Published in final edited form as:

Expert Opin Pharmacother. 2017 March ; 18(4): 399–409. doi:10.1080/14656566.2017.1288717.

Advances in the pharmacotherapy of chronic heart failure with preserved ejection fraction: an ideal opportunity for precision medicine

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Abstract

Introduction—Heart failure with preserved ejection fraction (HFpEF), which comprises approximately 50% of all heart failure patients, is a challenging and complex clinical syndrome that is often thought to lack effective treatments.

Areas covered—Despite the common mantra that HFpEF has no effective treatments, closer inspection of HFpEF clinical trials reveals that several of the drugs tested are associated with benefits in exercise capacity and quality of life, and reduction in heart failure hospitalization. Here we review major randomized controlled trials in HFpEF, focusing on renin-angiotensin-aldosterone system antagonists, organic nitrates, digoxin, beta-blockers, and phosphodiesterase-5 inhibitors. In addition, we review several classes of drugs currently in development for HFpEF such as neprilysin inhibitors, inorganic nitrates (nitrites), and soluble guanylate cyclase stimulators.

Expert opinion—HFpEF should not be viewed as lacking effective treatments. While there have been no breakthrough clinical trials, several existing medications are likely to benefit specific subgroups of HFpEF patients. HFpEF is now well known to be a heterogeneous syndrome; thus, the clinical management of HFpEF patients and future HFpEF clinical trials will both likely require a nuanced, phenotype-specific approach instead of a one-size-fits-all tactic. Drug development for HFpEF therefore represents an exciting opportunity for personalized medicine.

Keywords

heart failure with preserved ejection fraction; clinical trials; pharmacotherapy; phenotype

1. Introduction

Heart failure (HF) is one of the most common clinical syndromes and one of the leading causes of death globally.¹ Half of HF patients have HF with preserved ejection fraction

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

(HFpEF), the prevalence of which is rising.^{2–5} Considerable progress has been made in the treatment of HF with reduced EF (HFrEF) by targeting neurohormonal inhibition, with multiple large clinical trials indisputably meeting primary endpoints.⁶ On the contrary, HFpEF trials have not achieved their primary endpoint leading to the common viewpoint that “there are no available therapies for HFpEF”. However, several of these trials showed an improvement in important secondary endpoints, and interesting secondary analyses suggest a benefit underappreciated by initial interpretation of these trials. The perception of poor HFpEF trial outcomes and explanations for their failures continue to be a hot topic of scientific commentary, and have even raised concerns about the role of multinational trials.^{7–9} Lack of definitive results have led to innumerable HFpEF review articles that lament the failure of HFpEF trials, hopelessness, and lack of definitive therapy.^{10–14} Here we seek to challenge this notion of lack of therapies for HFpEF via (1) a reexamination of large-scale multicenter HFpEF clinical trials; (2) discussion of the recent progress in the field, including the critical role of “matchmaking” of the right therapy to the right patient (i.e., making progress towards the goal of precision medicine in HFpEF); and (3) suggestions for appropriate available treatments for this complex condition.

2. Pathophysiology of HFpEF

Although the mechanism of HFpEF is most likely multifactorial, a major component of the syndrome appears to be multiple comorbidities (e.g., hypertension, diabetes, obesity, chronic kidney disease) resulting in a pro-inflammatory state which ultimately causes widespread endothelial dysfunction in multiple organs. In the heart, coronary microvascular endothelial dysfunction results in reduced nitric oxide (NO) bioavailability, reduced cyclic GMP (cGMP)/protein kinase G (PKG) signaling, abnormalities in titin, and increased stiffness of cardiomyocytes (discussed in further detail below), all of which ultimately lead to the HFpEF syndrome.^{15, 16} In the heart, stressors such as hypertension also lead to T-tubule remodeling with reduced efficiency of cardiomyocyte calcium handling, which also results in abnormalities in cardiac mechanics (both systolic and diastolic). Eventually cardiomyocytes become overloaded with calcium and undergo apoptosis with eventual replacement fibrosis, further exacerbating the reduced compliance of the left ventricle (LV).

Several comorbidities such as hypertension, LV hypertrophy (LVH), diabetes, obesity, obstructive sleep apnea, atrial fibrillation are closely associated with the HFpEF syndrome.^{17–24} HFpEF can be thought of as an exaggeration of the normal aging cardiovascular system.²⁵ These patients have extremely stiff arteries and ventricles, far exceeding those of hypertensive or age-matched controls, and stiffness believed to play a major role in the disease process.^{26–30} There seems to be an inflammatory milieu serving as the pathologic driver of increased cardiovascular stiffness, which mediates increased collagen deposition, diastolic dysfunction, and monocyte myocardial tissue infiltration.^{31–38} Evidence suggests the source of this inflammatory milieu is extramyocardial, an idea garnered from experiments in healthy young animals, given blood from older animals with HFpEF which developed HFpEF features following the blood exchange and vice versa.³⁹ In short, this inflammation induces increased vascular cell adhesion molecule, E-selectin expression, macrophage translocation, oxidative damage and subsequent collagen deposition by macrophages.^{40–47} Although increased tissue collagen is a major cause of stiffening,

