Heart failure with preserved ejection fraction (HFpEF) is now recognized as a major and growing public health problem worldwide. Yet significant uncertainties still surround its pathophysiology and treatment, leaving clinicians in a dilemma regarding its optimal management. Whether HFpEF and heart failure with reduced ejection fraction (HFrEF) are two distinct entities or two ends of a common spectrum remains a matter of debate. In particular, the lack of benefit observed with renin–angiotensin system blockers has raised questions regarding our understanding of the pathophysiology of HFpEF. New paradigms including a prominent role of co-morbidities, inflammation, endothelial dysfunction, and pro-hypertrophic signalling pathways have been proposed. Recent proof-of-concept trials using a phosphodiesterase inhibitor, a mineralocorticoid receptor antagonist, an angiotensin receptor/neprilysin inhibitor, a soluble guanylate cyclase stimulator, or a sinoatrial blocker provide important insight for the development of novel therapeutic strategies in HFpEF.

Keywords: Heart failure • Pharmacology • Outcomes • Ejection fraction

Introduction

Large epidemiologic studies demonstrated that heart failure (HF) could occur in the presence of a normal LVEF, and patients with so-called HF with preserved ejection fraction (HFpEF) may represent up to half of the HF population. In contrast to heart failure with reduced ejection fraction (HFrEF), outcomes in HFpEF have not improved over the last decades, underscoring our continued lack of effective therapies for this important syndrome.

The purpose of this review is to provide a global perspective on HFpEF, to discuss the controversies surrounding the disease syndrome, to analyse the reasons for failure of clinical trials to improve outcomes, and to gain insight from recent proof of concept trials.

Is heart failure with preserved ejection fraction a specific syndrome?

Does the syndrome of heart failure with preserved ejection fraction exist?

The concept that HFpEF existed as an entity was challenged until two decades ago, ESC current guidelines now fully acknowledge HFpEF as an important HF syndrome, in line with robust evidence that (i) HFpEF comprises almost half the HF population in epidemiologic studies; (ii) classic haemodynamic changes of HF are present in HFpEF [elevated left ventricular (LV) filling pressures and abnormal vasorelaxation in both the systemic and pulmonary circulations]; and (iii) neurohormonal activation characteristic of HF (renin–angiotensin–aldosterone axis, sympathetic nervous system) also occurs in HFpEF.

Is heart failure with preserved ejection fraction just a transitory stage in the heart failure spectrum or is it a distinct disease phenotype?

The dilemma of whether to consider HFpEF as part of the same disease process as ‘conventional’ HFrEF, as opposed to a distinct disease entity in itself, remains unresolved (Figure 1). The demonstration of a unimodal distribution of LVEF in patients with HF from the CHARM Programme and the IMPROVEMENT of Heart Failure Programme; the existence of subtle LV systolic dysfunction in HFpEF and of diastolic dysfunction in HFrEF as well as the progression to eccentric LV remodelling and HFrEF in hypertensive heart disease, all argue for HFpEF and HFrEF being overlapping syndromes or stages in the same disease process.
However, a bimodal distribution of LVEF was revealed after accounting for the larger proportion of patients with low ejection fraction (EF) enrolled in the CHARM Programme\textsuperscript{20} and in registries.\textsuperscript{21} Two independent studies of patients with chronic HF with a wide range of EF\textsuperscript{12,22} have also confirmed the bimodal distribution of EF among patients with HF, thus providing strong argument for two separate diseases. In addition, the evolution of preserved to reduced EF in hypertensive heart disease is a rare occurrence and is largely attributable to an interim myocardial infarction in these uncommon cases.\textsuperscript{18,23}

Finally, despite overlapping systolic and diastolic abnormalities, there are fundamental differences in the pattern of LV remodelling at the chamber and ultra-structural levels between HFpEF and HFrEF. Left ventricular chamber dilation (eccentric remodelling) is a specific characteristic of HFrEF, whereas, in HFpEF, chamber size is normal or near normal with increased wall thickness relative to chamber dimension (concentric remodelling).\textsuperscript{5,9,24–26} These distinct structural changes in HFrEF vs. HFpEF are also associated with distinct functional consequences involving in particular the LV end-systolic pressure—volume relationship.\textsuperscript{17,24,29,30} The slope of the end-systolic pressure—volume relationship, or end-systolic elastance, is markedly reduced in HFrEF but elevated in HFpEF (Figure 2A). As a result, patients with HFrEF respond favourably to arterial vasodilators, with minimal drop in blood pressure and substantial improvement in stroke volume.\textsuperscript{30} In contrast, the steeper end-systolic pressure—volume relationship in HFpEF implies a marked sensitivity to volume changes and substantial drops in blood pressure with vasodilator therapy (Figure 2B). These differences may partially explain the failure of vasodilators to improve outcomes in clinical trials for HFpEF\textsuperscript{31–33} unlike what was observed in HFrEF.

