

## Therapeutic interventions for heart failure with preserved ejection fraction: A summary of current evidence

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(HFPEF) is common and represents a major challenge in cardiovascular medicine. Various pharmacological interventions available for heart failure with reduced ejection fraction have not been supported by clinical studies for HFPEF. This article presents a brief overview of the currently recommended therapeutic strategies for HFPEF.

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### Abstract

Heart failure with preserved ejection fraction (HFPEF) is common and represents a major challenge in cardiovascular medicine. Most of the current treatment of HFPEF is based on morbidity benefits and symptom reduction. Various pharmacological interventions available for heart failure with reduced ejection fraction have not been supported by clinical studies for HFPEF. Addressing the specific aetiology and aggressive risk factor modification remain the mainstay in the treatment of HFPEF. We present a brief overview of the currently recommended therapeutic options with available evidence.

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**Key words:** Heart failure; Diastolic dysfunction; Heart failure with preserved ejection fraction; Heart failure with normal ejection fraction

**Core tip:** Heart failure with preserved ejection fraction

### INTRODUCTION

Prevalence of diastolic heart failure (HF) has been rising steadily in the recent past. It is now well established that at least half of patients presenting with symptoms and signs of HF have preserved left ventricular (LV) ejection fraction, *i.e.*, heart failure with preserved ejection fraction (HFPEF), and that this portion of the HF population consists predominantly of women, older age group, and people with hypertension and other cardiovascular risk factors<sup>[1-3]</sup>. The prevalence of HFPEF varies from 1.1%-5.5%, depending on the age and other variables, *e.g.*, diagnostic criteria and methods, and rises to 3.1%-5.5% when studies are confined to a older population aged 65 years or above<sup>[6-9]</sup>. Chronic hypertension is the most common cause in addition to age, with suggestion of up to 60% of patients with HFPEF being hypertensive<sup>[10,11]</sup>. Obesity and Diabetes also contribute independently to the development of diastolic dysfunction<sup>[12-15]</sup>. Other conditions associated with diastolic dysfunction are Coronary artery disease and hypertrophic or restrictive cardiomyopathies.

It is observed that the morbidity and mortality associated with HFPEF is much higher than the normal population<sup>[16]</sup>. Several studies have reported an annual mortality rate ranging from 5% to 8% in this population<sup>[17-19]</sup>, much higher than the age-matched controls<sup>[20-22]</sup>. Given the accumulated data of various studies, it appears that all-cause mortality of HF patients in the community is similar whether their contractility is preserved or not.

Most of the current treatment of HFPEF is based on morbidity benefits and symptom reduction. Various pharmacological interventions available for heart failure with reduced ejection fraction (HFREF) have not been supported by clinical studies for HFPEF. Addressing the specific aetiology and aggressive risk factor modification remain the mainstay in the treatment of HFPEF. Current guidelines recommend the management should involve treatment of hypertension, control of heart rate, venous pressure reduction, and prevention of myocardial ischemia<sup>[23-25]</sup>. Here we present a brief overview of the currently recommended therapeutic options with available evidence.

## TREATING THE HYPERTENSION

Treatment of hypertension remains one of the most important factors in the management of diastolic dysfunction<sup>[23,25]</sup>. Effective management of increased blood pressure can reduce left atrial and LV end diastolic pressures, and enhance the LV filling by improving relaxation. It can further benefit by reduction of LV hypertrophy (LVH) and hence reducing the risk of development or progression of HF. Studies of hypertensive subjects indicate that diastolic dysfunction improves with LVH regression<sup>[26]</sup>. Angiotensin converting enzyme inhibitors (ACEi) inhibitors or aldosterone antagonists such as spironolactone can have protective effect against the exaggerated fibrous tissue response<sup>[27,28]</sup>. Thus theoretically, there may be benefits to inhibit renin-angiotensin-aldosterone system (RAAS) beyond blood pressure reduction.

