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Treatment Modalities for Heart Failure with Preserved Ejection Fraction (HFpEF) - Current State of Evidence and Future Perspective

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Abstract

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of patients with chronic heart failure and is associated with significant morbidity and mortality. To date, there are no approved therapies available for reducing mortality or hospitalizations for these patients. The failure to develop successful therapies for the management of HFpEF may be because of the poor understanding of the pathophysiology of HFpEF, inadequate standardization of the HFpEF diagnosis, the lack of strict definition and inadequate differentiation of disease subtypes. Several newer approaches, including Neprilysin inhibition therapy, offer promise for a new era of HFpEF treatment. This review article comprehensively summarizes the current state of evidence for the development of the therapies for HFpEF and the future/ongoing studies.

Keywords: Diastolic dysfunction; Heart failure with preserved ejection fraction; Therapeutic targets; Natriuretic peptides

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome characterized by presence of signs and symptoms of heart failure (HF) such as decreased exercise capacity and/or fluid retention in the setting of normal or near-normal left ventricular ejection fraction (LVEF) and impaired diastolic function [1]. More specific diagnostic criteria have evolved over time and include signs and symptoms of HF, objective evidence of diastolic dysfunction, disturbed left ventricular (LV) filling, structural heart disease, and elevated brain natriuretic peptides, as summarized in Table 1 [1-3].

It is now well established that approximately half of those patients who are hospitalized with clinical symptoms of heart failure have a preserved ejection fraction (HFpEF) [4]. The rate of hospitalization for HFpEF has increased over time, whereas those for HF with reduced ejection fraction (HFrEF) have declined [5]. Although the mortality of outpatient cohorts for HFpEF seems to be lower than that of HFrEF, the data is inconsistent for the in-patient mortality rates [5-7]. Unlike for HFrEF, there are no proven therapies that have shown to improve the morbidity and mortality in patients with heart failure with preserved EF. The few guideline-based therapies currently available are based on the recommendations from expert opinion [3,8]. This review article comprehensively summarizes the current state of evidence for the development of therapies for HFpEF and the future/ongoing studies.

Pathophysiology of HFpEF

It is important to understand the pathophysiology of HFpEF as most of the ongoing research for the development of therapies for HFpEF is focused on the underlying pathophysiologic mechanisms, with the goal of identifying a disease phenotype which may respond to treatment. However, the pathophysiology of HFpEF is quite complex and, thus far, not completely understood. It is related to cardiac structural and functional alterations, which together with systemic and pulmonary vascular abnormalities result in left ventricular (LV) abnormalities. These LV abnormalities are compounded by the poor vasodilator reserve, chronotropic incompetence, coronary disease and microvascular changes [9]. HFpEF is characterized by the abnormalities of both diastolic and systolic function that result in exercise intolerance. Most patients with HFpEF have normal LV size and ejection fraction but due to the increased LV mass, or relative wall thickness with concentric remodelling, the systolic function is often compromised [10]. Studies have shown that in HFpEF, longitudinal strain is generally reduced and radial strain is preserved, thus resulting in the appearance of a preserved EF. Diastolic dysfunction, the hallmark of HFpEF results in ineffective left atrium (LA) emptying and LV filling, along with a reduced ability to augment cardiac output on exertion, thus resulting in an increased pulmonary artery pressure and subsequent clinical sequelae of fluid retention [11,12].

Diastolic dysfunction can result either from increased LV stiffness due to hypertrophy and interstitial fibrosis or it may be due to abnormal LV relaxation secondary to abnormal calcium cycling. Animal studies have shown that cytoskeletal titin which functions, as a bidirectional spring, responsible for early diastolic recoil and late diastolic distensibility, are impaired in subjects with HFpEF [13,14]. Post translation modifications of titin have been recently described in patients with HFpEF, leading to impaired early recoil and reduced

compliance [15]. LV relaxation is an active process requiring energy [16,17].