Differences between HFpEF and HFrEF extend to the tissue and to the cellular level (Table 1): cardiomyocytes are narrow and elongated in HFrEF, with reduced myofibrillar density, whereas myocyte diameter and resting tension are both increased in HFpEF. At the subcellular level, there is an increased ratio of the stiffer isoform of the macromolecule titin in HFpEF compared with HFrEF, which may contribute to higher resting tension and the larger drop in tension in response to phosphorylation. Finally, at the level of the interstitium, matrix collagen turnover differs between HFrEF and HFpEF, where changes in matrix metalloproteinases and their inhibitors favouring increased extracellular matrix degradation appear to predominate in HFrEF.\textsuperscript{28,34–38,40}

**Figure 1** Arguments for heart failure with preserved ejection fraction as a transitory stage to heart failure with reduced ejection fraction (left) vs. heart failure with preserved ejection fraction as a distinct entity from heart failure with reduced ejection fraction (right). LV, left ventricular; EF, ejection fraction.

Does heart failure with preserved ejection fraction simply represent a collection of co-morbidities rather than a pathophysiologically distinct entity?

Since HFpEF is a disease of the elderly, it is not surprising that age-related cardiovascular (CV) and non-cardiovascular co-morbidities are highly prevalent among HFpEF patients.\textsuperscript{4} Indeed, the Charlson index, a weighted prognostic score of co-morbidity, was $\geq 3$ in 70% of community-based HFpEF patients.\textsuperscript{25} Co-morbidities herald the onset of symptomatic de-compensation in HFpEF, contribute to ventricular-vascular dysfunction, influence functional status and impact prognosis.\textsuperscript{29,41–43}
The recognition of the importance of co-morbidities in HFpEF has led some to question if HFpEF simply represents a collection of co-morbidities in elderly breathless patients, rather than a distinct disease entity. However, a comparison of mortality in patients with co-morbidities in elderly breathless patients, rather than a distinct disease entity, has led some to question if HFpEF simply represents a collection of co-morbidities.

Table 1: Cellular, subcellular, and interstitial differences between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFpEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyocyte diameter</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Myofibrillar density</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Passive cardiomyocyte resting tension</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiomyocyte calcium sensitivity</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Abnormal phosphorylation of sarcomeric proteins</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Titin isoform N2BA/N2B ratio</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Myocardial protein kinase G activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Myocardial oxidative stress</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Myocardial cyclic guanosine monophosphate concentration</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Myocardial pro-B-type natriuretic peptide-108 expression</td>
<td>↔/↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Mysial collagen volume fraction</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Perivascular collagen volume fraction</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Scar-related collagen volume fraction</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Endomyocardial MMP-1/TIMP-1 ratio</td>
<td>↔/↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Myocardial advanced glycation end products in diabetic HF</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

References: 29–39 MMP-1, matrix metallo protease-1; TIMP-1, Tissue Inhibitor of MetalloProtease-1.

The term ‘diastolic HF’ was first coined to reflect the leading pathological factor believed to cause the syndrome—LV diastolic dysfunction. In a landmark study, abnormalities in LV relaxation and compliance were uniformly demonstrated in 47 cases of HF with normal EF. However, population-based studies also showed that LV diastolic dysfunction was present in a large proportion of community-based adults without HF, and that patients with ‘systolic HF’ were even more likely to have moderate/severe diastolic dysfunction compared with patients with so-called ‘diastolic HF’. Nonetheless, progression of LV diastolic dysfunction was found to be a major mechanism distinguishing HFpEF from age-, sex-, and body-size-matched healthy controls and hypertensive individuals without HF in the general community.

Other mechanistic studies challenged the concept that HFpEF was a uniform syndrome of ‘diastolic HF’. These studies described various abnormalities, including abnormal ventricular–arterial coupling with exercise, impaired systemic vasodilator reserve, chronotropic incompetence, myocardial contractile dysfunction despite a normal EF, left atrial dysfunction, pulmonary hypertension with intrinsic pulmonary vascular disease, endothelial dysfunction, and volume overload related to extra-cardiac causes.

Figure 2: (A and B) Pressure–volume loop characteristics in heart failure with preserved ejection fraction (black) and heart failure with reduced ejection fraction (red) in baseline conditions (A), and in response to vasodilators (B). (A) Curved arrow depicts the steeper end-systolic pressure–volume relationship in heart failure with preserved ejection fraction compared with heart failure with reduced ejection fraction. (B) Pressure–volume loops before (solid) and after (dotted) administration of vasodilators. Arrows contrast the drop in blood pressure and changes in stroke volume between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction in response to vasodilators. In heart failure with reduced ejection fraction, administration of arterial vasodilators results in minimal drop in blood pressure and substantial improvement in stroke volume. In contrast, the steeper end-systolic pressure–volume relationship in heart failure with preserved ejection fraction results in more exaggerated drops in blood pressure with vasodilator therapy, with potential reduction in stroke volume.
It is possible that each of these mechanistic studies selected a specific subset of patients with HFpEF: only 2% of hospitalized patients with HFpEF were eligible in a study of static and dynamic LV diastolic function.53 This, in turn, suggests that HFpEF is not homogeneous, but is rather a heterogeneous condition consisting of several physiopathological subtypes.54 Those with exercise-induced diastolic dysfunction, those with chronic volume overload and those with associated right HF and/or pulmonary hypertension. The phenotype heterogeneity of HFpEF is probably more complex as illustrated in Table 2.

The importance of recognizing the heterogeneity of the physiopathology in HFpEF is highlighted by the fact that a ‘one size fits all’ approach for clinical trials in HFpEF has been disappointing and that treatments directed at HFpEF as a large undifferentiated group have failed to improve outcomes. Improved phenotypic characterization of different mechanistic sub-types might therefore allow the design of more targeted HFpEF clinical trials.