intrinsic myofibril dysfunction also plays a major role in this process through reduction in NO and oxidative damage as discussed above. This oxidative environment leads to a reduction in PKG, and subsequently reduced phosphorylation of the anchoring “spring-like” myocardial protein titin, causing increased passive stiffness of the myocardial fibers.^{44, 48} This stiffness sets off a pathological cascade, leading to increased left ventricle filling pressures, left atrial dysfunction, atrial fibrillation, pulmonary venous congestion, symptoms of dyspnea, renal hypoperfusion and dysfunction, water retention worsened pulmonary venous congestion, pulmonary hypertension, and in some cases right ventricular (RV) failure.

Additional hypotheses for the pathophysiologic basis of HFpEF exist. Several studies have implicated arterial stiffening in the pathogenesis of HFpEF.^{49–51} Central aortic stiffening results in increased magnitude of reflected waves, which can increase myocardial wall stress. The increase in wall stress, in turn, results in T-tubule disruption with abnormalities in cardiomyocyte calcium homeostasis, which leads to diastolic dysfunction and abnormalities in cardiac mechanics.⁵² Reno-cardiac mechanisms have also been implicated, whereby impaired renal function is a driver of both inflammation and chronic volume overload.^{53, 54} A study by Unger and colleagues demonstrated an association between chronic kidney disease and abnormal cardiac mechanics and worse outcomes in HFpEF.⁵⁵ Altered mitochondrial function has been recently suggested as a major mechanism of impaired cardiac and skeletal muscle metabolism precipitating exertional dyspnea.^{56, 57} These studies have been supported by exercise studies which have shown improvement in HF symptoms and mitochondrial density following exercise training intervention in HFpEF.⁵⁸ Understanding different phenotypes and associated pathophysiology are important to optimize and prioritize medical therapy. It is likely multiple pathophysiologic mechanisms are present in each patient. Proper recognition and better understanding of these HFpEF sub-phenotypes will help optimize treatment and should always be considered when treating these patients.^{59, 60}

Advances in our understanding of the pathophysiology of HFpEF allow us to put the prior HFpEF pharmacotherapy clinical trials into context. The majority of these trials have targeted neurohormonal inhibition given the success of these drugs in HFrEF and the fact that maladaptive neurohormones are elevated in HFpEF (though to a lower extent than HFrEF). However, in HFpEF neurohormonal activation appears to be an end-result of the HF syndrome, and not a primary driver of the myocardial abnormalities (which is likely the case in HFrEF). It is therefore not surprising that these classes of drugs have not led to major improvements in outcomes in HFpEF. In the next several sections, we describe in further detail the several classes of medications—including neurohormonal antagonists as well as other medications—that have been tested in large-scale, multicenter HFpEF clinical trials.

3. Angiotensin converting enzyme inhibitors

The largest trial to evaluate the use of ACE-inhibitors in patients with HFpEF was the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study.⁶¹ PEP-CHF was a randomized, double-blind study comparing perindopril 4 mg/day versus placebo in patients 70 years or older with a diagnosis of HF in the past 6 months, and an EF < 40%

with diastolic dysfunction. Of the 850 individuals randomized, 107 of those in the placebo arm and 100 from the perindopril arm reached the primary composite endpoint of all-cause mortality and unplanned HF hospitalization (HR 0.919, 95% CI 0.700–1.208; $P = 0.545$).

In PEP-CHF both enrollment and event rates were lower than anticipated, resulting in a statistical power of only 35% and the subsequent decision to terminate the study once all participants reached 1 year of follow-up. By 1 year, 28% of the perindopril arm and 26% of the placebo arm began taking open label ACE inhibitors, further diminishing any appreciable benefits beyond that point. Although the study was underpowered for its primary endpoint, secondary endpoint analyses revealed borderline, non-significant improvement in mortality, and analyses from the first year of the trial showed a significant reduction in HF hospitalizations and improvement in symptoms and exercise capacity. These results are suggestive of a potential benefit from ACE-inhibitors despite the fact that the trial did not meet its primary endpoint. Given the fact that ACE-inhibitors are indicated for many of the comorbidities associated with HFpEF (e.g., diabetes, hypertension, chronic kidney disease), it is perhaps not surprising that this class of medications is widely used in patients with HFpEF. For example, in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, which was conducted after the completion of PEP-CHF, 65% of patients with HFpEF were taking an ACE-inhibitor and 20% were taking an angiotensin receptor blocker (ARB), with a total of 84% of the patients on either/or an ACE-inhibitor or ARB.