Signs and Symptoms	Pulmonary Crackles/edema, ankle swelling, hepatomegaly, dyspnea on exertion and fatigue. Reduced Exercise Performance (reduced peak Oxygen consumption or 6 minute walking test).	Clinical Signs of failure, Chest X ray supporting presence of fluid, typical response to diuretics with or without evidence of low cardiac index.	Breathlessness, ankle swelling, fatigue, elevated jugular venous pressure, pulmonary crackles, displaced apex beat
LV Systolic Function	Normal/Mildly reduced LV systolic function.	LVEF ≥ 50% within 72 hours of HF	Normal/only mildly reduced LVEF with LV not being dilated.
Diastolic Dysfunction	Evidence of abnormal LV relaxation, filling, diastolic distensability or stiffness using invasive measurements or biomarkers.	Assessment of diastolic function is not needed for probable diagnosis	Relevant structural heart disease (i.e. LV hypertrophy/LA enlargement) and/or diastolic dysfunction

Table 1: Diagnostic criteria for HFpEF.

ATP is required to restore the physiologic cytoplasmic calcium concentrations. Disturbances in the ATP or calcium levels can impair LV relaxation as is often seen in patients with myocardial ischemia [18]. A recent study has shown that LV relaxation is virtually impaired in every patient with HFpEF, independent of presence of LVH or increased stiffness [19]. Considering that LV relaxation is an active physiological relaxation process, rather than a structural change, it is more likely to be responsive to pharmacological interventions.

Therapeutic targets for HFpEF

Therapy in HFpEF is aimed at amelioration of symptoms and improvement in function/quality of life. To date there has been no therapy that has shown to improve the mortality in patients with HFpEF. Clinical trials of several pharmacological interventions have failed to show any significant reductions in morbidity and mortality in patients with HFpEF (Table 2) [20-31].

Trial	No. of patients	Follow up duration (month)	Therapeutic intervention	Inclusion criteria	NYHA class	Primary endpoint	Outcomes
CHARM-Preserved [20]	3023	36.6	Candesartan 4-32 mg PO/day	Age ≥ 18; LVEF>40% and hospital admission for cardiac reason	II-IV	CV death or HF hospitalization	Candesartan vs placebo: CV death or HF hospitalization: 22% vs 24% ; HR 0.89 (95% CI 0.77-1.03)
I-Preserve [21]	4128	49.5	Irbesartan 75-300 mg PO/day	Age ≥ 60; LVEF ≥ 45% and symptomatic HF; NYHA class II-IV and hospitalized for HF in past 6 months	II-IV	Death from any cause or CV hospitalization	Irbesartan vs placebo: All-cause mortality or CV hospitalization: 36% vs 37%; HR 0.95 (95% CI 0.86-1.05)
PEP-CHF [22]	850	26.2	Perindopril 2-4 mg PO/day	Age ≥ 70; LVEF ≥ 40%; hospitalized for HF in past 6 months; Diastolic dysfunction on ECHO; Receiving diuretics for CHF	I-IV	All-cause mortality and HF hospitalization	Perindopril vs placebo: All-cause mortality or unplanned HF hospitalization: 23.6% vs 25.1% patients; HR 0.92 (95% CI 0.70-1.21)
RAAM-PEF [23]	44	6.5	Eplerenone 25-50 mg PO/day	Age ≥18; LVEF≥50%; clinical HF; BNP ≥ 100pg/ml	II-III	Change in 6 minute walk distance	Eplerenone vs placebo: Change in 6MWD Eplerenone- 271.4 + 75.7 m to 310.7 + 89.8 versus Placebo-249.0 + 66.8 m to 286.3 + 66.7 (p=0.91)
TOPCAT [24]	3445	39.6	Spironolactone 15-45 mg PO/day	Age ≥ 50; LVEF≥ 45%; hospitalized for HF in past 12 months or elevated BNP in 6 months	I-IV	CV death; HF hospitalization or aborted cardiac arrest	Spironolactone vs placebo: CV death, HF hospitalization, or aborted cardiac arrest: 18.6% vs 20.4%; HR 0.89 (95% CI 0.77-1.04)
Aldo-DHF [25]	422	11.6	Spironolactone 25 mg PO/day	Age ≥ 50; LVEF≥ 55%; ECHO evidence of diastolic dysfunction; peak VO_2 25ml/kg/min	II-III	Change in E/e', change in peak VO2	Spironolactone vs placebo: Spironolactone - E/e' 12.7 (SD, 3.6) to 12.1 (SD, 3.7) versus Placebo- E/e'