In the Systolic Hypertension in the Elderly Program study<sup>[29]</sup>, a good control of isolated systolic hypertension with chlorthalidone and atenolol in a population of 4736 patients aged 60 years and older during an average of 4.5 years of follow-up led to significant reduction in the risk of HF {55 *vs* 105 in placebo group; RR = 0.51; 95%CI: 0.37-0.71, *P* < 0.001; number needed to treat to prevent 1 event [number needed to treat (NNT)], 48} and LV mass index, by 13%. In particular, among patients with prior MI, an 80% risk reduction was observed.

The Valsartan In Diastolic Dysfunction<sup>[30]</sup> studied the effects of blood pressure reduction on the myocardial relaxation on Doppler tissue imaging after a 38 wk of exposure to different anti hypertensive agents, including renin-angiotensin system inhibitor Valsartan in one group matched with placebo in the other. The difference in blood pressure reduction between the two groups was not significant ( $12.8 \pm 17.2/7.1 \pm 9.9$  mmHg reduction in the valsartan group *vs*  $9.7 \pm 17.0/5.5 \pm 10.2$  mmHg in the placebo group). Diastolic relaxation velocity was in-

creased by  $0.60 \pm 1.4$  cm/s from baseline in the valsartan group (*P* < 0.0001) and  $0.44 \pm 1.4$  cm/s from baseline in the placebo group (*P* < 0.0001) by week 38. However, there was no significant difference in the change in diastolic relaxation velocity between the two groups (*P* = 0.29). This suggested that lowering blood pressure improves diastolic function irrespective of the type of antihypertensive agent used.

Effects of blood pressure reduction on LVH have also been studied. Beta-blockers and diuretics are well established interventions for prevention of cardiovascular morbidity and death in patients with hypertension. In the Losartan Intervention For Endpoint reduction in hypertension study<sup>[31]</sup>, regression of LVH after a year of anti-hypertensive therapy was associated with improvement of various LV diastolic filling parameters on echocardiography. In this trial, Dahlöf *et al*<sup>[31]</sup> demonstrated superiority of an angiotensin receptor blocker (ARB), losartan, to  $\beta$ -blockade in reducing the composite primary endpoint (cardiovascular death, myocardial infarction or stroke; *P* = 0.021) and in regression of LVH (*P* < 0.0001), suggesting that besides blood pressure reduction, blockade of the AT1 receptor by losartan offers additional benefits for cardiovascular morbidity and mortality as compared to  $\beta$ -blockade, for a similar reduction in blood pressure, and was better tolerated.

The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Preserved (CHARM-Preserved) trial<sup>[32]</sup> comparing the effects of candesartan *vs* placebo in HFPEF (EF > 40%) in 3023 patients (1514 in candesartan and 1509 in placebo group) reported a moderate impact of candesartan in preventing admissions for HF (230 *vs* 279, *P* = 0.017) over a period of 36.6 mo. There was however no difference in mortality between the two groups (170 *vs* 170 cardiovascular deaths). Similar results were observed in Perindopril In Elderly People With Chronic Heart Failure (PEP-CHF) trial<sup>[33]</sup> in which a total of 850 patients aged  $\geq 70$  with HFPEF were randomized to perindopril 4 mg or placebo. The mean follow up period was 26.2 mo. In the first year of treatment, the hospitalizations for HF were less frequent in the perindopril group (*P* = 0.033), and significant improvement in the New York Heart Association (NYHA) class and functional capacity on 6-min walk test was observed in patients receiving perindopril (*P* < 0.030), however the mortality rate in both groups was similar. This study had insufficient power for its primary endpoint, which may be attributable to the non significant results of perindopril effects on long-term (> 1 year) morbidity and mortality of these patients. Differential Effects of Antihypertensive Treatment on LV Diastolic Function<sup>[34]</sup> suggested that patients receiving treatment with an amlodipine-based regimen had better diastolic function than patients treated with the atenolol-based regimen, independent of blood pressure reduction and other factors that are known to affect diastolic function.