4. Angiotensin-receptor blockers

Two large-scale randomized controlled trials have evaluated ARBs in the treatment of HFpEF. Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (CHARM-Preserved) randomized 3023 HF patients with an LVEF $\geq 40\%$ to candesartan 32mg/day versus placebo.⁶² The primary outcome was cardiovascular death or hospitalization for HF, and patients were followed for an average of 36.6 months. Although candesartan did not improve the primary outcome, there were fewer patients who experienced at least one HF hospitalization among those in the candesartan group (230 vs 279 in the placebo group, $P=0.017$; Figure 1). Although the overall difference between candesartan and placebo groups just missed statistical significance ($P=0.051$) when analyzed by event, the improvement in HF hospitalizations was the primary driver of benefit, not death (HR 0.84 [95% CI 0.70–1.00], $P=0.047$ for HF hospitalization vs. HR 0.95 [95% CI 0.76–1.18], $P=0.635$ for death). Furthermore, Rogers et al. showed in a post-hoc analysis that candesartan reduced the endpoint of recurrent HF hospitalizations by a large margin in CHARM-Preserved.⁶³

The Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) randomized 4128 patients with HF, age ≥ 60 years, and an EF $\geq 45\%$ to either 300 mg/day of irbesartan versus placebo. The primary endpoint was death by any cause or hospitalization for a cardiovascular cause. After a mean follow-up of 49.5 months there was no difference in either the primary or secondary endpoints among the 2 treatment groups.⁶⁴ However, 39% and 40% of patients in the treatment and placebo arms respectively were taking an open label ACE inhibitor at some point during the trial, which may have adversely

affected the power of the study. Interestingly, Anand et al. showed in a post-hoc analysis of I-PRESERVE that patients enrolled in I-PRESERVE who were in the lowest tertile of N-terminal pro-B-type natriuretic peptide (NTproBNP) were most likely to benefit from irbesartan.⁶⁵

Taken together, CHARM-Preserved and I-PRESERVE show that ARBs may be helpful in HFpEF for reducing overall HF hospitalizations, and may be most useful in patients who have a less severe form of HFpEF, with lower levels of natriuretic peptides.

5. Mineralocorticoid receptor antagonists

The Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) investigators sought to determine if spironolactone was superior to placebo in improving diastolic function and exercise capacity.⁶⁶ In ALDO-DHF, 422 participants were randomized to spironolactone 25 mg/day versus placebo with a mean follow up of 11.6 months. Participants were eligible if they had NYHA class II or III HF, EF $\geq$ 50%, diastolic dysfunction grade I or atrial fibrillation, and a peak $\dot{V}O_2$ of 25 mL/kg/min or less. Spironolactone significantly improved LV diastolic dysfunction, LV remodeling, and reduced levels of NTproBNP but failed to improve exercise capacity or quality of life measures. The results of ALDO-DHF were congruent with other studies of mineralocorticoid receptor antagonists in HFpEF, which have consistently shown improvements in cardiac structure/function but no benefit in exercise capacity.⁶⁷

In TOPCAT, 3445 patients across 6 countries were randomized to spironolactone (15–45 mg/day) versus placebo with a median follow-up of 3.3 years. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF. Although there was no significant change in reduction of the primary endpoint, results showed a modest, but significant reduction in HF hospitalizations for those in the spironolactone group (Figure 2).⁶⁸

However, further analyses revealed major variations in event rates and treatment effects of spironolactone in Eastern Europe (Russia and the Republic of Georgia) compared to the Americas (United States, Canada, Argentina, and Brazil). Post-hoc analysis of the primary endpoints based on region revealed a significant decrease in the primary endpoint and HF hospitalizations in those receiving spironolactone in the Americas, with no difference observed in Russia/Georgia (Figure 3).⁶⁹ When comparing results from the 2 regions, there were significant differences in patient characteristics and event rates, suggesting that patients in Russia/Georgia did not have the HFpEF syndrome. Patients from Russia/Georgia were younger, had less comorbidities, and 89% were enrolled based on HF hospitalization criteria rather than natriuretic peptide criteria versus 55% of patients recruited into the HF hospitalization strata in the Americas.⁶⁹ Moreover, patients in the Americas receiving spironolactone experienced elevations in potassium and creatinine and reduction in blood pressure, effects that were not observed in Russia and Georgia, raising doubt about whether patients enrolled in Russia/Georgia were receiving study drug. These suspicions were recently confirmed and proven by measuring levels of spironolactone metabolites (canrenone) in blood samples in a TOPCAT biomarker substudy, which showed that patients

in Russia/Georgia on spironolactone were much more likely to have undetectable levels of canrenone, indicating that they were not taking the study drug. Based on the data from the Americas, the TOPCAT investigators have thus concluded that spironolactone is beneficial in patients with HFpEF and should be used to reduce cardiovascular mortality and HF hospitalization in these patients.

