

Controversies in cardiovascular medicine

Heart failure with preserved ejection fraction: a clinical dilemma

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Received 26 September 2013; revised 4 January 2014; accepted 27 January 2014; online publish-ahead-of-print 11 March 2014

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 sino atria, if current 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.¹ 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.^{2,3}

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;⁴ (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];^{5–8} and (iii) neurohormonal activation characteristic of HF (renin–angiotensin–aldosterone axis, sympathetic nervous system) also occurs in HFpEF.^{9,10}

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).^{11,12} The demonstration of a unimodal distribution of LVEF in patients with HF from the CHARM Programme¹³ and the IMPROVEMENT of Heart Failure Programme;¹⁴ the existence of subtle LV systolic dysfunction in HFpEF and of diastolic dysfunction in HFrEF;^{15–18} as well as the progression to eccentric LV remodelling and HFrEF in hypertensive heart disease;¹⁹ all argue for HFpEF and HFrEF being overlapping syndromes or stages in the same disease process.

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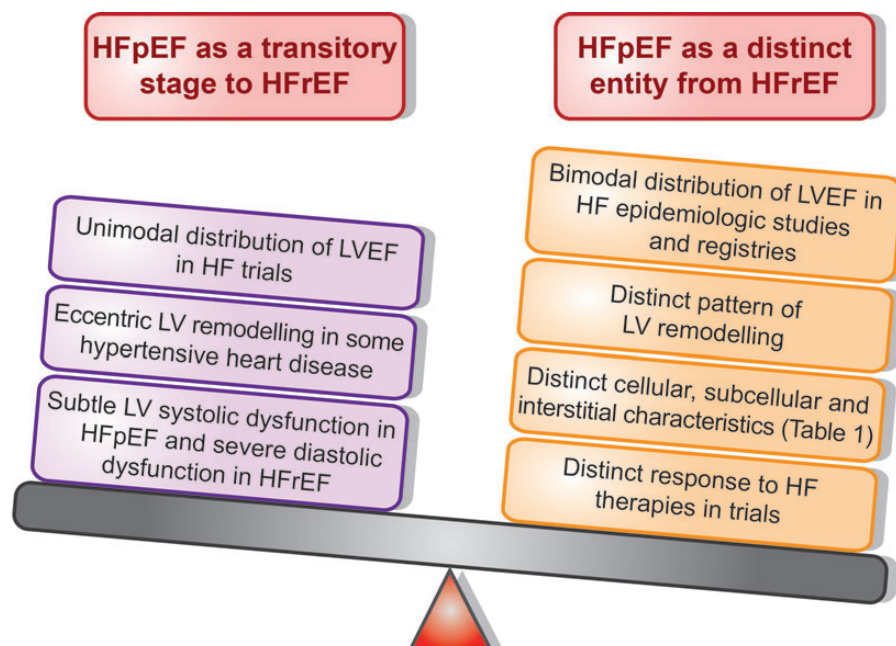


Figure 1 Arguments for heart failure with preserved ejection fraction as a transitory stage to heart failure with reduced ejection fraction (left) vs. heart failure with preserved ejection fraction as a distinct entity from heart failure with reduced ejection fraction (right). LV, left ventricular; EF,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

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 Programme²⁰ and in registries.²¹ Two independent studies of patients with chronic HF with a wide range of EF^{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.^{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).^{5,9,24–28} 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.^{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.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^{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 sub-cellular 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.^{28,34–38,40}

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.⁴ Indeed, the Charlson index, a weighted prognostic score of co-morbidity, was ≥ 3 in 70% of community-based HFpEF patients.²⁵ Co-morbidities herald the onset of symptomatic de-compensation in HFpEF, contribute to ventricular-vascular dysfunction, influence functional status and impact prognosis.^{39,41–43}