							12.8 (SD, 4.4) to 13.6 (SD, 4.3) (adjusted Mean difference, -1.5; 95% CI, -2.0 to -0.9; P=0.001). Spironolactone-Peak VO_2-16.3 [SD, 3.6] mL/min/kg to 16.8 [SD, 4.6] ml/min/kg versus Placebo -16.4 [SD, 3.5]ml/min/kg to 16.9 [SD, 4.4] ml/min/kg (adjusted mean difference,-0.1 ml/min/kg; 95%CI,-0.6 to-0.8 mL/min/kg; P=0.81)
ELANDD [26]	116	6	Nebivolol 2.5-10 mg PO/day	Age ≥ 40; LVEF>45%; ECHO evidence of diastolic dysfunction	II-III	Change in 6min walk distance	Nebivolol vs placebo: Change in 6MWD Nebivolol- 420 ±143 meters to 428 ± 141 meters versus Placebo- 412 ± 123 meters to 446 ± 109 meters (p=0.004)
SENIORS [27]	2128	21	Nebivolol 10 mg PO/day	Age ≥ 70; LVEF>35%; hospitalized for HF in past 12 months	I-IV	Death from any cause or CV hospitalization	Nebivolol vs placebo: All-cause mortality or CV hospitalization: 29% vs 33.6%; HR 0.81 (95% CI 0.63-1.04);
J-DHF [28]	245	38.4	Carvedilol 1.25-10 mg PO twice/day	Age ≥ 20; LVEF>45%; clinical HF	I-IV	CV death or unplanned HF hospitalization	Carvedilol vs no carvedilol: CV death or unplanned HF hospitalization: 21% vs 24%; HR 0.90 (95% CI 0.55-1.49)
RELAX [29]	216	6	Sildenafil 20 mg PO 3 times/day for 12 weeks, then 60 mg PO 3 times/day for 12 weeks	LVEF>50%; Objective evidence of HF; Reduced exercise capacity and either elevated NT-pro BNP or LV filling pressures	II-IV	Change in peak VO_2	Sildenafil vs placebo: Change in peak VO2 Sildenafil (-0.20 [IQR, -1.70 to 1.11] versus Placebo (-0.20 [IQR, -0.70 to 1.00]) (P=.90)
DIG Ancillary [30]	988	37.2	Digoxin 0.125-0.5 mg PO/day (median dose 0.25 mg PO/ day)	LVEF>45%; Clinical HF and Normal sinus rhythm	I-IV	HF hospitalization or HF mortality	Digoxin vs placebo: HF hospitalization or HF mortality: 23.4% versus 23.4% ; HR 0.82 (95% CI 0.63-1.07);
PARAMOUNT [31]	308	9	LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily	LVEF>45% NT-pro BNP >400 pg/ml	I-III	Change in NT-proBNP at 3 months	Ratio of change in proBNP for LCZ696/valsartan 0.77 (P=0.005)

Table 2: Randomized clinical trials of Heart Failure with preserved ejection fraction. CHARM: Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; I-PRESERVE: Irbesartan in Heart Failure with Preserved Ejection Fraction Study; PEP-CHF: Perindopril in Elderly People with Chronic Heart Failure; RAAM-PEF: Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction; Aldo-DHF: Aldosterone Receptor Blockade in Diastolic Heart Failure; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; ELANDD: Effects of Long-Term Administration of Nebivolol on the Clinical Symptoms, Exercise Capacity, and Left Ventricular Function of Patients with Diastolic Dysfunction; J-DHF: Japanese Diastolic Heart Failure; DIG: Digitalis Investigation Group; RELAX: Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; PARAMOUNT: Prospective Comparison of ARNI With ARB on Management of Heart Failure with Preserved Ejection Fraction; BNP: Brain Natriuretic Peptide; CHF : Congestive Heart Failure; CI: Confidence Interval; CV: Cardiovascular; DB: Double-Blind; E/E': Left Ventricular Diastolic Dysfunction; HF: Heart Failure; LV: Left Ventricular; LVEF: Left Ventricular Ejection Fraction; NT-Probnp: N-Terminal Brain Natriuretic Peptide Precursor; NYHA: New York Heart Association; Peak VO_2: Maximum Exercise Capacity; 6MWD: 6 Minute Walking Distance, Pg: Picogram.