There are 2 post-hoc analyses of TOPCAT that are worth mentioning. Anand et al. showed that TOPCAT patients in the lowest tertile of natriuretic peptides were the ones who benefited most from spironolactone, a finding which was also seen in the I-PRESERVE trial, in which HFpEF patients with NTproBNP values below the median benefitted from irbesartan therapy.⁶⁵ Although there are no definitive explanations for the finding that HFpEF patients with lower BNP levels respond more favorably to renin-angiotensin-aldosterone system (RAAS) antagonists, Anand et al. also found that higher BNP levels are strongly associated with worse structural heart disease and diastolic dysfunction in HFpEF. The authors suggest two possible mechanisms to this finding. High BNP may be a marker of permanent damage less amenable to medical intervention, supporting the hypothesis that RAAS blockade slows the progression of collagen deposition and myocardial stiffening. Therefore later intervention may offer less benefit than early in the disease course. These results may also be explained by the fact that HFpEF patients with higher BNP and worse diastolic dysfunction are more likely to have atrial fibrillation and/or CKD. In these instances ARBs and MRAs are less beneficial and may even be counter-productive. Solomon et al. found that TOPCAT patients with lower baseline EFs (45–50% range) benefited most from spironolactone.⁷⁰ One possible interpretation of these results is that the lower the EF, the more likely the patient truly has the HF syndrome (given the difficulty in diagnosing HFpEF). Based on these 2 substudies we can conclude that (1) less severe forms of HFpEF and obesity-related HFpEF (which is associated with lower natriuretic peptide levels) may be the subsets of HFpEF that benefit most from spironolactone therapy and (2) only patients who truly have the HF syndrome will benefit from spironolactone therapy.

6. Nitrates

Nitrates have long been used in the treatment of HFpEF patients, and recently the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) was conducted to scrutinize this approach.⁷¹ NEAT was a multi-center, randomized, double-blind, placebo-controlled, cross-over trial which evaluated isosorbide mononitrate versus placebo and its effects on physical activity. Physical activity was objectively measured using accelerometry, and the primary outcome was the comparison of accelerometry units when the patient was on study drug vs. placebo, with each patient serving as her/his own control. These patients underwent baseline testing before each study period in which drug or placebo was stepped up to a maximum possible dose of 120 mg/day for 2–4 weeks.

The results showed a non-significant worsening in the primary endpoint with isosorbide mononitrate, and significant worsening in the secondary endpoints leading the authors to conclude isosorbide mononitrate worsens physical activity and exercise tolerance in HFpEF. Nitrates are well known to come with non-critical but disabling side effects such as

headache, malaise, and lightheadedness. A total of 16 patients discontinued the study due to side effects, and it is reasonable to believe that several others may have experienced similar but less severe adverse effects, which discouraged patients from being active, the supporting the results observed. Recent data suggests that nitrates have minimal effects on systemic arterial stiffness but they result in carotid artery vasodilation, which could explain the headaches observed in the NEAT trial and clinically with nitrates.

Some limitations of the NEAT trial are worth acknowledging. First, isosorbide mononitrate (a long-acting nitrate) was used instead of shorter acting isosorbide dinitrate. While the long-acting formulation is easier to take due to once daily formulation, it may not be as effective and may lead to worse side effects. Second, there was a relatively quick titration from 30 mg to 120 mg of isosorbide mononitrate, which could have led to worsening adverse effects. Finally, the trial was relatively short in duration. Despite these limitations, given the compelling and concordant results of the study, the NEAT trial was a major contribution to the field, as it provides strong evidence that nitrates do not help patients, and may even cause harm.

7. Digoxin

The Digoxin Investigational Group (DIG) studied the effects of digoxin on morbidity and mortality in HFpEF as an ancillary trial to its primary study in HFrEF.⁷² The DIG-Ancillary trial was a prospective randomized, placebo-controlled trial of 988 HF patients in sinus rhythm with an EF >45% followed for a mean of 37 months to a primary outcome of HF hospitalization or death.⁷² The results of this study showed a non-significant trend towards a reduction in hospitalizations due to HF (HR 0.79, 95% CI 0.59–1.04; P = 0.094). However the DIG-Ancillary trial also showed a non-significant trend toward increased hospitalizations for unstable angina (HR 1.37, 95% CI 0.99–1.91; P = 0.061); therefore, digoxin is not recommended for use in most cases of HFpEF. The use of digoxin may be warranted in circumstances of significant RV dysfunction in right heart failure in patients with HFpEF who have pulmonary hypertension. In patients with pulmonary arterial hypertension with RV failure, digoxin was associated with modest improvements in cardiac output and reduced plasma norepinephrine levels.⁷³

8. Beta-blockers

Beta-blockers are used very commonly in HFpEF, likely due to the very high prevalence of comorbidities such as systemic hypertension, atrial fibrillation, and coronary artery disease. Indeed, in the TOPCAT trial, 78% of patients were taking a beta-blocker at the time of enrollment into the trial. Despite the common use of beta-blockers in HFpEF, there has been a paucity of large-scale randomized controlled trials of this class of medications in HFpEF. The Study of Effects of Nebivolol Intervention on Outcomes and Re-hospitalization in Seniors With Heart Failure (SENIORS) trial studied the role of nebivolol in elderly patients with HF across a spectrum of EF and stratified into 2 groups (EF ≤ 35% vs. EF > 35%). A total of 752 patients (mean EF = 49.2%, thus comprised of a combination of HF with mid-range EF and preserved EF) were enrolled in the SENIORS group with EF > 35%. The study participants were followed for 21 months for the primary endpoint of all-cause death

or cardiovascular hospitalization. Nebivolol reduced the primary endpoint by a similar amount in the 35% and > 35% groups. However, while there was a trend towards a beneficial effect of nebivolol in the EF > 35% group, the result was not statistically significant. The study was not sufficiently powered to analyze the EF subgroups, and because the mean EF in the EF > 35% group was below what is considered “preserved” this trial did not provide definitive evidence regarding the use of vasodilating beta blockers in HFpEF.⁷⁴