It has been suggested that aggressive blood pressure lowering with a combination of an ARB, valsartan; a calcium channel blocker (CCB), amlodipine; and potential

additional therapy with diuretics or  $\beta$ -blockers was associated with improved annular relaxation velocity ( $e'$ ) on tissue doppler imaging, a measure of diastolic function, in patients with hypertension and diastolic dysfunction<sup>[35]</sup>. In this study, the patients who achieved the greatest blood pressure reduction had the best improvement in diastolic function, which supports that lower blood pressure targets may be an effective means to improve this measure of myocardial target-organ damage in hypertension.

## CONTROLLING THE HEART RATE

Tachycardia is poorly tolerated in the presence of diastolic dysfunction and the guidelines recommend beta-blockers or CCB for decreasing heart rate<sup>[23]</sup>. These drugs may also be helpful in stabilising rhythm and preventing atrial arrhythmias [*e.g.*, atrial fibrillation (AF)], which can cause substantial increase in diastolic and atrial filling pressures, leading to abrupt hemodynamic deterioration due to loss of the atrial contribution to diastolic filling. AF is common in HFPEF patients with a prevalence of up to 41%<sup>[36]</sup> and a recent meta-analysis<sup>[37]</sup> of 16 studies for the prognostic significance of AF in HF involving 53969 patients suggested that the presence of AF is associated with an adverse prognosis in HF irrespective of LV systolic function.

The diastole accounts for nearly 70% of the cardiac cycle at a heart rate of 60 bpm, slightly over 50% at 120 bpm, and only 40% at 180 bpm. The LV filling time is therefore considerably shortened with increased heart rate because the relaxation between beats is incomplete. In addition, in people with HFPEF tachycardia results in delayed relaxation and increased diastolic pressure. Things get further complicated during exercise. In patients with HFPEF, the heart is unable to take advantage of the Frank-Sterling mechanism during exercise. A stiff ventricle, despite elevated filling pressure, does not increase in volume. As a consequence filling pressure increases but cardiac output does not.

Therefore, decreasing heart rate would result in reduced pressure in the early period of the diastole by improving relaxation. Similarly increasing the ventricular filling time would improve cardiac output, and reduce symptoms during exercise.

The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors With Heart Failure (SENIORS) demonstrated that nebivolol reduces the composite risk of all-cause mortality and cardiovascular hospital admission in elderly patients with chronic HF and, importantly, that ejection fraction does not influence the clinical effects of nebivolol<sup>[38]</sup>. This trial randomized 112 patients in 29 European centres, of whom 104 were evaluable for the study; 43 with EF  $\leq$  35% and 61 with an EF  $>$  35%. LV end-systolic volume (ESV), EF, mitral valve E/A ratio, and E-wave deceleration time were assessed at baseline and after 12 mo. In the group with EF  $\leq$  35%, nebivolol reduced ESV and improved EF; no changes were observed in the E/A ratio or E-wave deceleration time. In EF  $>$  35% group, no significant changes

in either systolic or diastolic parameters were observed. This absence of detectable changes with standard echocardiography in patients with predominant diastolic HF questions the mechanism of benefit on morbidity/mortality in this population. In the separate analysis of patients with an EF cut off greater than 40%, there was no noted statistical interaction, suggesting that nebivolol was of comparable benefit in reduced EF and preserved EF patients.

## VENOUS PRESSURE REDUCTION

Diuretics remain the mainstay of symptomatic treatment for venous congestion similar to the management of systolic dysfunction. However, in patients with HFPEF optimising the volume status may be complicated by a narrow therapeutic margin given that in this group of patients the pressure/volume curve differs from the physiological curve and even a small decrease in filling pressure can result in a marked reduction of LV diastolic volume, which may lead to a significant reduction of cardiac output, risk of hypotension and renal impairment<sup>[39,40]</sup>. The doses of diuretics in this group of patients are therefore much lower than those in patients with systolic dysfunction. Diuretics do not directly affect the myocardium, while nitrates improve the ability of the left ventricle to increase its volume by releasing nitric oxide (NO).