Many of the therapies that have been suggested for patients with HFpEF are currently still in need of further research. However, as we continue to increase our knowledge and understanding regarding the pathophysiology of HFpEF, we can begin to find potential targets for this increasingly prevalent condition.

Therapies targeting diastolic dysfunction

There are multiple left arteriolar and left ventricular parameters that predict outcome in patients with heart failure. Diastolic dysfunction leads to increase in the LV mass, mass/volume ratio, LA area and diastolic wall stress in patients with HFpEF [12,32-34]. A suggested target-specific therapy to counteract this pathophysiologic phenomenon would be one which can manipulate the cellular and molecular signalling pathways which cause an increased LV distensability, thus improving relaxation, recoil and filling, which would help improve diastolic function. Titin, a giant cytoskeletal structural protein is expressed in sarcomeres that function as molecular springs [13,14]. It stores energy during contraction and releases this energy during relaxation. Stiffer titin increases diastolic myocyte stiffness. Studies have shown that therapies that increase cyclic guanosine monophosphate (cGMP) can decrease myocardial diastolic stiffness in HFpEF by activating protein kinase G, which then phosphorylates the stiff titin isoform and thereby improves the LV diastolic function [35-38]. Further research is still needed in order to assess the magnitude and the time frame of these changes and how they would translate to clinical outcomes.

Therapies targeting late sodium current inhibition

Increased cytosolic calcium during diastole is another proposed potential mechanism of HFpEF pathophysiology. In the setting of ischemia or HF, there is an increase in the number of late sodium currents that occur during the myocyte depolarization process [39]. This process leads to excess calcium accumulation during diastole via the sodium/calcium exchange pump, which results in impaired relaxation [39,40]. In studies using non-ischemic cardiac myocytes, Ranolazine was found to decrease late sodium current and there by decrease calcium overload and diastolic dysfunction (Figure 1) [41,42]. The Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) [43] study was a proof-of-concept trial that evaluated the effect of Ranolazine versus placebo on the effects of hemodynamics and measures of diastolic dysfunction. After a thirty minute infusion of the drug, significant decreases from baseline were observed in LV end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP) in the Ranolazine group, but not in the placebo group [43,44]. Studies are still underway with regards to the true potential use of this medication and its long term effects on morbidity/mortality in patients with HFpEF.

Therapies targeting LV fibrosis and RAAS inhibition

Left ventricular fibrosis occurs early in the evolution to HFpEF and represents a worthwhile therapeutic target in the syndrome. Fibrosis comprises both the heart and vascular system, which impacts both diastolic and systolic function. Fibrosis leads to myocardial stiffening, impeding both suction and filling, and the loss of early diastolic suction and have major deleterious effects on exercise capacity in patients with HFpEF [45].

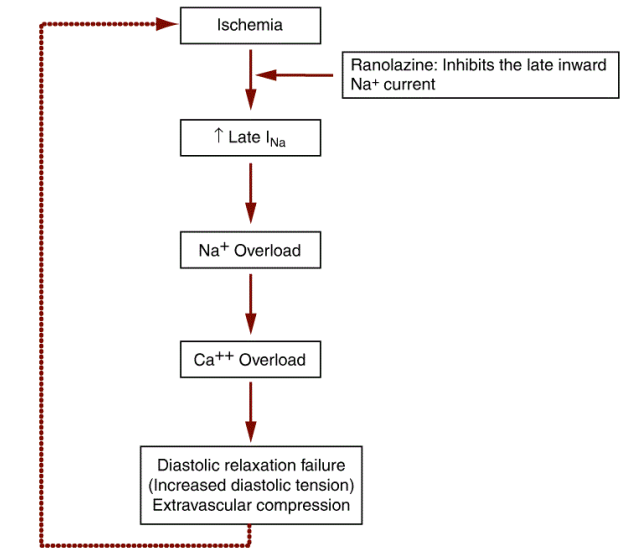

Figure 1: Mechanism of action of Ranolazine. It works by decreasing the magnitude of the pathologically enhanced late sodium which helps prevent calcium overload thereby avoiding the resulting myocyte stiffness.