The Effects of the Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction (ELANDD) trial was a randomized, double-blind, placebo-controlled study of nebivolol in patients with HFpEF. The study enrolled a total of 116 patients with NYHA class II-III HF, diastolic dysfunction, and an EF >45% for 6 months and examined change in 6-minute walk test distance (6MWT) as the primary endpoint. The nebivolol group failed to significantly improve 6MWT, whereas the placebo group saw a statistically significant improvement (from 420±143 to 428±141 m with nebivolol vs. from 412±123 to 446±119 m with placebo, P = 0.004 for interaction). No improvement was observed in peak VO₂ testing among either groups. The investigators attributed the negative chronotropic effects of nebivolol to the study outcome.

9. Phosphodiesterase-type 5 inhibitors

Phosphodiesterase type-5 (PDE-5) has emerged as a potential therapeutic target in the context of its role in enhancing cGMP levels, which could result in (1) systemic vasodilation; (2) enhanced myocardial relaxation; and (3) pulmonary vasodilation. A small randomized controlled trial (n=44) by Guazzi et al. examined the effect of sildenafil on hemodynamics and exercise capacity in HFpEF patients with LVH and RV dysfunction (and clear evidence of combined pre- and post-capillary pulmonary hypertension), and found that sildenafil therapy was associated with improvements in functional status and exercise capacity.⁷⁵ However a subsequent larger, multicenter randomized controlled trial, the Phosphodiesterase-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure (RELAX) trial, found that sildenafil was not associated with improved exercise capacity in HFpEF.⁷⁶ Differences between these 2 trials are significant and worth noting. The study by Guazzi et al. recruited a subgroup of HFpEF characterized by significant LVH, pulmonary vascular disease, and RV dysfunction, which may have been a key reason why sildenafil was beneficial in this study. RELAX, on the other hand, recruited patients across the spectrum of HFpEF, and did not specifically require the presence of pulmonary hypertension. A subsequent European trial of sildenafil in HFpEF (which was somewhat similar to RELAX in terms of the type of patients that were enrolled) also did not show any benefit.⁷⁷ Although inhibition of PDE5 in the myocardium theoretically should result in increased cGMP, subsequent studies have shown that PDE5 is not upregulated in the myocardium of HFpEF patients, and due to impaired soluble guanylate cyclase (sGC), there is likely a problem with cGMP production in HFpEF (as opposed to breakdown of cGMP by PDE5). Thus, in most HFpEF patients (particularly those without severe LVH), PDE5 inhibition is unlikely to be helpful. Alternatively, in HFpEF patients with superimposed pulmonary vascular disease (i.e., combined pre- and

post-capillary pulmonary hypertension), sildenafil may be beneficial through its effects on the pulmonary vasculature. Thus, the 3 clinical trials of PDE5 inhibitors draws attention to the exciting opportunity of personalized medicine in HFpEF through targeting of specific drug types to specific subsets of HFpEF patients.

10. Novel pharmacological agents for the treatment of HFpEF

The demand for better pharmacologic treatments for patients with HFpEF remains high, and several drugs targeting novel mechanisms are in development. (PARAMOUNT), a phase 2, double-blind randomized controlled trial, studied the angiotensin receptor-neprilysin inhibitor LCZ696 (valsartan + sacubitril) versus valsartan for 36 weeks in 308 patients with HFpEF. In PARAMOUNT, Solomon et al. found that LCZ696 therapy led to a reduction in NTproBNP and left atrial size.⁷⁸ A large-scale phase 3 pivotal trial (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON]) is currently being conducted to determine the effect of LCZ696 on morbidity and mortality in HFpEF.

Endothelin, a potent vasoconstrictor, is well known to be involved in the pathogenesis of systemic and pulmonary hypertension and HFpEF.⁷⁹ Endothelin receptor antagonists (ERA) represent an exciting pharmacologic approach to rectify systemic and pulmonary vascular dysfunction in HFpEF. Early studies have been promising, and a recent phase 2 study demonstrated improved exercise tolerance but no improvement in echocardiography findings with sitaxsentan.⁸⁰ Studies have shown bosentan improves hemodynamics and clinical outcomes in end-stage heart failure patients with pulmonary hypertension suggesting a possible opportunity in some HFpEF patients.⁸¹ A Phase 2A study of bosentan in patients with combined pre- and post-capillary pulmonary hypertension (MELODY) has been completed but the results are not yet available.