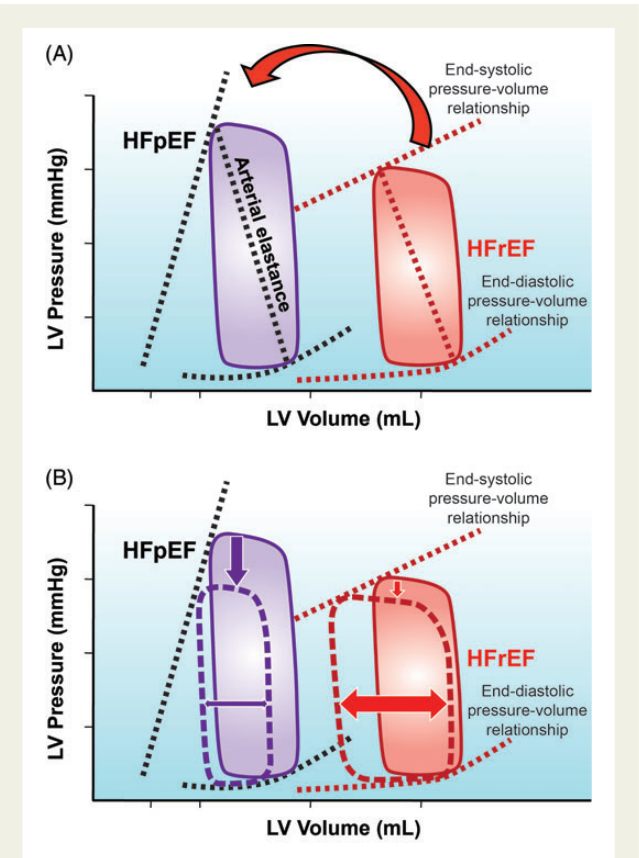


Figure 2 (A and B) Pressure–volume loop characteristics in heart failure with preserved ejection fraction (black) and heart failure with reduced ejection fraction (red) in baseline conditions (A), and in response to vasodilators (B). (A) Curved arrow depicts the steeper end-systolic pressure–volume relationship 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.

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.⁴⁴ However, a comparison of mortality in patients from HFpEF trials to patients with similar age, gender, and co-morbidity distribution in other trials of hypertension, coronary heart disease, and diabetes mellitus shows striking differences:⁴⁵ a much higher mortality was observed in HFpEF trials despite a ‘lower’ co-morbidity burden compared with non-HFpEF trial patients. Similarly, adjustment for co-morbidities do not fully account for the more severe CV abnormalities

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

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

References. ^{29,34–39} MMP-1, matrix metallo protease-1; TIMP-1, Tissue Inhibitor of MetalloProtease-1.

observed in HFpEF compared with gender/age-matched healthy controls and hypertensive patients without HF.⁴¹ These findings suggest that HFpEF is an independent entity.

Is heart failure with preserved ejection fraction a uniform syndrome?

The term ‘diastolic HF’ was first coined to reflect the leading pathophysiological factor believed to cause the syndrome—LV diastolic dysfunction. In a landmark study,⁵ 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,⁴⁶ and that patients with ‘systolic HF’ were even more likely to have moderate/severe diastolic dysfunction compared with patients with so-called ‘diastolic HF’.²⁵ 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.²⁴

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,^{26,29} impaired systemic vasodilator reserve,^{6,26} chronotropic incompetence,^{6,47} myocardial contractile dysfunction despite a normal EF,^{17,48} left atrial dysfunction,⁴⁹ pulmonary hypertension with intrinsic pulmonary vascular disease,^{8,50} endothelial dysfunction,^{26,51} and volume overload related to extra-cardiac causes.⁵²

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 pathophysiological 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 pathophysiology 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

Table 2 Heterogeneity of heart failure with preserved ejection fraction

Pathophysiologic mechanisms	Clinical phenotypes
LV diastolic dysfunction	'Pure' diastolic heart failure
Systolic LV-arterial stiffening	'Common' HfPEF (associated with hypertension, obesity, diabetes)
Abnormal LV-arterial coupling	
Myocardial contractile dysfunction	Coronary artery disease—associated
Impaired exercise reserve	Early HfPEF (with exercise-induced diastolic dysfunction)
Chronotropic incompetence	
Left atrial dysfunction	Atrial fibrillation—predominant
Pulmonary hypertension	Pulmonary hypertension and/or right heart failure
Volume overload	Non-cardiac cause—related volume overload (such as chronic kidney disease or anaemia)
Endothelial dysfunction	

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,⁶³ and ~70% in clinical trials. Among CV deaths, sudden death and HF death are the leading cardiac modes of death in HfPEF clinical trials.^{64,65} 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.⁶²

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

(1) Symptoms & Signs Of Heart Failure

- Typical symptoms: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, exercise intolerance, fatigue, swelling
- Typical signs: raised jugular venous pressure, hepatojugular reflux, third heart sound, oedema, pulmonary crepitations