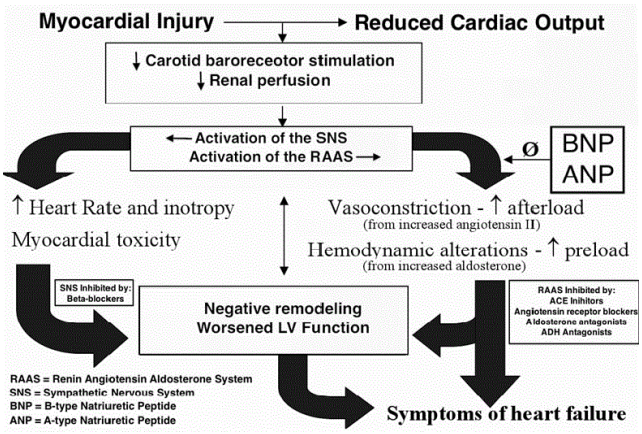

Figure 2: Mechanism of action of RAAS inhibitors in heart failure.

Aldosterone mediates vascular and cardiac remodelling and binds to the mineralocorticoid receptor stimulating cardiac fibroblasts, and increases collagen synthesis and deposition. These events lead to myocardial fibrosis and increased LV stiffness [46,47] (Figure 2). Blocking the renin-angiotensin-aldosterone system (RAAS), with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB), is aimed at improving the outcomes in patients with HFpEF, as it was thought to do in patients with HFrEF. However, the major outcome trials, namely CHARM-preserved (Candesartan), PEP-CHF (Perindopril), I-preserve (Irbesartan), RAAM-PEF (Eplerenone), TOPCAT and Aldo-DHF (Spironolactone), failed to show any mortality benefit in patients with HFpEF [20-25].

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial 20 compared candesartan versus placebo. After 37 months, there was no difference in the composite primary end point for cardiovascular death or heart failure readmission, though fewer patients were admitted with heart failure in the candesartan group (230 *vs* 279, P=0.017) [20]. The study did not include measurements of diastolic dysfunction, and the diagnosis of HFpEF was clinically determined by the site investigator. There was a low overall death rate of 23% during the extended trial follow-up [20]. In the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial of Irbesartan against placebo, there was no statistically significant difference in the primary outcome of death from any cause or cardiovascular admission [21]. Similar to previous trials, the HFpEF diagnosis was established by the site investigator, without requiring echocardiographic documentation of diastolic dysfunction, and with only modest elevations in the N-terminal-pro-brain natriuretic peptide (NT-pro-BNP, medians 360 pg/ml in the Irbesartan arm *vs* 320 pg/ml in the placebo arm) [21]. However, compared with the previous trials, the follow-up was longer (50 months) and the event rates were higher (36%), though study-drug discontinuation remained high (34%) [21]. A second trial, Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF), compared perindopril versus placebo [22]. The primary end point of all-cause mortality and heart failure admission was similar between groups. Although most patients had evidence of left atrial enlargement and LVH (>75%), the NT-pro-BNP was only mildly elevated and higher in the placebo group (mean 335 pg/ml in the perindopril group *vs* 453 pg/ml in the placebo group) [22]. The overall event rate was low (24%), limiting the power of the study. Moreover, at the end of follow-up, 35% of patients assigned to perindopril and 37% assigned to placebo were on open-label ACE-inhibitors [22].

The Treatment of Preserved Cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial was designed to address clinical outcomes of aldosterone blockade in HFpEF [24]. A total of 3445 patients with LVEF of 45% or higher and at least 1 admission for heart failure in the preceding 12 months (or BNP>100 pg/ml or NT-pro-BNP>360 pg/ml if no hospitalization) were randomized to spironolactone (target dose of 30 mg daily) or placebo [24]. After an average follow-up of 3.5 years, there was no difference in the primary end point of cardiovascular death, heart failure admission, or surviving a cardiac arrest (HR 0.89; 95% CI 0.77-1.04; P 5.138). There was a reduction in the secondary end point of heart failure readmissions (12% in spironolactone group *vs* 14.2% in the placebo group, HR 0.83; 95% CI 0.69-0.99; P 5.042) [24]. The results of these trials were likely related to the modest diuretic effect of spironolactone.

The Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial compared spironolactone 25 mg daily versus placebo in 422 patients with LVEF of 50% or higher, echocardiographic evidence of diastolic dysfunction or atrial fibrillation, and peak VO_2 of 25 ml/kg/min or less [25]. At 12 months, patients on spironolactone had improved left ventricular end-diastolic filling, left ventricular mass index, and neuro-humoral activation [25]. However, there was no difference in left atrial size or in the clinical end points of exercise capacity, clinical symptoms, or quality of life.