The inorganic nitrate-nitrite pathway has recently been explored as a novel pathway to restoring NO bioavailability in HFpEF. In contrast to organic nitrates, these substances have been shown to serve as important NO reservoirs, and have been shown to be utilized during hypoxia and acidosis thereby delivering NO at time of need. The benefits of inorganic nitrates-nitrites have been long known by endurance athletes to improve exercise performance, usually in the form of beet juice concentrate. Eggebeen et al demonstrated these benefits in HFpEF patients using a beetroot juice concentrate containing 12.9 mmol of inorganic nitrate which showed improved submaximal aerobic exercise capacity.^{82, 83} Borlaug et al showed hemodynamic benefits of sodium nitrite in two separate studies. The first study demonstrated an acute sodium nitrite infusion attenuates the maladaptive hemodynamic derangements during exercise in HFpEF patients.⁸⁴ A second study investigated inhaled sodium nitrite, and revealed reductions in biventricular and left atrial filling pressures both at rest and during exercise.⁸⁵ These studies suggest a possible role of this drug class in the treatment of HFpEF, particularly in improving symptoms and quality of life. INDIE and KNO3CKOUT-HFpEF are phase 2b randomized controlled trials testing inhaled and oral nitrites, respectively, on exercise capacity, physical activity, and quality of life in HFpEF.

Sodium-glucose cotransporter-2 inhibitors (SGLT-2) are a new type of hypoglycemic agent for diabetes that block glucose reuptake in the kidney tubule, inducing both hypoglycemic and diuretic effects. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG Outcomes) trial showed a substantial benefit in mortality and cardiovascular outcomes in patients with type 2 diabetes taking the SGLT-2 inhibitor empagliflozin.⁸⁶ Although speculative, the benefit of SGLT-2 inhibitors in HFpEF may be mediated by 2 primary mechanisms: (1) augmenting diuresis by their actions in promoting glycosuria (2) improving diabetes and promoting weight loss which could have secondary beneficial effects on myocardial and skeletal muscle function. Empagliflozin was especially effective in reducing HF hospitalization and progression, suggesting a potential benefit in HFpEF.⁸⁷

Soluble guanylate cyclase (sGC) stimulators are another class of pharmacologic agents targeted specifically at the driving pathologic mechanisms of HFpEF, by enhancing the activity of guanylate cyclase, an enzyme that synthesizes cGMP from GTP. By enhancing activity of sGC, these therapeutic agents have been shown to improve endothelial and myocardial function independent of NO.^{88–90} This is particularly important in HFpEF, where there may be a problem with cGMP production. Given the lack of cGMP production in HFpEF, stimulating sGC may therefore be more fruitful than inhibiting its breakdown (with PDE5 inhibitors).

The SOLuble guanylate Cyclase stimulator in heArT failure Study in preserved ejection fraction (SOCRATES-Preserved) study is a phase 2 dose-finding trial of the sGC stimulator vericiguat that measured changes in NT-proBNP and left atrial volume at 12 weeks in patients with worsening HFpEF who had recently been hospitalized for HF.⁹¹ Results were presented at the 2016 European Heart Failure Association meeting; vericiguat was well tolerated, but was not associated with an improvement in the co-primary endpoints of NTproBNP or left atrial volume. However, vericiguat was associated with significant, dose-dependent improvements in quality of life. The lack of improvement in NTproBNP and left atrial volume may have been due to the fact that the patients enrolled in SOCRATES-Preserved had more advanced HFpEF (given their recent hospitalization for HFpEF), which is known to be associated with larger left atrial volume and higher NTproBNP, both of which may have been difficult to improve within the short time frame of the trial. In addition, many patients in SOCRATES-Preserved had atrial fibrillation—improving left atrial volume in these patients is likely to be quite difficult. The improvement in quality of life may have been due to the effects of sGC stimulation on the vasculature and/or skeletal muscles. The tissue-to-plasma concentration ratio of sGC stimulators can vary from organ to organ, and may have been higher in non-cardiac tissues compared to the heart in the case of vericiguat.

Riociguat, which is similar to vericiguat except shorter-acting, was recently studied in the Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated with Diastolic Heart Failure (DILATE-1) trial. The investigators sought to describe the acute hemodynamic effects of riociguat infusion on invasive hemodynamics in HFpEF patients with elevated pulmonary capillary wedge pressure (PCWP) and mean PA pressure (mPAP). The drug did not reduce mPAP or PCWP, but did increase stroke volume

(+9 mL [95% CI, 0.4–17]; $P=.04$), reduced systolic BP (–12 mmHg [95% CI, –22 to –1]; $P=.03$), and reduced RV end-diastolic area (–5.6 cm² [95% CI, –11 to –.03]; $P=.04$), suggesting a possible benefit in this patient population.⁹²