Spironolactone combines diuretic action with beneficial effects on the structure of the left ventricle. The results of Treatment of Preserved Cardiac Function Heart failure with an Aldosterone Antagonist<sup>[41]</sup> was however a negative study, failing to show benefit for the clinical composite primary end point despite significantly fewer heart-failure hospitalisations, a part of the primary end point, over the average follow-up of 3.3 years. Aldosterone Receptor Blockade in Diastolic Heart Failure study<sup>[42]</sup> suggested that long-term aldosterone receptor blockade with spironolactone improved diastolic function but did not affect clinical symptoms or exercise capacity. Therefore, further investigation into the clinical significance of these echocardiographic findings will be required in larger studies.

## PREVENTION OF MYOCARDIAL ISCHEMIA

Myocardial ischemia is one of the most important mechanisms underlying HFPEF. Improved myocardial oxygen balance leads to better LV relaxation, reduced LVEDP, reduced risk of cardiac arrhythmias and stabilises the heart rate. It is therefore vital to use drugs that reduce oxygen consumption by the myocardium (beta-blockers, CCB, nitrates) and revascularization to improve oxygen supply to the myocardium. Flash pulmonary oedema frequently reoccurs in association with marked systolic hypertension, even after coronary revascularisation, suggesting that control of hypertension is important and that coronary revascularisation may not be adequate to

prevent reoccurrence of flash pulmonary oedema<sup>[43]</sup>.

## SPECIFIC THERAPEUTIC AGENTS

Given the limited evidence regarding directed therapy for HFPEF, treatment of factors known to exacerbate diastolic dysfunction plays a vital role. All patients with diastolic dysfunction should get adequately treated for associated conditions, *i.e.*, diabetes, obesity, primary myocardial disease, or pericardial disease in addition to above mentioned hypertension, myocardial ischemia.

### ACE inhibitors

The theoretical benefits of ACE inhibitors specifically in HFPEF rest on the basis that angiotensin II contributes to LV myocardial hypertrophy and fibrosis, impairs LV relaxation, and increases the stiffness of the left ventricle<sup>[44]</sup>. All of these factors, potentially improved by ACE inhibitors, will therefore improve diastolic function. Clinical studies evaluating ACE inhibitors in HFPEF have shown contradicting results. Secondary endpoints of reduced hospitalisation and improved exercise tolerance has been suggested by few<sup>[33,45]</sup> while other studies demonstrated no benefit except in patients with previous myocardial infarction<sup>[46]</sup>.

A small study assessed the effect of enalapril on 21 elderly patients with HFPEF (LVEF > 50%) and history of myocardial infarction<sup>[45]</sup>. These patients had received furosemide for 2 wk or greater before the initiation of the study, and were on a constant dose of furosemide, were randomized to receive enalapril, titrated up to 20 mg daily as tolerated, and followed for 3 mo. There was a significant difference from baseline to study termination in the study outcomes in the treatment group: NYHA class improved from 3 to 2.4 ( $P = 0.005$ ) and exercise time with the modified Bruce protocol increased from 224 to 270 s, versus no significant difference in the placebo group. Another small prospective study in France enrolled 358 subjects who were admitted for a first episode of HF but had ejection fractions  $\geq 50\%$ . Patients were separated into 2 groups based on whether or not they were prescribed an ACEi at discharge; lisinopril (32.3%), ramipril (25.6%), perindopril (23.8%), or enalapril (5.5%). The authors attempted to adjust for selection bias by developing a propensity score and comparing matched controls. Patients who had been prescribed ACEIs had a 10% reduction in 5-year mortality (NNT = 10). The largest and most well-designed study (PEP-CHF)<sup>[33]</sup> demonstrated no significant difference in the primary endpoint but showed significant reduction in the secondary endpoint of hospitalization for HF.

### ARB

Although well understood association of RAAS with many of the underlying processes behind HFPEF, various studies involving ARB use in HFPEF did not demonstrate significant benefits, except CHARM-Preserved, which relates reduced hospitalization with candesartan<sup>[32]</sup>.

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction trial compared irbesartan with placebo I 4128 patients with HFPEF<sup>[47]</sup>. It did not improve the outcomes of patients.

