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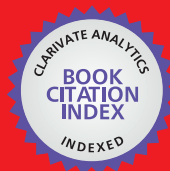
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Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is now recognized as a major and growing public health problem worldwide. This heart failure subtype disproportionately affects women and the elderly and is commonly associated with other cardiovascular comorbidities, such as hypertension, diabetes and chronic kidney disease. There are uncertainties and debates regarding the definition, diagnosis and pathophysiology with the consequence that all outcome trials performed so far cannot yield an effective treatment as in heart failure with reduced ejection fraction (HFrEF). Here we present an overview of epidemiology, pathophysiology, diagnosis and therapeutic approaches emerging from large outcome clinical trials.

Keywords: heart failure, ejection fraction, diastolic, diagnosis, treatment

1. Introduction

Heart failure (HF) is a clinical syndrome of dyspnea, fatigue and fluid retention secondary to impaired cardiac function [1]. Cardiac function may be impaired structurally or functionally with resultant decreased ejection or filling capacity both of which can reduce cardiac output and/or increase intracardiac pressures at rest or during exercise. Systolic dysfunction leading to reduced left ventricular ejection fraction (LVEF) (LVEF < 40%) had long been believed to be the predominant cause of heart failure. However, HF remains to be a growing health problem in the community despite recent improvements in the management of HF with reduced ejection fraction (HFrEF). Another subset of heart failure which occurs in the setting of normal or near normal left ventricular ejection fraction (LVEF > 50%) has been evolving for the last two decades. This distinct HF subtype has been called HF with preserved ejection fraction (HFpEF). Once included in HFpEF, the newly defined HF with midrange EF (HFmrEF) comprises the HF patients with EF between 40 and 50% [2]. HFmrEF will be discussed in

the context of HFpEF because most of the trials and epidemiological studies to date have included patients with EF > 40%.

Current data indicate that at least half of the HF population has a normal or near-normal LVEF [3]. Even more striking is the finding that the percent of patients with HFpEF appears to be increasing in relation to the percent that have HFrEF [4]. One of the reasons for this shift in the ratio between HFpEF and HFrEF is related to the greater availability of therapeutic interventions that limit myocardial damage (particularly, in the setting of an acute myocardial infarction), hence reducing incidence of HFrEF. Another important reason for this increase in prevalence of HFpEF is increasing number of obese and elderly patients. It is also worth mentioning that there is an increased number of patients with possible misdiagnosis of HFpEF who have otherwise alternative causes for their symptoms such as obesity, lung disease and myocardial ischemia [5].

In the past, HFpEF was thought to be a benign condition, but now it is well known that it causes substantial morbidity and mortality [6]. Despite being an enormous and dreadful problem of this era, there has been little progress in developing effective treatments that will alter the natural history of the condition. Contemporary medicine can offer nothing but only diuretic for treatment. This is partly due to an incomplete understanding of the disease and partly due to the huge diversity of clinical phenotype.

2. Epidemiology

Over 90% of patients with HFpEF are aged ≥ 60 years at the time of diagnosis making it obvious that this is a disease of elderly [7]. The prevalence in the community has varied from 1.1% to 5.5% of the general population [8]. This wide variation is primarily attributed to the different cutoff values of normal EF in different studies. Moreover, the prevalence has been found to vary with age and gender. A large community-based study found that the prevalence of HFpEF increased from 0% in males to 1% in females in the age group of 25–49 years to 4–6% in males and 8–10% in females above 80 years, indicating a dramatic rise in the prevalence with increasing age but additionally a higher prevalence among females as compared to age-matched males [9]. The demographic characteristics present in patients with HFpEF differ significantly from those in patients with HFREF. Compared with those with HFrEF, patients with HFpEF are older, more often female, more often have hypertensive heart disease and less often have ischemic heart disease [10]. There is a similar prevalence of DM but remarkably higher prevalence of obesity in patients with HFpEF compared to HFrEF. Atrial fibrillation (AF) is also more prevalent in HFpEF [11]. HFpEF patients also have a higher burden of both cardiovascular and non-cardiovascular comorbid diseases. **Table 1** summarizes various comorbidities usually seen in association with HFpEF. Comorbid conditions especially renal insufficiency and atrial fibrillation may be less common in randomized controlled trials than hospital-based registries due to exclusion criteria.