### How is the diagnosis of heart failure with preserved ejection fraction established?

The accurate diagnosis of HFpEF remains a challenging and controversial topic. Several diagnostic criteria have been proposed.55–58 The original criteria55 were criticized for a lack of sensitivity, since the definitive diagnosis mandated determination of EF within 72 h of presentation and invasive demonstration of LV diastolic dysfunction—a situation which is rarely performed or even available to clinicians. The stipulation that EF had to be measured during periods of acute de-compensation was deemed unnecessary in later guidelines, because these acute measurements were shown to be similar to those performed after in-hospital stabilization.59

The need for invasive demonstration of LV diastolic abnormalities was also questioned, because these were shown to be uniformly present in patients with clinical HF and a normal EF.5

However, given the lack of specificity of symptoms of HF, as well as the co-existence of age-related co-morbidities that could explain the symptoms, some form of demonstration of LV diastolic dysfunction is deemed necessary: the ESC consensus provided practical recommendations on the evaluation of diastolic dysfunction using echocardiography (both Doppler-based as well as structural assessments of LV mass and left atrial size), measurement of natriuretic peptides, and the presence of atrial fibrillation, in addition to cardiac catheterization.57

In general, all proposed diagnostic criteria to date share three features in common (Figure 3): (i) clinical signs or symptoms of HF; (ii) evidence of preserved EF; and (iii) evidence of abnormal LV structure and/or diastolic dysfunction. Some issues are not fully addressed in the available guidelines: (i) the lack of sensitivity in patients who have increased filling pressures only during exercise but not at rest; (ii) the phenotypic diversity of HFpEF and the identification of pathophysiologically distinct subsets; (iii) the impact of important co-morbidities on diagnostic thresholds. Other areas of continued controversy include the optimal cut-off to define ‘preserved’ or ‘normal’ EF, and how to classify patients who are in the ‘grey zone’ (40–50%) or those who transition between EF zones.60 Furthermore, none of the published criteria have been prospectively tested for their diagnostic utility in large cohorts of unselected patients.

### How do patients with heart failure with preserved ejection fraction die?

Since multiple age-related co-morbidities may co-exist in patients with HFpEF, knowledge of cause-specific mortality is important to discern the risk related to the co-morbidity vs. the risk associated with HFpEF itself.

Numerous studies have now shown that the mortality burden of HFpEF is substantial, ranging from 10 to 30% annually, and is higher in epidemiologic studies than clinical trials.61 The pooled death rate in HFpEF was 121 [95% confidence interval (CI): 117, 126] deaths per 1000 patient-years in a meta-analysis of 31 studies.62 Mortality rates are clearly elevated compared with age- and co-morbidity-matched controls without HF,46 and may be as high as in HFrEF.2,3 The majority of deaths in HFpEF are CV deaths, 51–60% of deaths in epidemiologic studies,43 and ~70% in clinical trials. Among CV deaths, sudden death and HF death are the leading cardiac modes of death in HFpEF clinical trials.54,62 However, compared with HFrEF, the proportions of CV deaths, sudden death and HF deaths are lower and conversely, non-cardiovascular death is higher in HFpEF.52

A greater non-cardiac co-morbidity burden in HFpEF offers a potentially simple explanation for the mortality differences between epidemiologic studies and clinical trials, or between HFpEF and HFrEF. However, the extent to which non-cardiac co-morbidities predict death in HFpEF remains unclear, and non-cardiac co-morbidities alone do not explain mortality differences between different HF cohorts. The extent of coronary artery disease appears

### Table 2 Heterogeneity of heart failure with preserved ejection fraction

<table>
<thead>
<tr>
<th>Pathophysiologic mechanisms</th>
<th>Clinical phenotypes</th>
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<tbody>
<tr>
<td>LV diastolic dysfunction</td>
<td>‘Pure’ diastolic heart failure</td>
</tr>
<tr>
<td>Systolic LV-arterial stiffening</td>
<td>‘Common’ HFpEF (associated with hypertension, obesity, diabetes)</td>
</tr>
<tr>
<td>Abnormal LV-arterial coupling</td>
<td>Coronary artery disease—associated</td>
</tr>
<tr>
<td>Myocardial contractile dysfunction</td>
<td>Early HFpEF (with exercise-induced diastolic dysfunction)</td>
</tr>
<tr>
<td>Impaired exercise reserve</td>
<td>Pulmonary hypertension and/or right heart failure</td>
</tr>
<tr>
<td>Chronotropic incompetence</td>
<td>Atrial fibrillation—predominant</td>
</tr>
<tr>
<td>Left atrial dysfunction</td>
<td>Non-cardiac cause—related volume overload (such as chronic kidney disease or anaemia)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Volume overload</td>
<td></td>
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<tr>
<td>Endothelial dysfunction</td>
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</table>
to be inversely related to non-cardiovascular deaths in both the Olmsted County community-based cohort and in the clinical trial population from TIME-CHF. A potential explanation for these observations is that patients with HFpEF ‘escape’ death related to coronary artery disease and subsequently die from their non-cardiac co-morbidities. Alternatively, patients with coronary artery disease may have been more likely to ‘transition’ to HFrEF following a myocardial infarction, thus enriching the HFrEF population with more coronary heart deaths.