### $\beta$ -blockers

The mechanism behind  $\beta$ -blockers' potential in improving diastolic function in patients with HFPEF is believed to be associated with the drugs' negative chronotropic and inotropic properties in stabilising the heart rate and helping the ventricle to relax<sup>[44]</sup>. SENIORS study was the largest trial evaluating the effect of nebivolol on the composite of all-cause mortality or hospitalization for a cardiovascular cause<sup>[48]</sup>, which reported that nebivolol, a beta-blocker with vasodilation properties, is an effective and well-tolerated treatment for HF in the elderly. The subgroup with ejection fraction > 35% was analysed in a pre-specified analysis. The interaction test showed that ejection fraction did not modify the effect of nebivolol in terms of the primary outcome (all-cause mortality or cardiovascular hospitalization) (HR = 0.86; 95%CI: 0.74-0.99,  $P = 0.039$  in the main analysis), implying that the effect of nebivolol is similar in patients with HF and an ejection fraction  $\leq 35\%$  and > 35%. However, when the ejection fraction threshold of 40% was used instead of 35% (which was not a pre-specified subgroup), there was no significant difference between those treated with nebivolol and those given placebo (HR = 0.83; 95%CI: 0.62-1.11,  $P = 0.203$ ).

Another study, conducted in elderly patients (mean age 81 years), enrolled patients 62 years and older with NYHA class II or III HF, prior Q-wave MI, and EF  $\geq 40\%$  who had also been on ACE inhibitors and diuretics for 2 mo<sup>[49]</sup>. This trial analysed the effect of propranolol on all-cause mortality and the composite of all-cause mortality and nonfatal MI after a follow-up period of 32 mo. All patients were on ACE inhibitors and diuretics during the study and digoxin was administered only in cases of atrial fibrillation. There was a significant difference between the groups in all-cause mortality (56% *vs* 76%;  $P = 0.007$ ) and all-cause mortality plus nonfatal myocardial infarction (59% *vs* 82%;  $P = 0.002$ ) favouring the patients treated with propranolol compared with those patients who were only on conventional therapy and no propranolol. The reduction in total mortality began 1 year after treatment initiation and the beneficial effects lasted until the end of the study. However, the percentage of deaths due to cardiac causes in each group did not differ significantly. Overall, studies that assessed the role of  $\beta$ -blockers in HFPEF have all found  $\beta$ -blockers to positively impact study outcomes (mortality in post myocardial infarction patients specifically and morbidity in others).

### Digoxin

The use of digoxin has beneficial effect on hospitalization in HFPEF<sup>[50]</sup>. This effect however has not been shown in HFPEF<sup>[51]</sup>. Furthermore, digoxin has not shown any



impact on mortality in either HFREF or HFPEF.

## OVERALL EFFECTS OF COMBINED PHARMACOTHERAPY ON EXERCISE TOLERANCE, CARDIAC FUNCTION, AND MORTALITY IN HFPEF

A recent meta-analysis was sought to determine whether pharmacologic interventions changed exercise capacity, diastolic function, and mortality in HFPEF<sup>[52]</sup>. Data from 53878 patients enrolled in 30 published reports were collated including 18 randomized controlled trials ( $n = 11253$ ) and 12 observational studies ( $n = 42625$ ). A combined pharmacotherapy for HFPEF demonstrated a quantifiable improvement in exercise tolerance but failed to show a mortality benefit.

## ROLE OF EXERCISE TRAINING

Exercise training is now widely used as an adjunct therapy for the stable HF patient. It is recommended by the American College of Cardiology and the American Heart Association at a Class 1 level<sup>[24]</sup>. Many physical activity benefits for HF patients have been documented, such as improvements in physical capacity (an increase of 10%-30% of the maximum physical capacity)<sup>[53,54]</sup>, improvements in quality of life<sup>[55]</sup>, endothelial dysfunction<sup>[56]</sup>, circulating catecholamine levels<sup>[57]</sup>, morbidity and hospital admissions<sup>[58]</sup>. However most of the studies have focused on patients with HFREF. Since the patients with HFPEF also experience exercise intolerance, dyspnoea, early fatigue, and similar mortality risk and re-hospitalization rates, a case can be made for exercise to be part of the management of people with HFPEF. In a recent study, 3 years of exercise-based lifestyle intervention was not effective in reducing progression of subclinical diastolic dysfunction in patients with type 2 diabetes mellitus<sup>[59]</sup>. Other studies have suggested an improvement in exercise tolerance, quality of life and depression scale with low-to-moderate intensity exercise<sup>[60-62]</sup>.