Whether overall mortality rates differ between patients with HFpEF and HFrEF is not clear. Some community-based epidemiological studies have shown that the annual mortality rate is

Comorbid conditions	Frequency
Hypertension	60–80%
Ischemic heart disease	35–70%
Diabetes	20–45%
Atrial fibrillation	15–40%
COPD	31%
Renal insufficiency	26%

COPD: Chronic obstructive pulmonary disease.

Table 1. Comorbid conditions seen in association with HFPEF.

same and approaches 15% for both groups of patients [4]. Conversely, data from randomized clinical trials suggest that patients with HFpEF have a lower annual mortality (approaching 5%) than patients with HFrEF. The lower mortality rate detected in the randomized trials can be explained by strict exclusion of comorbid diseases [12]. When the data from I-PRESERVE (The Irbesartan in Heart Failure With Preserved Ejection Fraction Study) trial was analyzed with respect to mode of death in HFpEF, it was seen that cardiovascular (CV) diseases (60%) are the leading cause of death including sudden cardiac death (26%), HF (15%), myocardial infarction (5%) and stroke (9%) followed by non-CV causes (30%) and unknown (10%) [13]. Compared with HFrEF [14], HFpEF patients have more non-cardiovascular (30% vs. 15%), fewer sudden (26% vs. 40%) and fewer heart failure deaths (15% vs. 35%). In parallel with I-PRESERVE trial results, the cause-specific mortality estimates show that the non-cardiovascular causes of death constitute nearly 30 to 50% of all deaths in HFpEF patients while only 15–18% in HFrEF patients [15]. The older age and high burden of comorbidities can explain the higher non-cardiovascular mortality in HFpEF patients. Large HFpEF trials showed that the patients with HFpEF have lower hospitalization rates than those with HFrEF [16]. Furthermore, HFrEF patients have nearly 1% absolute higher in-hospital mortality rate than HFpEF patients [17].

3. Pathophysiology

In contrast to HFrEF patients who have main abnormalities in systolic function, left ventricular dilation and eccentric remodeling, patients with HFpEF have main abnormalities in diastolic function, normal left ventricular size and concentric hypertrophy. Normal LVEF does not imply normal cardiac output. In HFrEF, decreased cardiac output can be explained more easily with reduced ejection fraction and subsequent reduced stroke volume. HFpEF patients also exhibit a low cardiac output that is comparable to that seen in HFrEF patients. The pathophysiological abnormality leading to decreased cardiac output in HFpEF is more complex and since HFpEF is a heterogeneous clinical diagnosis, it encompasses a variety of underlying pathophysiological processes.

HFpEF is caused by the complex interplay of multiple impairments in ventricular diastolic function, adverse cardiac remodeling, stiffening of the ventricles, pulmonary hypertension,

atrial dysfunction and abnormal ventricular-vascular coupling related to stiffening of the vasculature and hence decreased vascular compliance, endothelial dysfunction, impaired vasodilatation and coronary ischemia, impaired renal handling of salt and fluid and impairment of heart rate (HR) reserve [18]. Left ventricular diastolic dysfunction is the result of myocardial hypertrophy, fibrosis and/or altered myocyte calcium handling (delayed calcium uptake by the myocyte sarcoplasmic reticulum and calcium efflux from the myocyte) [19]. The pathophysiology of diastolic dysfunction includes delayed relaxation, impaired LV filling and/or increased stiffness. A slowing of the normal diastolic relaxation of the ventricle can in turn increase the left ventricular and left atrial pressures [20].