How are patients with heart failure with preserved ejection fraction treated?

Current international guidelines acknowledge a lack of evidence in the management of HFpEF. The ESC recommends the use of diuretic agents to relieve breathlessness and oedema, an optimal management of hypertension or myocardial ischaemia, and to control heart rate since elevated heart rate is usually poorly tolerated in these patients with stiff LV. The pattern of HF medications prescriptions differs significantly between HFpEF and HFrEF. In the large OPTIMIZE HF registry, a lower rate of prescription of angiotensin converting enzyme (ACE) inhibitors, aldosterone antagonists, β-blockers, loop diuretics, and digoxin as well as a higher rate of use of amiodipine were observed in patients with HFpEF than in those with HFrEF both at admission and discharge. This trend also existed comparing patients with EF >50% and those with 40% ≤ EF ≤ 50%.

The international meta-analysis MAGGIC using individual data from randomized clinical trials, from observational studies and from management strategy controlled trials found also different patterns of prescription in HFpEF and in HFpEF patients.

β-Blockers and calcium-channel blockers

Slowing the heart rate should result in an increase in the diastolic filling period in an abnormally stiff LV with prolonged relaxation. However, slowing the heart rate in the absence of increased heart rate tends to prolong diastasis where transmitral flow plays a minor role.

In addition, there is a high prevalence of chronotropic incompetence in HFpEF which is associated to exercise limitation, and chronotropic reserve might be a key factor to increase cardiac output during exercise. In this context, the role of β-blockers remains uncertain. Nebivolol was tested in 2128 patients >70 years with a history of HF or known EF <35% in the SENIOR trial. There was a 14% reduction in the primary composite outcome (all-cause mortality or CV admission). A similar benefit was observed in those patients with an EF >35% or <35%. As the threshold of EF used was very low (35%), no definite conclusion can be drawn from this subgroup of patients about the applicability of results to patient with HFpEF where EF ≥50%. Moreover, an echocardiographic sub-study did not show any effect of Nebivolol on parameters of systolic or diastolic dysfunction.

In another study, ELANDD, Nebivolol did not influence symptoms or exercise capacity in HFpEF; however, there was a direct correlation between the decrease in peak heart rate and the decrease in peak oxygen consumption in the Nebivolol group. In the OPTIMIZE HF registry, a risk and propensity-adjusted model showed no significant relationship between discharge use of β-blockers and mortality and/or rehospitalization rate at 60–90 days.
Finally, in the COHERE registry (Carvedilol Heart Failure Registry), the benefit of Carvedilol on mortality, clinical status, and need for hospitalizations was lower in patients with EF > 40%. Conversely, prescription of β-blockers was associated with a marked mortality reduction in a cohort of HFpEF patients followed up for 25 months. Data regarding the heart rate-lowering calcium-channel blocker verapamil are scarce. A small-size study suggested some improvement of symptoms and of exercise capacity in these patients.

There is, therefore, no conclusive evidence for the benefit of β-blockers or verapamil in HFpEF.

ACE inhibitors and angiotensin receptor blockers

Three outcome trials have been conducted in HFpEF with ACE inhibitors or angiotensin receptor blockers (ARBs) (Table 3). The rationale in the use of a renin–angiotensin system antagonist (RAS) is to block the pro-hypertrophic and pro-fibrotic effects of angiotensin II.

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM Preserved) trial included 3023 patients with an EF > 40% and compared Candesartan, uptitrated to 32 mg/day to placebo (Pbo). This trial failed to demonstrate a significant benefit on CV mortality, whereas a reduction in HF hospitalizations was observed.

The Perindopril for Elderly People with Chronic Heart Failure trial (PEP CHF) enrolled elderly patients with EF > 40% and with echocardiographic evidence of diastolic dysfunction. No reduction in the occurrence of the primary composite endpoint (all-cause mortality or HF hospitalization) was observed in the Perindopril arm titrated to 4 mg/day. A long recruitment period with, as a result, a number of crossovers together with the limited sample size, might explain the neutral result of this trial. A post hoc analysis performed after 1 year of follow-up, suggested indeed a favourable trend in the Perindopril arm.

The large Irbesartan in HF with Preserved Systolic Function trial (I-PRESERVE) enrolled 4128 elderly HF patients with EF > 45% who were randomly assigned to Irbesartan or Pbo. No reduction in the composite outcome (all-cause mortality or CV hospitalization) or in any secondary outcome was observed after nearly 50 months of follow-up.

These disappointing results with ACE inhibitors/ARBs contrast with the benefit observed in HFrEF. However, in a large prospective cohort of unselected HFpEF patients form Sweden, the use of a RAS antagonist was associated with a lower all-cause mortality.