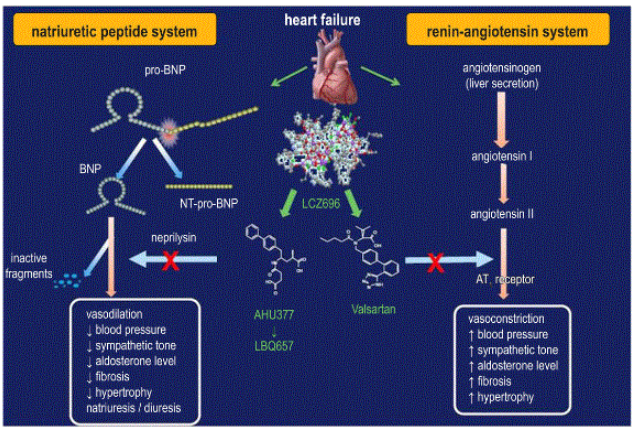

Figure 3: Schematic showing the mechanism of LCZ696: Heart failure stimulates both the renin-angiotensin system and the natriuretic peptide system. LCZ696 is composed of 2 molecular moieties, the angiotensin receptor blocker valsartan and the neprilysin inhibitor.

Similar to previous HFpEF trials, the population was healthier (87% NYHA II), had low NT-pro-BNP levels (median 153 ng/L), and fewer comorbidities (5% with atrial fibrillation) [25]. However, at 12 months, there was significant decrease in the systolic and diastolic blood pressure, which may support the importance of strict blood pressure control in this population [25].

In conclusion, RAAS antagonism for the primary goal of improving outcomes in HFpEF provides modest benefits at best. However, such a therapeutic strategy does not appear harmful and should be considered for the treatment of appropriate concomitant common comorbidities in HFpEF.

Therapies targeting natriuretic peptides

Natriuretic peptides (NP), including BNP and atrial NP (ANP), have both anti-proliferative and natriuretic properties which play a crucial role in fluid homeostasis. They are released in response to ventricular stretch, resulting in vasodilation, natriuresis and myocardial relaxation. Natriuretic peptides have been shown to be decreased with HFpEF, with many patients having B-type NP levels of <100 [48]. Neprilysin is a protease enzyme that degrades NPs, thus inhibition of this enzyme could potentially help in reducing fluid overload in patients with heart failure. The novel drug LCZ696, which contains both angiotensin receptor (similar to valsartan) and neprilysin inhibitors, has shown promising results in patients with HFpEF (Figure 3) [31]. The PARAMOUNT 31 trial was a phase II trial, comparing LCZ 696 with valsartan in 308 patients with symptomatic heart failure, LVEF of at least 45% and elevated NT-proBNP levels. At 12 weeks, N-terminal pro-BNP levels were reduced by 26% in the LCZ696 arm as compared to the Valsartan group [31]. Additionally at 36 weeks, patient in the LCZ696 arm had greater improvements in left atrial size; with symptom severity improvement (thus diminished their NYHA classification index) [31]. PARAGON-HF is a large phase III trial, currently enrolling patients, which aims to investigate the impact of LCZ696 on cardiovascular death and HF hospitalization in patients with HFpEF (clinicaltrials.gov NCT01920711).

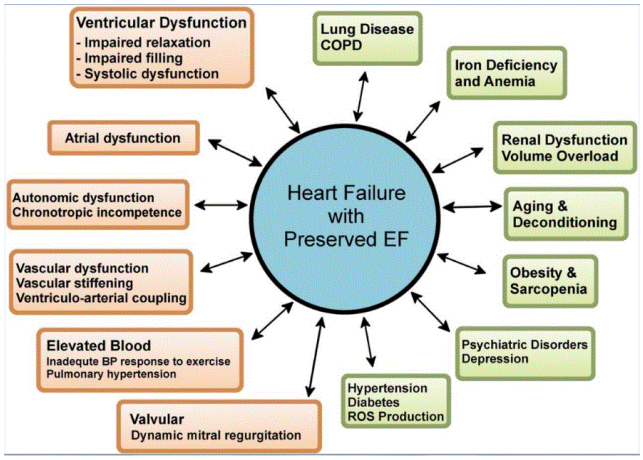

Figure 4: Heterogeneity of heart failure with preserved ejection fraction.