Effects of exercise training on LV diastolic function in patients with systolic dysfunction have included a significant reduction in LV diastolic wall stress at low work rates resulting in a 30% increase in peak oxygen consumption after 2 mo<sup>[63]</sup>. Belardinelli *et al.*<sup>[64]</sup> evaluated patients with dilated cardiomyopathy and a Doppler mitral inflow profile suggestive of concomitant abnormal diastolic LV function. Only people with delayed relaxation improved their functional capacity after training. In these patients, the diastolic filling pattern normalised after training. Those with a restrictive filling pattern, however, were found to have a worse prognosis and did not improve functional capacity or diastolic filling pattern after training.

The standard recommendations for exercise training in general include aerobic activity performed at least 30 min, 5 or more days/week. Exercise intensity in HF train-

ing has varied between studies, and some study protocols have used interval or variable intensity training. In most clinical settings, an intensity range of 70%-80% of peak HR determined from a symptom-limited exercise test is used. Although aerobic exercise remains the mainstay of clinical training programs, resistance training has also shown benefits, including improved muscle strength, endurance, and blood flow associated with a lower VO<sub>2</sub> at submaximal workloads<sup>[65-67]</sup>. While beta blockers have numerous benefits in patients with HF, they blunt heart rate responses to exercise. It has therefore been suggested that heart rates should not be used to determine exercise capacity in these patients<sup>[68,69]</sup>. Exercise tolerance for CHF patients may be affected by the dose changes of some medications used for CHF, and exercise prescription may need to be modified accordingly. Generally self perceived exercise workload is more practical way of determining exercise intensity than parameters like maximum heart rate<sup>[70]</sup>.

## EMERGING THERAPIES

### *Alagebrium chloride*

A thiazolium derivative, Alagebrium chloride (ALT-711) is a novel compound that breaks advanced glycation end products (AGE) crosslinks and may improve ventricular distensibility and arterial compliance. A recent prospective, open-label trial of alagebrium in elderly patients found that in clinically stable HFPEF, the 16-wk treatment with alagebrium caused regression of LVH, improved Doppler indices of diastolic function, and enhanced quality of life without altering blood pressure, arterial stiffness, or exercise tolerance<sup>[71]</sup>. A more recent however did not support these findings<sup>[72]</sup>. Prevention of the formation of new AGEs with exercise and breakdown of already formed AGEs with ALT may represent a therapeutic strategy for age-related ventricular and vascular stiffness<sup>[73]</sup>.

### *Statins*

Statins have a variety of potential benefits in addition to lipid reduction that may more directly impact diastolic function. Statins may exert beneficial effects on LVH and fibrosis, and thus may directly impact HFPEF<sup>[74]</sup>. It appears to be associated with improved survival in HFPEF<sup>[74,75]</sup>. A study involving 270 patients with HFPEF and a follow up of 5 years demonstrated improved survival compared to patients without statin therapy (HR = 0.65; 95%CI: 0.45-0.95,  $P = 0.029$ )<sup>[75]</sup>. The survival benefit was maintained after adjusting for differences in baseline characteristics, comorbidities, and other medications.

### *Growth differentiation factor 11*

A protein belonging to the TGF- $\beta$  family, growth differentiation factor 11 (GDF-11) can reverse age-related cardiac hypertrophy in mice<sup>[76]</sup>; a finding with implications for the experimental treatment of HFPEF<sup>[77]</sup>. Although functional benefits as measured by means of echocar-

diography were not detected after GDF-11 treatment, the results suggest that the reversal of age-related cardiac hypertrophy by pharmacologic means is potentially feasible<sup>[76]</sup>.