Digoxin

In the Digitalis Interaction Group trial (DIG), a subgroup of 988 patients with EF > 45% was randomized to Pbo or to Digoxin. No difference was observed in all-cause, HF, or CV mortality, or in the

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Outcome trials in heart failure with preserved ejection fraction</th>
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<tr>
<td></td>
<td>PEP CHF</td>
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<td>No. of patients</td>
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<tr>
<td>Mean follow-up (months)</td>
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<td>Age at inclusion (years)</td>
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<tr>
<td>Mean age (years)</td>
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</tr>
<tr>
<td>Men/women %</td>
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<tr>
<td>HF aetiology</td>
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<tr>
<td>Ischaemic</td>
<td>26a</td>
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<tr>
<td>Hypertensive</td>
<td>79a</td>
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<tr>
<td>EF% at inclusion</td>
<td>LV WMI** 1.4–1.6</td>
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<tr>
<td>BNP/NT proBNP at inclusion (pg/mL)</td>
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<tr>
<td>NT proBNP/BNP median value at baseline (pg/mL)</td>
<td>453 (Pbo)/335 (Active)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.5</td>
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<tr>
<td>6 min walk test (m)</td>
<td>297 (Pbo)/290 (Perindopril)</td>
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<tr>
<td>Primary composite endpoint</td>
<td>All-cause mortality/HF hospitalization</td>
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<tr>
<td>Hazard ratio</td>
<td>0.92 (0.70–1.21)</td>
</tr>
<tr>
<td>P value</td>
<td>0.54</td>
</tr>
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</table>

aPrior hypertension/prior myocardial infarction for PEP CHF.
bHypertension history TOP CAT. BMI, Body mass index; BNP, B type Natriuretic Peptide; WMI, wall motion index.

HFrEF: a clinical dilemma

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A composite outcome of HF death or hospitalization after 37 months of follow-up. However, a trend towards a reduction of HF hospitalization was observed.

**Why did the prior trials fail?**

**Patient factors**

The identification of patients with HfP EF is particularly challenging since: (i) signs and symptoms of HF are not specific and may be observed in other conditions such as obesity, anaemia, renal dysfunction, or pulmonary disease—all conditions which are frequently associated with HfP EF; (ii) there is no real consensus on the definition of normal EF: The ESC guidelines recommend a threshold of 50% but randomized clinical trials conducted in HfP EF have used lower values (>40% CHARM Preserved, >45% I-PRESERVE), which might indicate an already significantly altered systolic performance, and hence a clinical profile closer to that observed in HFrEF; (iii) invasive confirmation of the presence of LV diastolic dysfunction is not feasible in daily practice and non-invasive markers are therefore needed: a central place has been given to the echo-Doppler parameters of diastolic dysfunction was PEP CHF.33 The concern was that of recent proof of concept studies, including Aldo-DHF, PARAMOUNT, or RELAX, reveals notable heterogeneity with regards to age or level of neurohormonal stimulation as assessed by B type Natriuretic Peptide (BNP)/NT proBNP plasma levels (Table 4). This suggests differences in the stage of disease of patients enrolled in these trials. Elderly HfP EF patients with a long-standing history of hypertension and significant accumulation of cardiac extracellular matrix may be poor responders to any pharmacological intervention (too sick to benefit).

For instance a post hoc analysis of I-PRESERVE showed that Irbesartan improved clinical outcomes in those patients with below the median values of NT proBNP but not in those with higher levels.78

It is therefore possible that a pharmacological intervention using an ARB would benefit at an earlier stage of the disease.

On the other hand, it was argued that spironolactone was not ideally tested in Aldo-DHF since patients were ‘too well’ and had only mild cardiac dysfunction based on EF/ value, NT proBNP plasma levels, and exercise capacity. This explanation was put forward to explain the lack of improvement of exercise capacity in patients with early stage HfP EF.79 Yet, in the Exercise Training in Diastolic Heart Failure—Pilot (Ex-DHF-Pilot) Study, exercise training was effective at increasing peak VO2 in patients with early stage HfP EF. Furthermore, half of the patients in Aldo-DHF had disease that was advanced enough to fulfil ESC criteria of HfP EF, and the effects of spironolactone on EF/ and peak VO2 in these patients were similar in those who did not fulfil the ESC criteria. It is therefore possible that pharmacological and non-pharmacological therapeutic approaches in HfP EF vary in their effects on exercise capacity at different stages of the disease.

**Table 4** Recent proof-of-concept studies

<table>
<thead>
<tr>
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<th>Aldo DHF</th>
<th>PARAMOUNT</th>
<th>RELAX</th>
</tr>
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<tbody>
<tr>
<td>Reference</td>
<td>99</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td>No. of patients</td>
<td>422</td>
<td>266</td>
<td>216</td>
</tr>
<tr>
<td>Drug</td>
<td>Spironolactone</td>
<td>Angiotensin receptor Nerylisin inhibitor (LCZ 696) vs. Valsartan</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Men/women (%)</td>
<td>48/52</td>
<td>43/57</td>
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</tr>
<tr>
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<tr>
<td>Baseline E/E'</td>
<td>12.7</td>
<td>12.4/13</td>
<td>16</td>
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<tr>
<td>6 min walk test (m)</td>
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<td>N/A</td>
<td>305 (Pbo)/308 (Sildenafil)</td>
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<tr>
<td>Target dose (mg/day)</td>
<td>25</td>
<td>400 (ARNi)/320 (Valsartan)</td>
<td>60–12 weeks</td>
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<tr>
<td>EF at inclusion (%)</td>
<td>≥50</td>
<td>≥45</td>
<td>≥50</td>
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<tr>
<td>NT proBNP at inclusion (pg/mL)</td>
<td>–</td>
<td>≥400</td>
<td>&gt;400 if elevated LV filling pressure</td>
</tr>
<tr>
<td>NT proBNP baseline geometric mean (pg/mL)</td>
<td>–</td>
<td>794 (ARNi)/870 (Valsartan)</td>
<td>–</td>
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<tr>
<td>Median (pg/mL)</td>
<td>148 (Pbo)/179 (Spironolactone)</td>
<td>828 (ARNi)/939 (Valsartan)</td>
<td>648 (Pbo)/757 (Sildenafil)</td>
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<tr>
<td>Primary endpoint</td>
<td>E/E'/peak VO2</td>
<td>Change NT proBNP</td>
<td>Change peak VO2</td>
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<tr>
<td>Duration</td>
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<td>12 weeks</td>
<td>24 weeks</td>
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</table>
Trial factors

