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REVIEW

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After TOPCAT: What to do now in Heart Failure with Preserved Ejection Fraction

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Although patients with heart failure and preserved ejection fraction (HF-PEF) represent nearly half of the population with chronic heart failure, few evidence-based medical therapies are available. The neutral overall results of the TOPCAT trial of spironolactone in HF-PEF leave clinicians who treat heart failure with an ongoing clinical dilemma. In this review, we outline an approach to the clinical management of the patient with HF-PEF synthesizing data from available clinical trials and expert consensus.

Keywords Heart failure with preserved ejection fraction • Spironolactone • Clinical management

Background

Approximately one-half of patients with heart failure have normal or near normal left ventricular ejection fraction and the proportion is growing.[1,2] Although patients with heart failure and preserved ejection fraction (HF-PEF) experience rates of hospitalization, functional decline, and mortality similar to patients with heart failure and reduced ejection fraction (HF-REF),[3] limited understanding of key pathophysiologic mechanisms has challenged the development of targeted pharmacologic therapy for this population.

The dramatic success of renin–angiotensin system inhibition as a strategy for reducing morbidity and mortality amongst patients with HF-REF has fuelled several efforts to replicate these benefits in heart failure and preserved ejection fraction (HF-PEF). Even though neurohormonal activation typical of the heart failure syndrome is apparent in HF-PEF,[4] three large-scale, prospective randomized trials have shown no statistically significant impact of angiotensin-converting enzyme inhibition[5] or angiotensin receptor blockade (CHARM-Preserved,[6] I-PRESERVE[7]) on clinical outcomes in HF-PEF. Moreover, therapeutic trials of digoxin (Ancillary Digitalis Investigation Group trial[8]) and β-blockers (SENIORS[9]) that enrolled HF-PEF patients have failed to demonstrate conclusive benefits in this subgroup. Accordingly, treatment guidelines for this population underscore that no specific therapies are available to reduce morbidity and mortality in the HF-PEF population.[10,11]

The mineralocorticoid receptor antagonists spironolactone and eplerenone reduce morbidity and mortality in patients with HF-REF.[12,13] Since activation of the mineralocorticoid receptor by aldosterone is known to promote hypertension, endothelial dysfunction, left ventricular hypertrophy, and progressive vascular, renal, and myocardial fibrosis, all of which may contribute to the development of HF-PEF, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial sought to test the value of spironolactone as a treatment for HF-PEF.[14,15] In 3445 patients followed for a mean of 3.3 years, spironolactone did not reduce the incidence of the primary composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure compared with placebo, though a nominally significant reduction was noted in the pre-specified secondary outcome of hospitalization for heart failure.[16]

The neutral findings of the TOPCAT trial leave clinicians who care for patients with HF-PEF with an ongoing therapeutic dilemma. In this brief review, we outline a practical approach to evaluation and management of this complex population, in hopes of facilitating effective treatment where evidence-based guidelines are lacking (*Figure 1*).

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Confirming the diagnosis: is this really heart failure and preserved ejection fraction?

According to consensus-based guidelines, the diagnosis of HF-PEF is made based on the presence of typical heart failure signs and symptoms in patients with preserved left ventricular ejection fraction and imaging or haemodynamic evidence of abnormal diastolic function.[17] Abnormal diastolic function is commonly identified noninvasively through Doppler echocardiographic abnormalities (e.g. elevated ratio of mitral inflow velocity to early diastolic velocity of the mitral annulus, *E*/*E*′) or surrogate markers such as left ventricular hypertrophy, left atrial enlargement, or elevated natriuretic peptide levels. In patients with normal resting haemodynamics, assessment of haemodynamics during exercise may help to bring out diastolic filling abnormalities and facilitate early diagnosis.[18]