(2) Preserved LV Ejection Fraction

- Currently taken as LV ejection fraction $\geq 50\%$
- Without LV dilatation

(3) LV Diastolic Dysfunction

- Structural: LV hypertrophy, left atrial dilatation
- Doppler: raised E/e' ratio, abnormal mitral inflow, prolonged pulmonary venous A reversal duration
- Biomarkers: raised NT-proBNP, BNP
- Rhythm: atrial fibrillation
- Invasive hemodynamics: increased LV end-diastolic pressure, prolonged tau, increased LV stiffness

Figure 3 Scheme for diagnosis of heart failure with preserved ejection fraction. In general, all proposed diagnostic criteria to date share three features in common: (1) symptoms and signs of heart failure; (2) evidence of preserved left ventricular (LV) ejection fraction; and (3) evidence of LV diastolic dysfunction, which may include structural, Doppler echocardiographic, biomarker, rhythm, or invasive haemodynamic criteria.

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.⁶⁶ 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.¹

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 amlodipine 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 $40\% \leq \text{EF} \leq 50\%$.²²

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 HFrEF patients.⁶²

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.⁶⁷

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.^{26,68}

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.⁶⁹ 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 $< 35\%$.⁷⁰ 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 $\geq 50\%$. Moreover, an echocardiographic sub-study did not show any effect of Nebivolol on parameters of systolic or diastolic dysfunction.⁷¹

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.⁷² 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.²²

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%.⁷³ Conversely, prescription of β -blockers was associated with a marked mortality reduction in a cohort of HFpEF patients followed up for 25 months.⁷⁴

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.⁷⁵

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%³¹ 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.³³ 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.³² 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 from Sweden, the use of a RAS antagonist was associated with a lower all-cause mortality.⁷⁶

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 3 Outcome trials in heart failure with preserved ejection fraction

	PEP CHF	CHARM preserved	I-PRESERVE	TOP CAT
Reference	35	33	34	100
No. of patients	850	3,023	4,128	3,445
Drug tested	Perindopril	Candesartan	Irbesartan	Spironolactone
Target dose (mg/day)	4	32	300	30/45
Mean follow-up (months)	26.2	36.6	49.5	42 estimate
Age at inclusion (years)	≥ 70	≥ 18	≥ 60	≥ 50
Mean age (years)	76	67	72	68.6
Men/women %	45/55	60/40	40/60	48/52
HF aetiology				
Ischaemic	26 ^a	57	25	59
Hypertensive	79 ^a	23	64	91 ^b
EF% at inclusion	LV WMI ^a 1.4–1.6	>40	≥ 45	≥ 45
BNP/NT proBNP at inclusion (pg/mL)	–	–	–	>360 (NT proBNP) >100 (BNP)
NT proBNP/BNP median value at baseline (pg/mL)	453 (Pbo)/335 (Active)	–	320 (Pbo)/360 (Active)	950 (NT proBNP)/234 (BNP)
BMI (kg/m ²)	27.5	29	30	32
6 min walk test (m)	297 (Pbo)/290 (Perindopril)	N/A	N/A	N/A
Primary composite endpoint	All-cause mortality/HF hospitalization	CV death/HF hospitalization	All-cause death/CV hospitalization	CV death/HF hospitalization/aborted cardiac arrest
Hazard ratio	0.92 (0.70–1.21)	0.89 (0.77–1.03)	0.95 (0.86–1.05)	0.89 (0.77–1.04)
P value	0.54	0.12	0.35	0.14

^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.

composite outcome of HF death or hospitalization after 37 months of follow-up.⁷⁷ However, a trend towards a reduction of HF hospitalization was observed.

Why did the prior trials fail?

Patient factors

The identification of patients with HFpEF 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 HFpEF; (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 HFpEF 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 *E/E'* ratio but there is increasing use of surrogate markers including left atrial enlargement, LV hypertrophy or raised natriuretic peptide plasma levels. The only randomized clinical trial using comprehensive echo parameters of diastolic dysfunction was PEP CHF.³³ The concern therefore remains that the patients recruited in the neutral trials above did not have HFpEF but had LV hypertrophy with a non-cardiac reason for dyspnoea such as obesity. Nonetheless, the fact remains that the rate of CV mortality or HF hospitalizations is much higher in HFpEF trials than that observed in clinical trials on hypertension with or without LV hypertrophy, suggesting that patients enrolled in these HFpEF trials indeed had HF.⁴⁵