The outcome trials PEP CHF and I-PRESERVE were associated with a prolonged recruitment period. This is likely attributable to the inherent difficulties in confirming the clinical diagnosis of HFpEF and the need for cardiac imaging expertise. As a result, a high rate of drop-out was observed together with a significant number of randomized patients receiving an open-label RAS antagonist during the course of the trials. In I-PRESERVE, approximately one-fifth of patients randomized to Irbesartan were prescribed an ACE inhibitor during the follow-up period and one-third dropped out of the active arm. Similarly in PEP CHF, 40% of the patients randomized to Perindopril and 36% of those randomized to Pbo stopped the study treatment and one-third received an open-label ACE inhibitor.

As discussed above, CV mortality and morbidity are the most prevalent outcomes in HFpEF.64,65 However, the proportion of patients dying of non-cardiovascular causes increases with EF.13 CV drugs might therefore have a limited effect in a condition where the non-cardiovascular mode of death is more than in HFrEF.

Drug factors

The final pathway of ACE inhibitors and ARBs is to inhibit the synthesis or the action of angiotensin II and Aldosterone which promote cardiac fibrosis and hypertrophy. Furthermore, ARBs have been shown to be more efficient on LV hypertrophy than β-blockers in hypertension.81 There is, therefore, no clear explanation why blockade of the RAS system failed to bring benefit in HFpEF.

A lower level of neurohormonal stimulation assessed by NT proBNP/BNP has been reported in HFpEF than in HFrEF and up to one-third of patients show plasma levels within the normal range.82 However, in HFpEF, NT proBNP elevation remains a very powerful predictor of poor outcome.83 Also, increased plasma levels of peripheral collagen turnover markers were not influenced by Irbesartan in I-PRESERVE although fibrosis and increased extracellular matrix are believed to be key factors in HFpEF.84

It is therefore possible that a differential pattern of neurohormonal activation and its downstream consequences or of cardiac remodeling plays a role in the lack of response reported so far in HFpEF with RAS antagonists.

Overall, the lack of benefit of traditional HF therapies in HFpEF underscores our lack of understanding of the pathophysiology of this syndrome and emphasizes the fact that a uniform approach does not work in HFpEF. A paradigm shift in our understanding of the mechanisms that may be targeted in HFpEF, and the patients most likely to benefit from these targeted approaches, is urgently needed.

New paradigm in heart failure with preserved ejection fraction

A new paradigm based on observation of specific myocardial structural and functional changes observed in HFpEF has been put forward.85 This paradigm emphasizes the role of a pro-inflammatory state with widespread endothelial dysfunction, leading to reduced nitric oxide (NO) bioavailability in cardiomyocytes, reduced myocardial cyclic guanosine 3’,5’-monophosphate (cGMP) content and low-protein kinase-G activity (PKG).

The central role of the NO-cGMP–PKG pathway is described in this paradigm (Figure 4).51,86,87 Endothelial dysfunction occurs in diabetes and hypertension, both important risk factors for HFpEF, and causes oxidative stress with high levels of reactive oxygen species which interfere with NO production in endothelial cells. This leads to reduced NO bioavailability to adjacent cells such as...
cardiomyocytes. cGMP is the second messenger that plays a role in various key physiologic pathways, including CV homeostasis, cellular growth and contractility, and inflammation. Guanylate cyclases are enzymes that catalyse the conversion of guanosine-5’-triphosphate to cGMP. Membrane-bound particulate guanylate cyclase (pGC) serves as a receptor for natriuretic peptides, whereas soluble guanylate cyclase (sGC) acts as a receptor for NO. Subsequently, cGMP effectors include cGMP-dependent protein kinases, such as PKG. The disruption of the NO–cGMP–PKG signalling pathway can therefore explain the development of concentric LV remodelling, increased stiffness of the cardiomyocyte through hypo-phosphorylation of titin, and increased collagen deposition in HfPEF (Figure 4).

Lessons from recent proof-of-concept studies

Until now, attempts to target the NO–cGMP–PKG pathway in HfPEF have been unsuccessful (Table 4). Administration of exogenous nitrates or NO donors is dependent on bio-transformation to the active, NO-containing compound and is limited by tolerance in the long term or can even paradoxically cause endothelial dysfunction, oxidative stress, and release of endothelin-1.87

Phosphodiesterase-5 inhibitors

As cGMP is inactivated by Phosphodiesterase-5 (PDE-5), blockade of cGMP degradation by inhibition of PDE-5 could have beneficial effects such as improvement in cardiac relaxation and LV reverse remodelling.