There are a number of causes, which lead to HFpEF. Age seems to be the dominant risk factor for HFpEF. Heart failure with preserved EF is exclusively a disease of elderly. As one ages, there is an increased collagen deposition with a reduction in the amount of elastin, which can lead to increased stiffness of the heart and blood vessels leading to ultimate HFpEF. Chronic hypertension, which is highly prevalent in HFpEF, leads to left ventricular hypertrophy and increased connective tissue content, both of which decrease cardiac compliance. Due to decreased compliance, in HFpEF LV functions on a steeper diastolic pressure-volume relationship compared with the normal ventricle. This leads to decreased LV end-diastolic volumes and a compensatory rise in LV filling pressure to maintain cardiac output. This high LV filling pressures lead to fluid accumulation in the lungs, which cause dyspnea, which is the common symptom of heart failure. As well as leading to symptoms of dyspnea, elevation in LV filling pressures produces secondary pulmonary hypertension and atrial remodeling that can predispose a patient to the development of right ventricular (RV) dysfunction and atrial fibrillation, respectively. Although epicardial coronary artery disease causing ischemic heart disease is less common in patients with HFpEF compared to HFrEF, subendocardial ischemia related to increased left ventricular diastolic pressures in a left ventricle with concentric remodeling is more common in patients with HFpEF. Multiple studies have shown an association between endothelial dysfunction and HFpEF and endothelial dysfunction was suggested to be as a prominent determinant of HFpEF [21]. Vascular stiffness is also an important contributor to pathophysiological process that leads to HFpEF. As a result of ventricular-arterial uncoupling, cardiac output decreases. Regardless of EF, ultimate decrease in cardiac output causes activation of neurohormonal mechanisms that lead to activation of vasoconstriction, salt and water retention and increased diastolic filling pressures [22]. HFpEF patients display neurohormonal profiles similar to HFrEF, with elevated circulating neurohormones, such as natriuretic peptides and norepinephrine [23].

Chronotropic incompetence (CI) is a potential pathophysiological factor in HFpEF, contributing to reduced exercise capacity. The increase in heart rate as a result of an activity or exercise is one of the two main contributors of increased cardiac output to meet the excess need of energy consumption. Moreover, the increase in HR is the strongest contributor to the ability to perform sustained aerobic exercise [24]. Phan et al. have shown that CI can be seen in patients with HFpEF during maximal exercise [25]. In this study, the prevalence of CI was 35% in HFpEF subjects. Chronotropic incompetence may be a significant contributor to severe, symptomatic exercise intolerance, which is the most common symptom in HFpEF. Atrial fibrillation (AF) is also common in patients with diastolic dysfunction and contributes

to the pathophysiology of HFpEF. AF eliminates the late diastolic atrial contribution to LV filling, upon which patients with diastolic dysfunction are dependent and is poorly tolerated leading to both pulmonary edema and decreased cardiac output.

4. Diagnosis

The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. Part of the challenge is the fact that the HFpEF is a heterogeneous clinical entity, whose manifestations and outcomes remain difficult to be predicted. In essence, it's a diagnosis of exclusion. According to the recent ESC 2016 HF guideline [2], for the diagnosis of HFpEF, three essential criteria should be met. **Table 2** shows these criteria for diagnosis of HFpEF. As in HFrEF, HFpEF is a clinical diagnosis. Symptoms are often nonspecific and do not, therefore, help discriminate between HFpEF and HFrEF. Exercise dyspnea may be the only symptom with no detectable sign especially in the early stages of HFpEF. Exercise dyspnea is particularly difficult to interpret in elderly and in obese, comprising most of the HFrEF population. Objective evidence of reduced exercise capacity provided by cardiometabolic exercise testing with measurement of peak exercise oxygen consumption (VO_{2max}) or by the 6 min walking test can be used for judgment of exercise dyspnea in the context of HF symptom. Signs of congestive HF such as lung crepitations, pulmonary edema, jugular venous distention and ankle edema may not always be present, especially in the early stages. The "presence of signs or symptoms of congestive heart failure" as the first criterium for the diagnosis of HFpEF is therefore put instead of the "presence of signs and symptoms of congestive heart failure" [2].