Although these criteria neatly encapsulate the broad syndrome of HF-PEF, patients meeting these criteria comprise a markedly heterogeneous group that includes a number of distinct pathophysiologic entities that may require specific treatment (*Figure 2*) as well as patients with definable abnormalities of systolic function, those who have 'recovered' from a previously low ejection fraction but continue to experience heart failure symptoms,[19,20] and patients with dyspnoea unrelated to cardiovascular disease that may have simply been misdiagnosed. Lack of consistency in the threshold used to define 'preserved' left ventricular function further amplifies this heterogeneity and has led to variable inclusion of patients with mid-range, but not normal, ejection fraction (40–50%) into clinical trials.[21] Since patients with primary pericardial disease, infiltrative or restrictive cardiomyopathies, hypertrophic cardiomyopathy, lysosomal or glycogen storage diseases, high output heart failure (e.g. due to thyrotoxicosis or shunt), valvular heart disease (especially tricuspid regurgitation[22]), and those with primary right ventricular failure may present with heart failure and apparently normal left ventricular ejection fraction, systematic assessment for these specific conditions should be a routine part of the initial diagnostic evaluation of patients with HF-PEF. A thorough history (including a careful family history) is essential, and may provide clues to familial disease, systemic illness, region-specific entities, relevant exposures, or suggestive comorbidities. Specific diagnoses may be suggested by findings on routine physical examination or laboratory testing such as macroglossia (amyloidosis, acromegaly), periorbital bruising/petechiae (amyloidosis), angiokeratomas (Fabry disease), erythema nodosum (sarcoidosis), peripheral neuropathy (amyloidosis, Fabry disease), anaemia (amyloidosis), iron overload (haemochromatosis), or eosinophilia (Loeffler's endocarditis, endomyocardial fibrosis).

The development of HF-PEF in patients who do not exhibit typical demographic, clinical, or echocardiographic features of the disease, such as younger patients without diabetes or hypertension,