Experimental data suggest that PDE-5 over-expression induces cardiac cardiomyocyte hypertrophy and that this is reversed by the selective PDE-5 inhibitor Sildenafil.88

A small clinical study showed that Sildenafil improved LV diastolic function, hypertrophy, and reduced pulmonary pressures after 12 months of exposure in HfPEF patients with pulmonary hypertension.89

However, these beneficial effects were not confirmed by the RELAX trial including 216 elderly HfPEF patients.90 After 24 weeks of treatment, no effect on maximal exercise capacity, on 6 min walking distance, on clinical status, quality of life, LV remodelling, or diastolic function was observed.

Several explanations have been put forward in order to explain these neutral results: absence of pulmonary hypertension, high prevalence of chronotropic incompetence, insufficient duration of the trial. Basal plasma levels of NT proBNP were also markedly elevated, suggesting that these patients were in an advanced stage of the disease and, therefore, less likely to benefit from this pharmacological intervention. Furthermore, it is postulated that impaired cGMP ‘production’, rather than increased ‘degradation’, may be the predominant pathophysiological mechanism in HfPEF. This may explain the relative lack of effectiveness of therapies targeting inhibition of cGMP degradation, and suggest that stimulation of cGMP production may be an important therapeutic strategy in HfPEF.

Soluble guanylate cyclase stimulators

Small molecules can directly stimulate the sGC pathway with a dual mode of action: the sensitization of sGC to endogenous NO by stabilizing the NO–sGC binding and direct stimulation of sGC via an NO-independent binding site.

The phase IIa Acute haemoDynamic effects of riociguat in patients with pulmonary hypertension Associated with diastolic heart failure (DILATE-I) study characterized the hemodynamic effects, safety, and pharmacokinetics of three different single doses of riociguat, a sGC stimulator, in patients with HfPEF and pulmonary hypertension.91 There was no significant change in the primary endpoint of peak change in mPAP from baseline to 6 h in the riociguat 2 mg arm vs. Pbo. Riociguat significantly increased stroke volume and decreased systolic blood pressure without significantly changing pulmonary vascular resistance, or heart rate and was well tolerated.

In the Soluble Guanylate Cyclase Stimulator Heart Failure Studies (SOCRATES)-preserved trial, a new oral sGC stimulator BAY1012189 will be tested in patients with worsening chronic HfPEF requiring hospitalization (clinicaltrials.gov identifier NCT01951638).

Neprilysin inhibitors

LCZ 696 is a complex molecule (angiotensin receptor Neprilysin inhibitor) which combines an inhibitory effect of Neprilysin (endopeptidase 24–11) together with an angiotensin receptor blocker. Neprilysin is the enzyme responsible for the degradation of biologically active natriuretic peptides. The blockade of Neprilysin increases intracellular cGMP and improves relaxation and hypertrophy.92 This new compound was tested against Valsartan in 301 HfPEF patients treated for 36 weeks in the PARAMOUNT trial.92

The primary endpoint was the change in NT proBNP, a marker of wall stress, from baseline to 12 weeks. LCZ 696 significantly reduced the plasma level of NT proBNP compared with Valsartan but the difference was no longer significant at 36 weeks. Left atrial volume and dimension were also favourably influenced at the end of the trial whereas there was no change in other echocardiographic parameters, including diastolic function.

A large outcome study is planned to determine if this new class might be beneficial in HfPEF (Efficacy and Safety of LCZ696 Compared with Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF], ClinicalTrials.gov Identifier: NCT01920711).

Mineralocorticoid receptor antagonists

Activation of the mineralocorticoid receptor by Aldosterone results in sodium retention, cardiac fibrosis, endothelial dysfunction, and cardiac hypertrophy.93 Small studies suggest that mineralocorticoid receptor antagonists (MRAs) might be beneficial in diastolic HF.94 In the Aldosterone receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial, 422 HFpEF patients were randomized to Spironolactone 25 mg/day or Pbo and followed up for 12 months.95 Diastolic function assessed primarily by the e’/e ratio on Doppler echocardiography was significantly but modestly improved by Spironolactone, along with reduction in LV mass and NT proBNP, whereas no change was observed in maximal exercise capacity, patient symptoms, or quality of life.
An explanation put forward to explain the lack of change in exercise capacity was the fact that patients enrolled in this trial had only mild cardiac dysfunction and modest symptom limitation at baseline. Of note, even in HFrEF where MRAs are considered a Class I therapy, spironolactone had only a marginal effect on functional capacity in HFrEF patients.96

The large outcome trial TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) has just been presented. It compares Spironolactone uptitrated to 45 mg/day vs. Pbo on a composite outcome of CV mortality, aborted cardiac arrest, or HF hospitalization in an elderly population of 3445 patients.97 TOPCAT failed to demonstrate a significant improvement in the primary outcome. However, there was a significant 17% risk reduction in HF hospitalizations, suggesting that spironolactone improves morbidity in HFrEF elderly patients.

Ranolazine
Ranolazine is a selective inhibitor of the late sodium (INa')current which is activated in HF and leads to Ca2+/ overload, impaired relaxation and pro-arrhythmic after depolarizations.98

The RALI DHF trial was a small trial including 20 patients which suggested that Ranolazine administered i.v. for 24 h modestly improved haemodynamic parameters but had no effect on relaxation.99

The acute phase was followed by 13 days of oral administration which did not result in any change of echocardiographic parameters, NT proBNP, or exercise performance.