Disease factors

An analysis of the inclusion criteria of the outcome trials as well as 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 level (Table 4). This suggests differences in the stage of disease of patients enrolled in these trials. Elderly HFpEF 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 *E/E'* 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 HFpEF.⁷⁹ Yet, in the Exercise Training in Diastolic Heart Failure—Pilot (Ex-DHF-Pilot) Study,⁸⁰ exercise training was effective at increasing peak VO_2 in patients with early stage HFpEF. Furthermore, half of the patients in Aldo-DHF had disease that was advanced enough to fulfil ESC criteria of HFpEF, and the effects of spironolactone on *E/e'* and peak VO_2 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 HFpEF vary in their effects on exercise capacity at different stages of the disease.

Table 4 Recent proof-of-concept studies

	Aldo DHF	PARAMOUNT	RELAX
Reference	99	96	93
No. of patients	422	266	216
Drug	Spironolactone	Angiotensin receptor Nephylisin inhibitor (LCZ 696) vs. Valsartan	Sildenafil
Men/women (%)	48/52	43/57	52/48
Mean age (years)	67	71	69
Baseline <i>E/E'</i>	12.7	12.4/13	16
6 min walk test (m)	—	N/A	305 (Pbo)/308 (Sildenafil)
Target dose (mg/day)	25	400 (ARNi)/320 (Valsartan)	60–12 weeks 180–12 weeks
EF at inclusion (%)	≥50	≥45	≥50
NT proBNP at inclusion (pg/mL)	—	≥400	≥400 <400 if elevated LV filling pressure
NT proBNP baseline geometric mean (pg/mL)	—	794 (ARNi)/870 (Valsartan)	—
Median (pg/mL)	148 (Pbo)/179 (Spironolactone)	828 (ARNi)/939 (Valsartan)	648 (Pbo)/757 (Sildenafil)
Primary endpoint	<i>E/E'</i> /peak VO_2	Change NT proBNP	Change peak VO_2
Duration	12 months	12 weeks	24 weeks

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

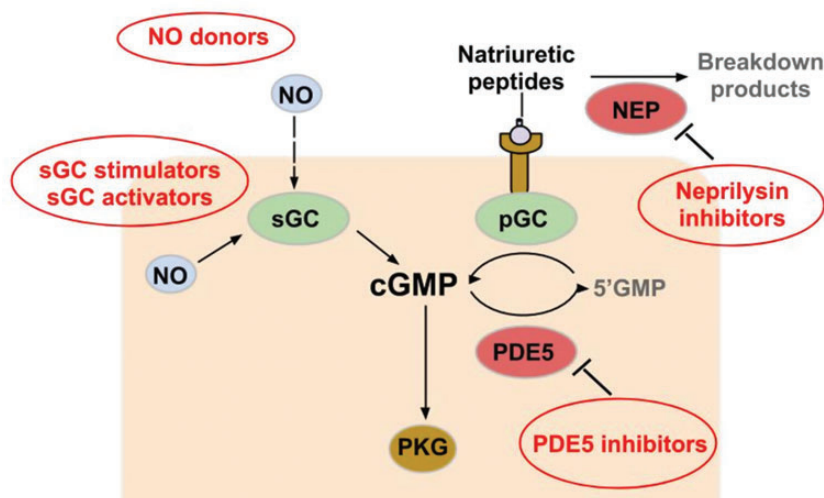


Figure 4 Role of NO—cyclic guanosine 3',5'-monophosphate (cGMP)—protein kinase-G activity (PKG) pathway in heart failure with preserved ejection fraction. NO, nitric oxide; sGC, soluble guanylate cyclase; NEP, neutral endopeptidase; pGC, particular guanylate cyclase; PKG, protein kinase G; PDE5, phosphodiesterase-5; cGMP, cyclic guanylate monophosphate.

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 pathophysiologic 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-1) 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 BAY1021189 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 Ca^{2+} 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 diastole without significant lusitropic 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 alagebrium 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

Statins

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 Ca^{2+} 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 Ca^{2+} 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 haemodynamics, 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 VO_2 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 and improved LV diastolic function. A larger study examining the effects of exercise training in HFpEF is in progress (<http://www.controlled-trials.com/ISRCTN86879094>).

Conclusion

The accurate diagnosis and optimal pharmacological treatment of HFpEF 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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