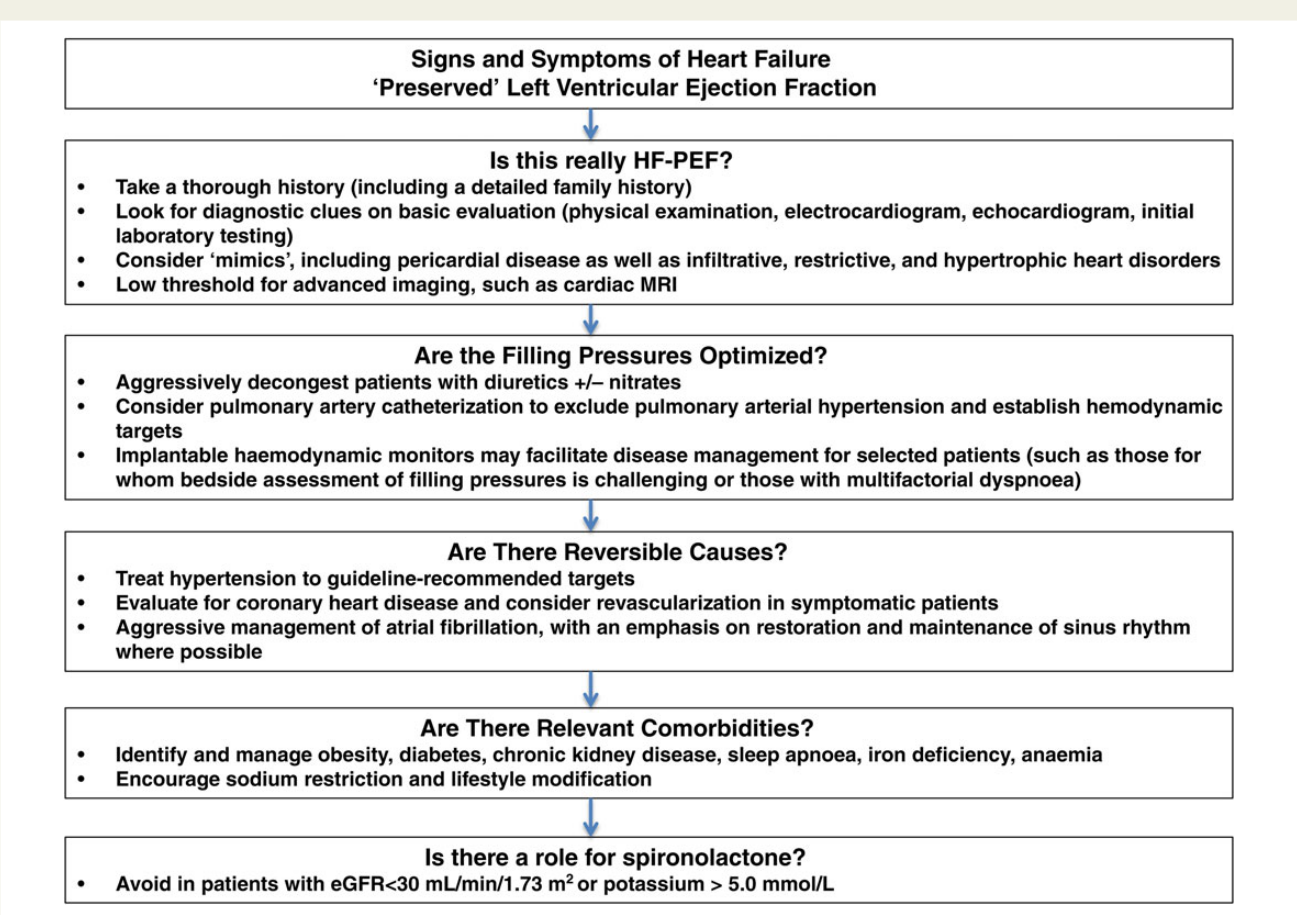

Figure 1 A proposed clinical approach to management of heart failure and preserved ejection fraction.