Once a clinical diagnosis of HF has been made, the presence of HFpEF can be established by confirming a normal or near-normal LVEF, often by an echocardiogram. Echocardiography is an essential tool in evaluating patients with unexplained dyspnea. Bearing in mind that HFpEF is a diagnosis of exclusion, echocardiography should first provide information about the left ventricular systolic performance (commonly assessed using ejection fraction), valvular disease and pericardial disease. After exclusion of other possible explanations for HF, echocardiography should provide evidence of structural heart disease such as left ventricular hypertrophy, left atrial enlargement and pulmonary hypertension. Diastolic dysfunction can also be diagnosed further using the Doppler echocardiography (based on mitral inflow

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- 1) Symptoms and/or signs of congestive heart failure
 - 2) Non-dilated left ventricle (LV end-diastolic volume index (LVEDVI) $< 97 \text{ mL/m}^2$) with preserved ejection fraction ($\geq 50\%$)
 - 3) a) Elevated levels of natriuretic peptides
 - b) At least one additional criterion
 - i) Relevant structural heart disease (LVH and/or LAD)
 - ii) Diastolic dysfunction

BNP, B-type natriuretic peptide; HFPEF, heart failure with preserved ejection fraction; LAD, left atrial dilation; LV, left ventricular; LVH, left ventricular hypertrophy.

a Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

b $\text{BNP} > 35 \text{ pg/ml}$ and/or $\text{NT-proBNP} > 125 \text{ pg/mL}$.

Table 2. Criteria for the diagnosis of HFPEF.

velocities). It is graded based on the ratio of the early, E, to late diastolic, inflow velocity, A (mild, moderate and severe) [26]. Grade I is abnormal relaxation pattern ($E < A$), grade II is pseudonormal pattern ($E > A$), grade III is restrictive pattern ($E \gg A$) and grade IV is irreversible restrictive pattern [27]. The pseudonormal stage (grade II), which refers to a situation when filling pressures are elevated but the mitral inflow pattern appears normal, is creating a state of confusion. Assessment of pulmonary vein flow (PVF) velocity waveforms provide information complementary to that obtained from transmitral flow (TMF) patterns. Therefore, PVF pattern can be used to differentiate a normal from a pseudonormal TMF pattern. Grade III and grade IV diastolic dysfunctions are called restrictive filling dynamics. These are both severe forms of diastolic dysfunction and patients tend to have advanced HF symptoms at this stage.

Elevated LV filling pressures are the main and essential physiologic consequence of diastolic dysfunction. In the presence of symptoms and/or signs of HF and normal or near-normal EF, high LV filling pressures help a lot to put the diagnosis of HFpEF. Pulsed-Doppler-derived TMF is largely influenced by preload. Left ventricular filling pressures can also be estimated by myocardial tissue-Doppler-derived early diastolic annular velocity, designated E' which is, to a large extent, regarded as a preload-independent index of diastolic performance. The use of tissue Doppler imaging-derived indices that correct for the influence of myocardial relaxation on the load-dependent early diastolic mitral flow E/E' ratio (i.e., the ratio of mitral inflow, E, to early diastolic annular velocity, E') as a means of estimating LV filling pressure is more reliable. Therefore, noninvasive diagnostic evidence of diastolic LV dysfunction is preferably derived from myocardial TD. If myocardial TD yields values $E/E' > 15$, it puts diagnosis of high LV filling pressure. When the ratio is lower than 8, LV filling pressures are considered low. If TD yields an E/E' ratio suggestive of LV diastolic dysfunction but not diagnostic ($15 > E/E' > 8$), then additional echo variables are required for diagnostic evidence of LV diastolic dysfunction, which include Doppler flow profile of mitral valve or pulmonary veins, measurement of LV mass index (LVMi) or left atrium volume index (LAVi), electrocardiographic evidence of atrial fibrillation, or high levels of BNP or NT-proBNP. No single echocardiography variable is sufficiently accurate to be used in isolation to make a diagnosis of LV diastolic dysfunction. Therefore, a comprehensive echocardiography examination incorporating all relevant two-dimensional and Doppler data is recommended [2]. Invasive method of measuring filling pressure is more precise and yields higher diagnostic performance but not practical. Invasive diagnostic evidence of diastolic LV dysfunction can be obtained by LV end-diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP). Filling pressures are considered elevated when the mean PCWP is >12 mm Hg or when the LVEDP is >16 mm Hg.

It is noteworthy that diastolic dysfunction is not always present in HFpEF, being observed by echocardiography in only two-thirds of patients at rest [28]. However, many patients with HFpEF display elevated LV filling pressures only during the stress of exercise, indicating an earlier stage of disease [29]. In such patients, the diagnosis of HFpEF could only be made using exercise hemodynamic evaluation using supine bicycle diastolic stress test. After stress, an increase in E/E' and tricuspid regurgitation (TR) velocity indicating a high pulmonary artery systolic pressure can truly put the diagnosis of HFpEF [2].