Many HFpEF patients exhibit marked increases in left atrial pressure during exercise, which can result in profound dyspnea and inability to exercise.⁹³ The Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial is a prospective, randomized, sham-controlled clinical trial evaluating a novel interatrial shunt device (IASD) in patients with HFpEF and offers a non-pharmacologic approach to unload the left atrium without compromising LV filling or output.⁹⁴ This phase II study has recently finished enrollment, and previous unblinded, single-arm studies have demonstrated promising results for safety and efficacy.^{95, 96}

11. Conclusions

Although much work needs to be done, substantial progress has been made in the pharmacologic treatment of HFpEF. It is important to realize that in this complex patient population, with multiple competing factors for morbidity and mortality, overwhelmingly positive results from a single agent in the broad HFpEF population (which is highly heterogeneous) is unlikely. Nevertheless, lack of breakthrough trial results should not deter providers from using the agents discussed above when appropriate, as some of them have been shown to improve exercise capacity and reduce HF hospitalizations. Furthermore, as described above, there are several promising treatments currently being tested in patients with HFpEF.

12. Expert Opinion

Although the aforementioned HFpEF clinical trials are encouraging, they still have fallen far short of the expectations and successes seen in HFrEF. Recently, it has been argued the failure of these prior trials can be attributed to the presence of heterogeneity within the HFpEF syndrome, with the realization that multiple different HFpEF phenotypes exist, along with several drivers of disease pathogenesis in HFpEF.^{8, 11, 59, 78, 97–101} Failure to match these specific HFpEF phenotypes to the most appropriate clinical trials and therapy has been postulated as a contributor to recent failures.¹⁰² Targeted therapy is already well established in modern cancer care, and has improved outcomes in that field.^{103–108} Novel analytic techniques such as machine learning, coupled with deep phenotypic data, genomics, proteomics, and metabolomics, will hopefully allow us to determine which medicines will work for specific subtypes of HFpEF patients, and is likely the only way forward to truly improve outcomes for this challenging clinical syndrome. These techniques should also be applied to predict probability of side effects, which pose a major challenge in this complex patient population.

Drivers of disease pathogenesis in HFpEF include obesity, hypertension, and renal insufficiency, which propagate cardiac dysfunction by inflammation and endothelial dysfunction.^{94, 109, 110} These underlying pathogenic factors affect other organs, leading to pulmonary hypertension, skeletal muscle weakness, and sodium retention which serve as

distinct clinical features to be targeted by specific therapies.¹¹¹ Given the diverse etiologic factors and clinical presentations of HFpEF, we advocate the use of a “matrix approach” to guide individualized therapy in HFpEF (Table 1).

When treating HFpEF patients, we use the following stepwise approach: (1) confirm the correct diagnosis of HFpEF (including invasive hemodynamic and/or exercise testing if necessary), and determine the underlying etiology; (2) aggressively treat comorbidities such as coronary artery disease and diabetes; (3) counsel on caloric restriction, low sodium diet, and maintaining mobility and regular exercise; (4) treat volume overload with loop diuretics, but once euvolemic minimize the loop diuretic dose by using thiazide diuretics and mineralocorticoid receptor antagonists; (5) control systemic hypertension using a “HFpEF-centric” approach by controlling volume overload first and then treating with ACE-inhibitors/ARB and vasodilating beta-blockers such as carvedilol; (6) look for and treat for chronotropic incompetence, pulmonary vascular disease, and cardiac microvascular dysfunction in patients who do not respond to initial measures or who have specific clinical manifestations that warrant additional work-up; (7) follow the matrix in Table 1 to personalize HFpEF therapy; and (8) enroll in a HFpEF clinical trial. This treatment strategy enables the physician to design, based upon the underlying pathophysiology and salient features, a treatment regimen personalized to each individual.

In the theme of personalized HFpEF therapy, it is important to remind ourselves that the patients’ preferences should ultimately drive our decision making. Although no study has yet been conducted assessing patients’ preference for quality versus quantity of life gained by therapy, it is inappropriate to assume this population maintains the same preferences described in HFrEF.^{112–115} Compared to HFrEF, these patients tend to be much older, with significant disabling comorbidities, which means that HFpEF patients are even more likely than HFrEF prefer an improved quality of life over quantity of life. Such preferences are vitally important as we consider the design of future HFpEF clinical trials, which should be focused more on improving quality of life rather than simply trying to reduce mortality.

Optimizing pharmacologic therapy for the treatment of HFpEF is best done on an individualized basis, based upon each patients’ drivers of pathophysiology, dominant disease features, and goals of therapy. As the field progresses and we gain a better understanding of the different mechanisms at play, this model of precision medicine will become standard of care for the complex HFpEF syndrome.

Acknowledgments

SJ Shah has received grant support from the National Institutes of Health R01 HL107577 and R01 HL 127028; and the American Heart Association #16SFRN28780016 and #15CVGPPSD27260148.

SJ Shah has received grant support from Actelion, AstraZeneca, Corvia, and Novartis; and consulting fees from Actelion, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Ironwood, Merck, Novartis, Pfizer, and Sanofi.