Therapies targeting pulmonary hypertension

Pulmonary hypertension is a hemodynamic consequence of HFpEF. Pulmonary hypertension is associated with higher mortality in patients with HFpEF, leading to the hypothesis that it is an active pathophysiological factor in HFpEF progression, rather than solely an effect of left heart dysfunction. Inhibition of phosphodiesterase-5 leads to the accumulation of intracellular cGMP and nitric oxide-induced pulmonary vasodilation in patients with pulmonary arterial hypertension. In a study performed by Guazzi and colleagues [48,44] patients with HFpEF with LVEF ≥ 50%, who were in sinus rhythm with a pulmonary artery pressure measured >40 mmHg (estimated by echocardiography) were randomized to receive placebo or sildenafil 50 mg three times daily for 12 months [48]. At 6 and 12 months, patients receiving Sildenafil had significantly lower right atrial pressure, pulmonary artery pressures, wedge pressure, and increased quality of life scores as compared with the placebo group [48]. The PhosphdiesteRasE-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure (RELAX) trial enrolled a total of 216 outpatients with heart failure, LVEF of 50% or higher, elevated NT-pro-BNP (or elevated filling pressures) with reduced exercise capacity. Patients were randomized to sildenafil 20 mg three times daily for 12 weeks, followed by 60mg three times daily for 12 weeks versus placebo [29]. The participants were representative of a typical HFpEF population with mean age of 69 years, 48% women, and 53% with moderate heart failure symptoms. Comorbidities were common (85% hypertension, 51% atrial fibrillation, 55% stage 3/4 kidney disease) and there was significant diastolic dysfunction (median NT-pro-BNP 700 pg/ml, median left atrial volume index 43 ml/m^2) [29]. At 24 weeks, there was no difference between groups in any end point, including peak oxygen consumption, 6-minute walk distance, quality of life, diastolic function, or left ventricular remodelling. Although results from the RELAX trial could not statistically validate the use of sildenafil in the management of HFpEF, patients with the pulmonary hypertension phenotype were not specifically targeted [29]. Small randomized clinical trials with sildenafil are on-going in patients with HFPEF with evidence of pulmonary hypertension [49]. Another group of agents currently being studied are stimulators of soluble guanylate cyclase which act as receptors for nitric oxide stimulation of soluble guanylate cyclase, thus resulting in increased activity of the cGMP-PKG pathway. The oral soluble guanylate cyclase stimulator, BAY1021189, is currently being investigated in patients with worsening HFpEF (SOCRATESPRESERVED; clinicaltrials.gov NCT01951638).

Therapies targeting heart rate and beta receptor blockade

Increased heart rate has been correlated with adverse outcomes in HFpEF. A sub-study of the I-Preserve trial found an inverse association between heart rate (in sinus rhythm) and the incidence of cardiovascular death or heart failure hospitalizations [50]. Ivabradine, an If-channel inhibitor, which works directly on the sinus node to decrease heart rate without negative inotropic effects, holds promise in diastolic dysfunction, as slower heart rates would permit greater diastolic filling time, and may be particularly well-suited for patients whose symptoms predominantly occur with exercise. Favourable data from an animal model indicated improvements in vascular stiffness, ventricular elastance, and diastolic function following selective heart rate reduction with Ivabradine [51]. One clinical study has recently reported on the short-term use of Ivabradine in HFpEF [52]. Sixty one patients were randomized to take Ivabradine or placebo for 7 days. This small clinical study of Ivabradine showed significant improvements in exercise capacity, peak oxygen uptake and diastolic function as measured by echocardiography [52]. Ivabradine may be a promising therapy for patients with symptoms that only occur during exercise.