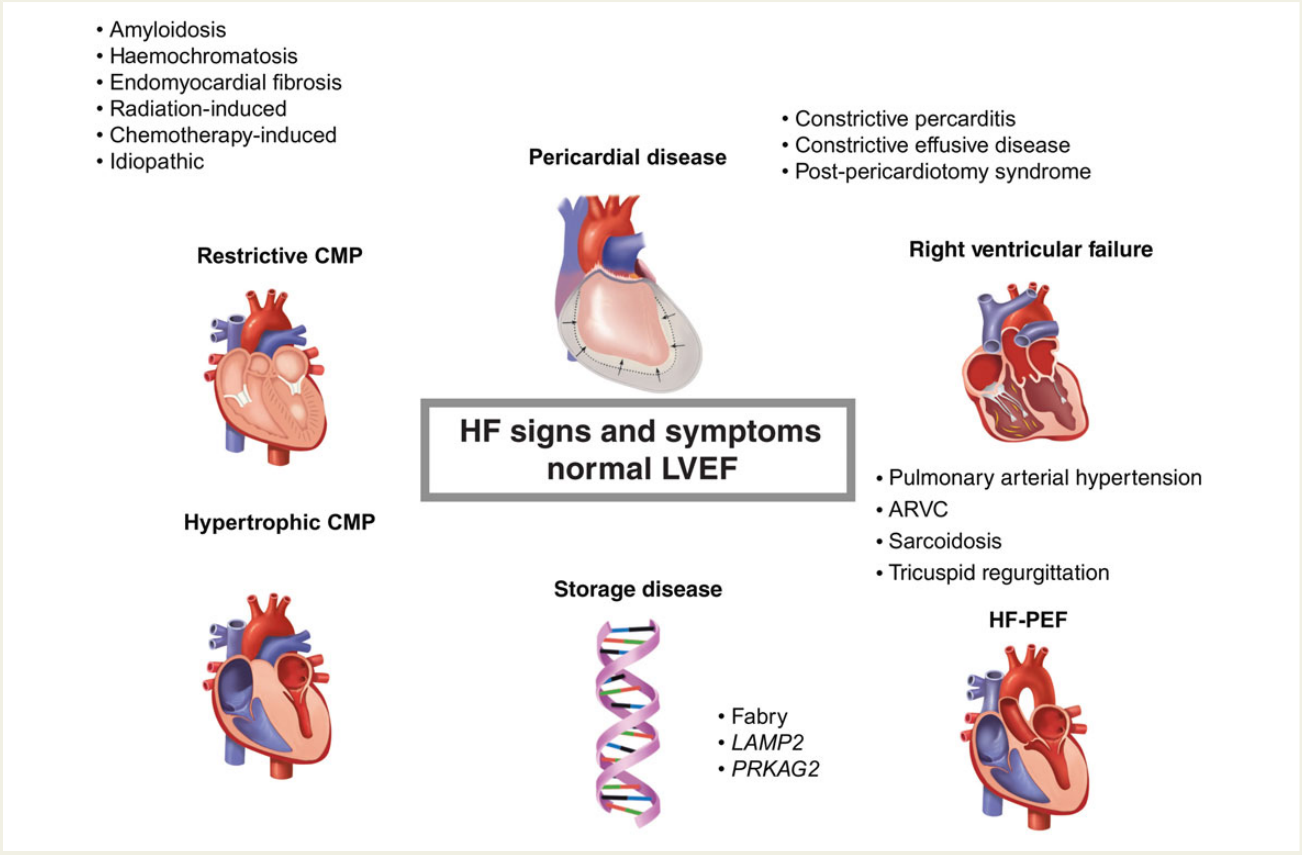

Figure 2 Differential diagnosis of heart failure in the setting of preserved left ventricular ejection fraction.

those with heart failure in the absence of significant diastolic dysfunction, pulmonary hypertension, or left atrial enlargement, and those with 'massive' or biventricular hypertrophy, should signal the need to investigate unusual diagnoses and encourage clinicians to pursue additional diagnostic testing. Where an infiltrative aetiology is suspected, such as in patients with low ECG lead voltage despite increased ventricular mass or those with unexplained ventricular hypertrophy, advanced cardiac imaging may be helpful in narrowing the differential diagnosis; abnormal findings on gadolinium-enhanced cardiac magnetic resonance imaging or unusual patterns of longitudinal myocardial strain should prompt consideration of endomyocardial biopsy for pathologic diagnosis.

While previously thought to be a rare cause of heart failure, cardiac amyloid deposits are detectable in as many as 25% of octogenarians, with higher estimated prevalence in older cohorts.[23] In autopsy series, roughly 5% of subjects with a pre-mortem diagnosis of HF-PEF have evidence of moderate or severe interstitial wild-type transthyretin (TTR) deposition consistent with senile systemic amyloidosis as the primary aetiology of heart failure.[24] Together, these data suggest that a large proportion of heart failure in patients with preserved ejection fraction may in part be related to undiagnosed cardiac amyloidosis.[25] With the increasingly promising therapies emerging for management of TTR amyloidosis, identification of the subset of HF-PEF patients with this diagnosis may be particularly important.[26]

Relief of symptoms: are filling pressures optimized?

Similar to those with HF-REF, hospitalizations in patients with HF-PEF are frequently related to congestive exacerbations related to progressive rise in intra-cardiac filling pressures in the weeks prior to decompensation.[27] Symptomatic patients with HF-PEF exhibit typical clinical symptoms and signs of congestion as well as elevations in natriuretic peptide levels suggesting volume overload.[27] Though not specifically tested in prospective trials enrolling HF-PEF patients, aggressive management of congestion using loop diuretics empirically improves symptoms and functional capacity and may help to limit the risk of hospital readmission.[28] Targeted management of filling pressures in the CHAMPION trial was associated with a reduction in the cumulative burden of heart failure hospitalizations in patients with both reduced and preserved ejection fraction.[29] Patients with HF-PEF allocated to PA-pressure guided management experienced a 50% reduction in the rate of heart failure hospitalizations over the 17-month period of randomized access relative to placebo, statistically indistinguishable from the reduction seen in patients with HF-REF. These benefits were achieved without a signal of increased risk, and appear to have been related to more aggressive adjustment of loop diuretics and nitrates in the patients whose providers had access to PA pressure

data. While these data require additional validation in an adequately powered randomized trial, the CHAMPION data suggest that aggressive management of filling pressures may improve outcomes in selected patients with HF-PEF and underscore the potential value of implantable haemodynamic monitoring as an adjunct to longitudinal heart failure management in this population. Implantation of a PA pressure sensor is neither practical nor cost-effective for every patient with HF-PEF, but these results also suggest the potential value of pulmonary artery catheterization as a means of defining targets for therapy in patients with HF-PEF, particularly when estimation of filling pressures is challenging at the bedside or non-invasive data are equivocal.