ABBREVIATIONS

ACE angiotensin converting enzyme

ARB	angiotensin receptor blocker
cGMP	cyclic guanosine monophosphate
CI	confidence interval
EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrfEF	heart failure with reduced ejection fraction
HR	hazard ratio
LV	left ventricular
LVH	left ventricular hypertrophy
NO	nitric oxide
NTproBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PDE-5	phosphodiesterase-5
PKG	protein kinase G
RV	right ventricular
sGC	soluble guanylate cyclase

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HIGHLIGHTS

- HFpEF—a complex and heterogeneous clinical syndrome that affects the heart multiple other organs—is due to multiple different etiologies and pathophysiologies and therefore is unlikely to benefit from a one-size-fits-all treatment approach.
- Although there are several disease mechanisms that contribute to HFpEF, central to its pathogenesis in common forms of the syndrome is inflammation-induced endothelial dysfunction (with reduced nitric oxide availability) and impaired natriuretic peptide signaling lead to reduced cyclic GMP and protein kinase G, with resultant titin hypophosphorylation and increased cardiac stiffness. This disease mechanism, which is also likely present in multiple other extra-cardiac organs in HFpEF patients, is fundamentally different from HFrEF.
- Several completed large-scale clinical trials in HFpEF have been viewed as “failures” because they did not meet their primary outcome, which often included mortality. However, several drugs tested have resulted in improvements in quality of life and exercise capacity, and reduction in heart failure hospitalization, which are likely more meaningful outcomes to elderly, debilitated HFpEF patients compared to reduced mortality.
- Given the existence of multiple different HFpEF phenotypes, a phenotype-specific approach to HFpEF will likely lead to improved outcomes for these patients; thus HFpEF represents an ideal opportunity within cardiovascular medicine for precision medicine.
- Several novel pharmacotherapies are in development for HFpEF; clinical trials of these drugs will be most successful if therapies are targeted to HFpEF patients most likely to benefit based on mechanism of action and clinical phenotype.

Number at risk

Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

Figure 1.
CHARM-Preserved: Time to Cardiovascular Death or Hospital Admission for Heart Failure, Candesartan vs. Placebo. Used with permission from Yusuf S, et al. *Lancet* 2003; 362(9386): 777–81. [62]

Figure 2.
TOPCAT: Time to First Heart Failure Hospitalization, Spironolactone vs. Placebo. Used with permission from Pitt B, et al. *N Engl J Med* 2014; 370(15):1383–92. [68]

Figure 3.

TOPCAT Regional Differences: Cumulative Hazard Plots for Outcomes—Spironolactone vs. Placebo, Stratified by Region (Americas vs. Russia/Georgia). Panel A: time to primary outcome of cardiovascular death, aborted sudden cardiac death, or heart failure hospitalization; Panel B: time to cardiovascular death; and Panel C: time to first hospitalization for heart failure. Used with permission from Pfeffer M, et al. *Circulation* 2015; 131(1):34–42. [69].

Phenotype-specific HFpEF treatment strategy using a matrix of predisposition phenotypes and clinical presentation phenotypes

Table 1

HFpEF Clinical Presentation Phenotypes					
HFpEF Predisposition Phenotypes	Lung congestion	+Chronotropic incompetence	+Pulmonary hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial fibrillation
	Overweight/obese/metabolic syndrome/type 2 DM	<ul style="list-style-type: none">• Diuretics• Caloric restriction• Statins• Inorganic nitrite/nitrate• Sacubitril• Spironolactone	+Rate adaptive atrial pacing	+Exercise training program	+Cardioversion +Rate Control +Anticoagulation
	+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Exercise training program	+ACEI/ARB +Cardioversion +Rate Control +Anticoagulation
	+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Exercise training program	+Ultrafiltration if needed +Cardioversion +Rate Control +Anticoagulation
	+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Exercise training program	+ACEI +Revascularization +Cardioversion +Rate Control +Anticoagulation

A stepwise approach is proposed that begins in the left hand upper corner of the matrix with general treatment recommendations, presumed to be beneficial to the vast majority of HFpEF patients as they address the presentation phenotype of lung congestion and the predisposition phenotype of overweight/obesity present in >80% of HFpEF patients. Subsequently, supplementary (+) recommendations are suggested for additional predisposition-related phenotypic features when moving downward in the matrix and for additional presentation-related phenotypic features when moving rightward in the matrix. Arterial hypertension, renal dysfunction, and coronary artery disease are proposed as additional predisposition phenotypes. Additional clinical presentation phenotypes, in which specific therapeutic interventions could be meaningful, include chronotropic incompetence, pulmonary hypertension (especially combined precapillary and postcapillary pulmonary hypertension [CpcPH]), skeletal muscle weakness, and atrial fibrillation. Only therapeutic measures indicated in bold are currently established. All other therapeutic measures require further testing in specific phenotypes. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; and PDE5I, phosphodiesterase 5 inhibitor. Used with permission from Shah SJ, et al. *Circulation* 2016.