Ivabradine
Ivabradine is an inhibitor of the sino atrial node if current which reduces heart rate when elevated. It has shown benefit in HFrEF in sinus rhythm.100 Selective heart rate reduction improves diastolic filling by prolonging the diastoile without significant isotrophic or inotropic effects.101

In a mouse model of diabetes with diastolic dysfunction, Ivabradine reduced effective arterial elastance, increased aortic distensibility and decreased LV end-systolic elastance.102 In addition, a favourable effect was observed on the activity of SERCA 2a, a key player in the uptake of calcium by the sarcoplasmic reticulum.

Recently, 61 patients with HFrEF and an increased baseline heart rate were assigned to Ivabradine 5 mg b.i.d. or Pbo for 7 days.103 A significant increase was observed in exercise capacity with a contribution from LV improved filling pressure response to exercise as reflected by e/e' ratio. The EDIFY study (EUDRA CT no 2012 002742-20) will enrol 400 HFrEF patients and will assess the effect of Ivabradine uptitrated to 10 mg b.i.d. on e/e' ratio as well as on other echocardiographic parameters, on 6 min walking distance, and on NT proBNP plasma levels after 8 months of follow-up.

Advanced glycation end products cross-link breakers
Increased diastolic LV stiffness is a marker of LV dysfunction induced by diabetes mellitus, a major co-morbidity in HFrEF. This has been related to myocardial deposition of advanced glycation end products (AGEs) which are formed by oxidative or non-oxidative reactions between proteins and carbohydrates and form cross-links in the extracellular matrix.104 AGEs cross-link breakers such as alagebrum chloride have been tested in experimental models and in a small open label clinical study enrolling 23 elderly patients with diastolic HF.105 After 16 weeks of follow-up, an improvement in diastolic function was observed. Whether this class might have beneficial effects in patients with HFrEF and diabetes needs to be evaluated in a properly designed large-scale and long-term clinical trial.

Other potential perspectives
Statsis
By blocking the activity of several Guanosine Triphosphate binding proteins, statins suppress LV hypertrophy and decrease collagen synthesis in experimental models.106,107 However, in the clinical area, only one small study suggested a beneficial effect of statins on mortality in HFrEF patients108 whereas in the GISSI HF trial, no benefit was observed with Rosuvastatin in the 10% of patients enrolled with relatively preserved EF.109

Calcium-cycling modulators
Ryanodine receptors which trigger calcium release from the intracellular stores, the sarcoplasmic reticulum, are dysfunctional in HF and lead to Ca2+/ leakage, impaired relaxation, and after depolarizations.110 A Ryanodine receptor stabilizer, K 201, has been tested in vitro with favourable effects111 but there are as yet no data on the clinical effects of this compound. Down-regulation of the sarcoplasmic reticulum Ca2+/ ATPase 2a isoform (SERCA2), which is responsible for the reuptake of calcium in the sarcoplasmic reticulum, is observed in HF and leads to impaired relaxation. A non-pharmacological approach using SERCA2 gene treatments by an adenovirus has been tested with some promising results in HFrEF.112 Whether this approach could be beneficial in HFrEF deserves consideration.

Micro-RNAs
In the last 5 years, evidence has rapidly accumulated indicating a pivotal role for micro-Ribonucleic acid (RNAs) (miRNAs), a class of small non-coding RNAs, in CV development and response to injury.113,114 Precursor ‘primary’ miRNAs undergo processing to the mature form which binds with complementary sequences on target messenger RNA and prevents translation and/or accelerates degradation of message RNA. Micro-RNAs may also return to the nucleus and act upon DNA as transcription factors. Micro-RNAs have been shown to be differentially expressed in the failing myocardium and to play an important role in progression of HF by targeting genes that govern diverse functions in LV remodelling.115 The strategy of replacement of miRNAs of interest or of blockade of potentially harmful miRNAs (anti-MIRs) is currently being tested in pre-clinical studies.

Exercise
Exercise training in chronic HF may improve symptoms and quality of life, via beneficial effects on endothelial function, central hemodynamics, inflammatory markers, neurohormonal activation, as well as skeletal muscle structure and function. The Ex-DHF-Pilot Study80 randomized 64 patients with HFrEF to supervised endurance/resistance training in addition to usual care or to usual care...
alone. Peak VO₂ increased with exercise training after 3 months and remained unchanged with usual care alone. Exercise training was also associated with improvements in a physical functioning score (36-Item Short-Form Health Survey), atrial reverse remodelling associated with improvements in a physical functioning score remained unchanged with usual care alone. Exercise training was also but need to be tested in properly designed clinical trials.

The accurate diagnosis and optimal pharmacological treatment of HfPcEF remain challenging. Progress has been made in the understanding of the pathophysiology of this condition, and there is increasing emphasis on therapeutic strategies aimed at altering specific signalling pathways. It is critical for future clinical trials to ensure a proper characterization of the phenotype of patients to be tested. Several novel approaches appear promising in pre-clinical or early clinical studies, but need to be tested in properly designed clinical trials.

Conflict of interest: M.K. is member of Steering Committee of studies on ivabradine and was member of the executive committee of I-Preserve sponsored by Bristol Myers Squibb. C.L. is funded by a clinical scientist award from the National Medical Research Council of Singapore, receive research grants from Boston Scientific, Medtronic and Vifor Pharma, and serve as a consultant for Bayer and Novartis.

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