Similarly to patients with HFrEF, patients with HFpEF have elevated serum levels of norepinephrine, suggesting a potential target for therapy [53]. Beta-blockers have demonstrated improved survival, left ventricular function, and myocardial remodelling in animal models of hypertension with diastolic heart failure [54,55]. Initial retrospective data in patients with LVEF >40% suggested improved survival in patients treated with beta-blockers, but this concept has being challenged in other registry analyses and RCTs [56,57]. The Effect of Long-term Administration of Nebivolol on clinical symptoms, exercise capacity and left ventricular function in patients with Diastolic Dysfunction (ELANDD) trial randomized 116 patients with NYHA II to III, LVEF greater than 45%, and echocardiographic evidence of diastolic dysfunction to Nebivolol 10mgdaily versus placebo [26]. After 6 months of treatment, there was no change in six minute walk test distance or peak oxygen uptake. The investigators suggested that the negative chronotropic effects of nebivolol could be implicated in the lack of response to exercise capacity [26]. In the Study of the Effects of Nebivolol Intervention on Outcomes and Re-hospitalization in Seniors (SENIORS) trial of nebivolol versus placebo, there was a modest decrease in the primary composite end point of all-cause mortality or cardiovascular admission (HR 0.86; 95% CI 0.74-0.99; P=0.039) with nebivolol [27]. The effects of nebivolol were similar in patients with LVEF 35% or higher and less than 35%, but only a third of patients had an LVEF greater than 35%, with the trial not powered to identify a difference in reduced versus preserved EF subgroups. The subgroup of patients with an LVEF greater than 50% was too small to draw meaningful conclusions [27].

The Japanese Diastolic Heart Failure (J-DHF) study compared the effects of carvedilol versus placebo in 245 patients with a clinical diagnosis of heart failure and LVEF greater than 40% [28]. After a median follow-up of 3.2 years, there were no differences in the composite end point of cardiovascular death or heart failure admission [28]. The study did show lower rates of the primary end point in

patients who achieved standard doses (defined >7.5 mg daily) compared with controls (HR 0.54; 95% CI 0.303-0.959; P 5.0356). However, the study was underpowered and had a low event rate of 8% compared with the expected 30% [28].

The available evidence does not provide conclusive evidence for beta-blockade in HFpEF. Moreover, beta-blockade may exacerbate chronotropic incompetence, which is common in HFpEF. For these reasons, routine use of beta blockade for the treatment of HFpEF cannot be advocated. However, specific subgroups, such as patients with concomitant atrial fibrillation, may derive a clinical benefit from empiric beta blockade to improve diastolic filling time.

Therapies targeting comorbidities

Important targets for HFpEF, as with other form of HF, include co-morbidities because poorly controlled co-morbidities increases the risk of readmission in patients with HFpEF. These co-morbidities include coronary artery disease, hypertension, obstructive sleep apnea, atrial fibrillation, diabetes and chronic kidney disease (Figure 4). Treatment with continuous positive airway pressure has shown promise with reversing diastolic dysfunction [58]. The maintenance of sinus rhythm in patients with HFpEF is also important; and, catheter ablation of atrial fibrillation has been shown to improve diastolic function [59]. Diabetes mellitus is a major risk factor for diastolic dysfunction and the development of HFpEF. Diabetes directly affects myocardial structure and function through a variety of mechanisms independent from other cardiovascular risk factors [60]. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, diabetes was an independent predictor of cardiovascular death or cardiovascular hospitalization in patients with either HFpEF or HFrEF [61]. Treatment of elevated systolic and diastolic blood pressure is important, because lowering BP is associated with reduced risk of developing HF in patients with hypertension [62,63]. Because myocardial ischemia can worsen HFpEF, it should be detected and treated with either pharmacological agents such as beta blockers, calcium channel blockers and nitrates, or with revascularization.

Conclusion

The ideal treatment modality for HFpEF should be one that is able to relieve symptom but also provide mortality and morbidity benefit. Unfortunately, to date, there has been no treatment that has proven to accomplish both aims. Studies of neuro-hormonal blocking agents in patients with HFpEF have failed to show a mortality benefit or a clear improvement in quality of life. Although inhibitors of the RAAS and sympathetic nervous system should continue to be used in the population of patients with HFpEF who have other comorbidities such as HTN, diabetes mellitus, or CAD, the use of these drugs for the primary treatment of HFpEF remains unsupported by the available evidence. While usage of drugs like LCZ696 seems promising, research is still on-going with regards to whether this would truly help patients with multiple comorbidities, such as atrial fibrillation, which makes the myocardium less responsive to intervention. With the global health impact of HFpEF, more research will need to be conducted in order to find the appropriate combination of medications required to decrease both mortality and morbidity for patients suffering with this disease.

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