Optimizing diastolic function: are there reversible causes?

Although the pathophysiology of effort limitation in patients with HF-PEF is complex and controversial,[30] progressive myocardial stiffening and associated impairment of diastolic filling is universally acknowledged to be a central feature.[31,32] Accordingly, aggressive management of cardiovascular co-morbidities known to exacerbate diastolic dysfunction is uniformly encouraged by treatment guidelines.[10,11] Hypertension is highly prevalent in patients with HF-PEF, and is known to increase the risk of developing heart failure. Specific data supporting aggressive treatment of hypertension in HF-PEF are limited, but treatment of systolic and diastolic blood pressure to guideline-directed targets is generally associated with improvement in diastolic filling, regression of left ventricular hypertrophy, and reduction in the risk of heart failure progression.[33,34] In treating hypertension, clinicians should be alert to the heightened sensitivity of arterial pressure to vasodilator treatment in HF-PEF than in HF-REF due to the steeper nature of the end-systolic pressure volume relationship.[35]

Myocardial ischaemia may also contribute to impaired diastolic filling, and significant coronary artery disease is known to be present in more than half of patients with HF-PEF.[36] Heart failure and preserved ejection fraction patients with coronary artery disease tend to experience a higher risk of progressive ventricular dysfunction and mortality in follow-up compared with those without coronary artery disease, and there is a suggestion of improved outcomes with coronary revascularization in appropriate patients.[37] These data suggest that much as for patients with HF-REF, systematic investigation of patients with HF-PEF for the presence of CAD and consideration of revascularization (e.g. in patients with significant ischaemic burden) may be appropriate. While the optimal approach to evaluation for CAD is not well defined, the limited sensitivity and specificity of non-invasive stress imaging[37] and associated risk for both false-positive and false-negative results favours a low threshold to pursue invasive angiography in patients where the index of suspicion is high.

Atrial fibrillation occurs in nearly two-thirds of patients with HF-PEF at some point during the course of their disease,[38] and may contribute to functional impairment both due to uncontrolled ventricular rates and due to the loss of the atrial contribution to myocardial filling in diastole. Patients with atrial fibrillation and HF-PEF are at higher risk for both stroke[39] and subsequent mortality.[41] Although the optimal management of atrial fibrillation in HF-PEF remains undefined, anticoagulation and control of ventricular rate at a minimum is necessary. A trial of restoration of sinus rhythm with direct current cardioversion is appropriate for most subjects, though durable maintenance of sinus rhythm may frequently be difficult without anti-arrhythmic drugs and this strategy has yet to be tested in a clinical trial. Where ventricular response cannot be adequately controlled using agents that block the atrioventricular node, selected patients may benefit from atrioventricular junction ablation though this strategy brings with it obligate dependence on ventricular pacing. Since right ventricular apical pacing may exacerbate heart failure, cardiac resynchronization therapy may be appropriate for some patients undergoing an 'ablate and pace' strategy for the treatment of atrial fibrillation.[40] Importantly, however, there is no evidence for the routine use of cardiac resynchronization therapy to remedy dyssynchrony in HF-PEF.

Alternate management strategies: are there relevant comorbidities?