### Gene therapy

Calcium mishandling is implicated in heart disease. Efforts are ongoing in a number of gene therapy approaches to address the calcium mishandling issue, *e.g.*, by normalising the function of calcium handling proteins such as sarcoplasmic reticulum calcium ATPase, or to introduce calcium buffers to facilitate relaxation of the heart<sup>[78]</sup>.

Parvalbumin is a calcium binding protein found in fast-twitch skeletal muscle and not normally expressed in the heart. Gene transfer of parvalbumin into normal and diseased cardiac myocytes increases relaxation rate but also markedly decreases contraction amplitude<sup>[78]</sup>. Szatkowski *et al.*<sup>[79]</sup> have shown that parvalbumin gene transfer to the heart *in vivo* produces levels of parvalbumin characteristic of fast skeletal muscles, causes a physiologically relevant acceleration of heart relaxation performance in normal hearts, and enhances relaxation performance in an animal model of slowed cardiac muscle relaxation. They suggested that parvalbumin may offer the unique potential to correct defective relaxation in energetically compromised failing hearts because the relaxation-enhancement effect of parvalbumin arises from an ATP-independent mechanism.

### NO donors

In patients with dysfunctional endothelium, the constrictor effects of catecholamines can act unopposed, which may contribute to impaired dilator responses of epicardial and resistance vessel and thereby to myocardial ischemia, which slows ventricular relaxation and increases myocardial wall stiffness. Studies have suggested that diastolic function of the heart appears to benefit from exogenous NO whereas its endogenous production does not play a major role in myocardial relaxation<sup>[80]</sup>. Similarly, NO donors have been shown to exert a relaxant effect on the myocardium which is associated with a decrease in LV end-diastolic pressure<sup>[80]</sup>.

### Ranolazine

Ranolazine is a new anti-ischemic and antianginal agent that inhibits the late sodium current, reducing the Na-dependent Ca-overload, which improves diastolic tone and oxygen handling during myocardial ischemia<sup>[81]</sup>. In addition, ranolazine seems to exert beneficial effects on diastolic function. Most of the experimental studies performing acute exposure to ranolazine in HF report on positive effects on diastolic performance<sup>[81]</sup>. A recent proof-of-concept study however revealed that ranolazine improved measures of hemodynamics but there was no improvement in myocardial relaxation parameters<sup>[82]</sup>.

### Angiotensin receptor neprilysin inhibitor

LCZ696, a first-in-class angiotensin receptor neprilysin

inhibitor, has been assessed in patients with HFPEF in PARAMOUNT trial<sup>[83]</sup>, a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with NYHA)class II-III HF, LV ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. In comparison with Valsartan, LCZ696 reduced NT-proBNP to a greater extent at 12. Whether these effects would translate into improved outcomes needs to be tested prospectively.

### Phosphodiesterase-5 and endothelin inhibition

Despite initial encouraging results for a commonly used erectile dysfunction drug “sildenafil” to treat patients with HFPEF, the large multicentre trial “RELAX Study” failed to show any significant improvement in exercise capacity or clinical status when compared with placebo after 24 wk<sup>[84]</sup>.

Preliminary findings have suggested that cardiac endothelin-1 overexpression in a status of NO deficiency may have a role in oxidative stress, myocytes contractility, and energy metabolism<sup>[85]</sup>.

### Ivabradine

Animal studies have suggested that long-term heart rate reduction induced by ivabradine may improve diastolic LV function probably involving attenuated hypoxia, reduced remodelling, and/or preserved NO bioavailability<sup>[86]</sup>. This however is yet to be translated in human beings.

## CONCLUSION

HFPEF is common and represents a major challenge in cardiovascular medicine. In contrast to advances in therapeutic options for systolic HF, there is no definitive evidence that ACE inhibitors, ARBs, beta-blockers, or aldosterone antagonists may improve outcomes in these patients. Addressing the specific aetiology and aggressive risk factor modification currently remains the mainstay in the treatment of HFPEF.

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