Biomarkers have been recently used in the diagnostic workup of HF. BNP is synthesized and released upon LV wall stretch from increased pressure or volume. The plasma levels of BNP are raised in HF regardless of EF. However, natriuretic peptides (NPs) are less elevated in HFpEF compared to HFrEF. NPs are an important aid for the diagnosis of HF, especially in the non-acute setting when echocardiography is not immediately available. In the Breathing Not Properly study, BNP levels at the time of emergency admission were significantly elevated in HFpEF, when compared to other causes of dyspnea (median 413 vs. 34 pg/ml, $p < 0.001$) but significantly lower than in patients with HFrEF (median 413 vs. 821 pg/ml, $p < 0.001$) [30]. Many patients with HFpEF display elevated filling pressures only during exercise. This intermittent nature of pressure elevation is likely to explain the reduced BNP level observed in patients with HFpEF [31].

5. Challenges in the diagnosis of HFpEF

Diagnosis of HFpEF is more difficult than the diagnosis of HFREF because it is largely one of the exclusions, i.e., potential noncardiac causes of patients' symptoms (lung disease, anemia, chronic kidney disease, or obesity) that must first be eliminated. For most patients with a diagnosis of heart failure but preserved left ventricular systolic function based on symptoms and signs of HF which are highly nonspecific and normal EF, the diagnosis of HFpEF is rarely needed [5]. Before ascribing symptoms to HFpEF for which there is no evidence-based treatment, we should thoroughly investigate patient for other possible treatable causes of dyspnea with calculation of body mass index, pulmonary function testing, exercise electrocardiography and probably stress echocardiography.

The diagnostic criteria put forward for HFpEF has some important pitfalls. In HFpEF, exertional dyspnea is frequently the earliest symptom due to increased LV filling pressures ensuring some degree of pulmonary congestion. Since many patients with HFPEF present with dyspnea and no signs of fluid overload, exertional dyspnea was considered sufficient clinical evidence to suggest the presence of clinical heart failure in the recent guidelines [2]. Keeping in mind that dyspnea is a ubiquitous complaint especially in elderly and obese who represent a large proportion of HFpEF patients and other comorbid conditions such as chronic obstructive pulmonary disease and renal insufficiency which are usually present concomitant with HFpEF, dyspnea cannot be a reliable diagnostic criteria without objective evidence of reduced exercise performance provided by metabolic exercise testing. Meanwhile, because early signs and symptoms of HFpEF such as exercise dyspnea may also be the presenting symptoms of other alternative conditions or diseases, delayed diagnosis has also been a matter.

Diastolic dysfunction as assessed noninvasively by echocardiography is highly prevalent in elderly population who has no symptoms attributable to HF. This condition suggests some controversy regarding the accuracy of noninvasive measures of diastolic function by echocardiography [32]. Assessment should take into consideration patients' ages and heart rates (mitral E, E/A ratio and annular e' decrease with increasing heart rate). Specifically, in older individuals without histories of cardiovascular disease, caution should be exercised before concluding that grade I diastolic dysfunction is present. Because the majority of subjects aged

over 60 years without histories of cardiovascular disease have E/A ratios, <1 and E deceleration time (EDT) > 200 ms, such values in the absence of further indicators of LV dysfunction (e.g., LV hypertrophy and LA enlargement), can be considered normal for age. In other words, echocardiogram suggesting diastolic dysfunction on the basis of an abnormal E/A ratio is not diagnostic and represents insufficient investigation. Second, the echocardiographic markers of diastolic dysfunction may be absent in a significant proportion of patients diagnosed with HFpEF.