Non-cardiac comorbidities are common in HF patients and are a recognized contributor to adverse outcomes including hospitalization and mortality.[41] Although comorbidities are prevalent in both HF-PEF and HF-REF, the contribution of non-cardiovascular illness to the total hospitalization burden is greater in HF-PEF than in HF-REF.[42] In the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, nearly 40% of deaths in HF-PEF patients were attributed to non-cardiovascular causes, with diabetes, chronic obstructive pulmonary disease, and renal dysfunction identified as key predictors of overall mortality.[43]

Although comorbid disease may be expected to increase the risk of non-cardiovascular outcomes, it seems increasingly clear that non-cardiovascular illness may also contribute to deterioration of cardiovascular function in HF-PEF. Comorbidities including obesity, diabetes, anaemia, and chronic kidney disease have each been associated with unique structural and functional changes in the heart and vasculature in HF-PEF patients,[44] and the cumulative burden of comorbidities is strongly associated with the severity of abnormalities in systolic and diastolic function.[45]

Based on these observations, Paulus and Tschöpe have postulated a novel pathophysiologic paradigm for HF-PEF in which cardiovascular abnormalities are understood as the downstream consequence of comorbidity-driven systemic inflammation that produces coronary microvascular endothelial dysfunction.[46] Endothelial inflammation generates reactive oxygen species and reduces nitric oxide bioavailability, which in turn reduces levels of cyclic guanosine monophosphate (cGMP) and lowers activity of protein kinase G (PKG). Declining PKG activity is postulated to accelerate pro-hypertrophic signalling and increase myocyte stiffness by promoting hypophosphorylation of titin, enhancing diastolic dysfunction and ventricular stiffening. Recent evidence suggests that enhanced passive myocardial stiffness as a consequence of changes in collagen and titin homeostasis may be a central mechanism in the development of HF-PEF, providing experimental support for this hypothesis.[47]

Collectively, these data suggest that targeted management of key comorbidities including chronic obstructive pulmonary disease,

anaemia, iron deficiency, diabetes, chronic kidney disease, obesity, and obstructive sleep apnoea may have benefits in HF-PEF, though there is limited data to guide what specific treatment approaches are most effective.[48] In the absence of data specific to HF-PEF, aggressive management of these illnesses according to published disease-specific guidelines may reduce their contribution to the burden of non-cardiovascular morbidity and mortality

Revisiting Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist: a role for spironolactone?

Although spironolactone had no effect on the primary composite of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest in TOPCAT, *post hoc* analyses have highlighted a nearly 4-fold variance in the composite event rates between the 1678 patients randomized from Russia and Georgia compared with the 1767 enrolled from the United States, Canada, Brazil, and Argentina (the Americas; event rates in spironolactone and placebo-treated patients 10.4 and 12.6 per 100 patient-years in the Americas and 2.5 and 2.3 per 100 patient-years in Russia/Georgia, respectively).[49] Profound regional differences in the basic demographics of the patients enrolled, combined with lack of expected changes in potassium and creatinine in response to spironolactone treatment in Russia/Georgia have raised questions about whether or not the enrolment criteria were uniformly applied. Amongst patients with the expected event rates for an HF-PEF population enrolled in the Americas, the hazard ratio for treatment with spironolactone was 0.82 (95% CI, 0.69–0.98); in Russia/Georgia, it was 1.10 (95% CI, 0.79–1.51). Although there was no statistical interaction between treatment and region with regard to the primary outcome, these data suggest that regional variations in enrolment may have obscured a treatment benefit of spironolactone in the overall study. Although not powered to examine clinical outcomes, the Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial did demonstrate that spironolactone improves diastolic function (measured by *E*/*e*′) in patients with HF-PEF.[50] Accordingly, in the absence of alternative evidence-based pharmacologic therapy, clinicians treating HF-PEF patients who meet the TOPCAT inclusion criteria (HF-PEF with prior hospitalization for HF or elevated natriuretic peptide levels) may wish to consider utilization of spironolactone, being mindful to monitor carefully for hyperkalaemia and worsening renal function. This recommendation to consider spironolactone for selected patients with HF-PEF is included in a recent update to the Canadian Cardiovascular Society Guidelines.[51]

Hope for heart failure and preserved ejection fraction? New therapies on the horizon

