multidisciplinary Technology**

14 **Deployment**

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

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

3

4 **Multidisciplinary care integration and health services in HFpEF**

5

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

14

15 **Conclusions**

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

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

7

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9 Parts of Figure 1 by Servier Medical Art (<http://smart.servier.com>) used under CC-BY-3.0
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11 **Conflicts of interest**

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5

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1 **Tables**

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

3 likelihood of HFpEF.

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

4 PASP: pulmonary artery systolic pressure; E: mitral valve inflow E velocity; e': mitral

5 annular tissue Doppler velocity.

6

7

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

P	Initial work up (Step 1 (P): Pre-test assessment)	<ul style="list-style-type: none"> • 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): Echocardiographic and Natriuretic Peptide Score)	<ul style="list-style-type: none"> • Comprehensive echocardiography • Natriuretic peptides, if not measured in Step 1
F1	Advanced work up (Step 3 (F1): Functional testing in case of uncertainty)	<ul style="list-style-type: none"> • Diastolic stress test: exercise stress echocardiography • Invasive hemodynamic measurements
F2	Etiological work up (Step 4 (F2): Final Aetiology)	<ul style="list-style-type: none"> • Cardiovascular magnetic resonance imaging • Cardiac or non-cardiac biopsies • Scintigraphy/CT/PET • Genetic testing • Specific laboratory tests

3 HF: heart failure; ECG: electrocardiogram; 6MWT: 6 minute walk test; CPET:
 4 cardiopulmonary exercise testing; CT, computed tomography; PET, positron emission
 5 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	<ul style="list-style-type: none"> -Chest pain -ECG changes -Abnormal stress testing -Abnormal LV GLS 	<ul style="list-style-type: none"> - Coronary CT angiography - Invasive angiography 	<ul style="list-style-type: none"> - CAD→ risk of HFpEF.[38] - Complete revascularization of epicardial stenosis →improved overall outcomes.[5] - Effect of therapies targeted towards microvascular dysfunction →under investigation.
Microvascular	<ul style="list-style-type: none"> -ECG evidence of ischemia in the absence of focal wall motion abnormalities or perfusion defects on stress testing -Can cause abnormal LV GLS 	<ul style="list-style-type: none"> - Invasive angiography with pharmacological provocation - Stress perfusion CMR - Stress cardiac PET 	
Infiltrative cardiomyopathies and storage disorders			
Amyloidosis	<ul style="list-style-type: none"> -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 	<ul style="list-style-type: none"> - CMR - Endomyocardial biopsy - ^(99m)Tc-DPD or -PYP scintigraphy - Serum/urine immunofixation, free light chains - Genetic testing 	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> -Extracardiac manifestations of sarcoid -Conduction system disorders -Ventricular arrhythmias in preserved LVEF -Basal septal thinning 	<ul style="list-style-type: none"> - CMR - Cardiac PET - Noncardiac biopsy 	
Storage disorders incl. haemochromatosis	<ul style="list-style-type: none"> -Family history, young age of onset -Skin, hair, muscle, neurologic abnormalities -Elevated serum creatine kinase, liver enzymes -Diabetes 	<ul style="list-style-type: none"> - CMR - Endomyocardial biopsy - Lab tests - Genetic testing 	
Hypertrophic cardiomyopathies	<ul style="list-style-type: none"> -Family history, young age of onset -LV hypertrophy in absence of hypertension -Biventricular hypertrophy -LV GLS abnormal in the anteroseptum or apex 	<ul style="list-style-type: none"> - Echocardiography - CMR - Genetic testing 	<ul style="list-style-type: none"> - 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 \geq 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)	Spirololactone	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

1 **Figure Legends**

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

12

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

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

6

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

10

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