New pathophysiologic models for HF-PEF have spawned a number of clinical trials of novel pharmacologic therapies targeting inflammation, deficient cGMP/PKG signalling, and comorbid medical illness. A pilot study of the recombinant IL-1 receptor antagonist anakinra, in patients with HFPEF, found that exercise capacity could be improved after 14 days of treatment[52] and a longer-term trial of this approach to HFPEF is currently underway (DHART-2, clinical trials.gov, NCT02173548). Although the NEAT-HFPEF trial recently reported adverse impacts of isosorbide mononitrate on exercise capacity in HF-PEF patients,[53] ongoing studies are examining the effect of inhaled nitrite (NCT02262078) as an alternative approach to increasing nitric oxide bioavailability and stimulating the cGMP pathway based on promising data from acute haemodynamic studies.[54] Phosphodiesterase (PDE) type 5 inhibitors limit breakdown of cGMP, but do not improve exercise capacity in HF-PEF.[55] However, since cGMP deficiency in HF-PEF may not arise from excessive PDE activity, molecules that enhance cGMP activity independent of nitric oxide may be more effective. The SOCRATES-PRESERVED[56] trial will examine whether the soluble cyclic GMP stimulator vericiguat can improve NT-proBNP and left atrial volume at 12 weeks in patients with HFPEF. Enhancing endogenous levels of natriuretic peptides and other endogenous vasodilators through inhibition of neprilysin may be another effective approach for stimulation of the cGMP pathway. The dramatic impacts of neprilysin inhibition in HF-REF[57] and the promising results of the PARAMOUNT trial in which treatment with LCZ696 lowered NT-proBNP, reduced LA volume, and improved functional capacity relative to valsartan[58] have fuelled a definitive phase III trial of this approach in HF-PEF (PARAGON-HF, NCT01920711).

A trial of IV iron repletion in patients with HF-PEF will determine whether treatment of iron deficiency has benefits comparable with those that have been observed in HF-REF.[59] Trials of ivabradine (to slow the sinus rate, EduraCT 2012-002742-20) and rate adaptive pacing (to enhance the heart rate response to exercise, RAPID-HF, NCT02145351) promise to further clarify the optimal approach to heart rate management in HF-PEF. Other non-pharmacologic therapies that are being explored include renal sympathetic denervation (DIASTOLE,[60] NCT01840059, NCT02041130) and a novel atriotomy device (to permit decompression of the left atrium by providing a left–right shunt, reduce LAP-HF[61]) though most of these early phase studies are targeted at safety and intermediate endpoints rather than long-term clinical outcomes.

Summary

Despite the disappointing results of randomized clinical trials of pharmacologic therapy in HF-PEF, treatments are available to improve symptoms and clinical outcomes for many patients. Clinicians must remember that the syndrome of HF-PEF is comprised of a number of diverse pathophysiologic entities. Evaluation of the patient with HF-PEF begins with a thorough clinical assessment to refine the diagnosis, systematically identifying patients with valvular heart disease, myocardial disease, pericardial disease, renovascular disease, and pulmonary arterial hypertension that may direct targeted intervention. For those with 'isolated' HF-PEF, aggressive decongestion and optimization of filling pressures with diuretics (with or without haemodynamic monitoring) as well as attention to reversible factors that may exacerbate diastolic dysfunction such as hypertension, coronary artery disease, and atrial fibrillation may improve functional capacity and clinical outcomes. Treatment of

comorbidities including obesity, diabetes, sleep apnoea, chronic kidney disease, iron deficiency, and anaemia helps to limit the burden of non-cardiovascular morbidity and may influence disease progression. In the face of pressing clinical need and the lack of available evidence-based treatment, treatment with spironolactone may be appropriate for many patients with HF-PEF despite the overall neutral results of TOPCAT, being mindful of the need to monitor potassium and creatinine. A wide range of novel therapies under investigation in the next generation of randomized trials of HF-PEF raises the hope for availability of targeted pharmacologic and device therapies with unequivocal benefit in the coming decade.

Authors' contributions

A.S.D. and P.S.J. acquired the data, conceived and designed the research, drafted the manuscript, and made critical revision of the manuscript for key intellectual content.

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