Natriuretic peptides could give inconclusive results in a number of situations. In normal individuals, the concentration of NT-proBNP rises with age and is higher in women than in men [33]. Therefore, age-stratified cutoff points for NT-proBNP (≥ 450 for ages < 50 years, ≥ 900 for 50–75 years and ≥ 1800 pg/mL for > 75 years) were shown to perform the best diagnostic performance for rule in acute HF setting [34]. Beyond HF, a number of cardiopulmonary disorders are also associated with elevated BNP or NT-proBNP values: acute coronary syndrome, myocarditis, valvular heart disease, hypertrophic cardiomyopathy, cardiotoxic drugs, atrial fibrillation, or flutter and right ventricular dysfunction in the setting of significant pulmonary disease (pulmonary hypertension, pulmonary embolism). Other conditions that are associated with higher BNP or NT-proBNP levels may be related to comorbidities such as advanced age, renal dysfunction, stroke, sepsis and other high output states. It should be kept in mind that plasma levels of BNP rise independently of LV filling pressures once glomerular filtration rate falls below 60 mL/min because renal dysfunction is highly prevalent in HFpEF population. AF also confounds the utility of BNP for diagnosing HFpEF [35, 36].

6. Treatment

Prevention of HFpEF through treatment of risk factors (e.g., hypertension, diabetes and coronary artery disease) especially at early stages is effective and still the most important part of management of HFpEF since specific treatments are yet to be discovered [37]. Hypertension antedates the development of HFpEF in nearly 90% of the cases and it confers a two- to three-fold increased risk of developing HFpEF [38]. Therefore, strict control of hypertension will inevitably prevent development of HFpEF. Improving cardiorespiratory fitness among low-fit sedentary individuals by exercise training could be another preventive approach against HFpEF. And, targeting obesity in the early childhood will also prevent development of HFpEF in the future.

As a non-pharmacologic therapy, exercise training has clearly been shown to benefit cardiorespiratory health in patients with HFrEF. Recent studies have addressed the effects of exercise training in patients with HFpEF. Although the effects on HF-related mortality and hospitalizations were not studied, these reports showed that moderate supervised exercise program had positive effects on the quality of life, exercise tolerance but not left ventricular EF [39, 40]. No pharmacologic therapy has been shown to be effective in improving outcomes in patients with heart failure with HFpEF. There is no single explanation for the negative results of past HFpEF trials. Potential contributors include an incomplete understanding of HFpEF pathophysiology, inadequate diagnostic criteria, recruitment of patients without true HF or at

early stages of the syndrome, poor matching of therapeutic mechanisms and primary pathophysiological processes, suboptimal study designs, inadequate statistical power, or patient heterogeneity [41]. Another possible explanation is the fact that non-cardiovascular mortality is higher in HFpEF than HFrEF highlighting one of the difficulties in the development of an effective therapeutic strategy in the overall patients with HFpEF.

The treatment recommendations from the American Heart Association have set four goals in the management of these patients: (a) control of hypertension, (b) control of heart rate especially in the patients with atrial fibrillation, (c) control of pulmonary and peripheral edema and (d) prevention of myocardial ischemia [1]. 2013 ACC/AHA Guideline on HF had only two class I recommendations for HFpEF treatment. One of them is the use of diuretics in order to reduce volume overload and improve dyspnea. The second one is the control of blood pressure. The guideline also recommends revascularization in patients whom symptoms or demonstrable ischemia are thought to contribute HF symptoms as class II recommendation. Management of AF is another class II recommendation of the American guideline. The guideline does not underscore rhythm control or rate control in HFpEF since there was no specific trial comparing these two strategies in HFpEF until now. The recent 2016 European Society of Cardiology (ESC) Guideline could not make any further recommendations on top of 2013 American guideline in this regard except recommending screening patients with HFpEF for both cardiovascular and non-cardiovascular comorbidities, which then should be treated accordingly [2].

Table 3 summarizes the major clinical trials that have evaluated the efficacy of various therapeutic drugs in patients with HFpEF. The renin-angiotensin-aldosterone system (RAAS) is involved in many of the pathophysiological processes associated with this disease (including hypertension, left ventricular hypertrophy, myocardial fibrosis and vascular dysfunction) and inhibitors of this system can prevent neurohormonal activation and prevent ventricular remodeling [22]. RAAS blockers have been long time investigated whether they could be effective therapeutic option for these patients. Three large trials have evaluated inhibitors of the RAAS in patients with HFpEF but none of them proved to be beneficial. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-preserved trial evaluated the effect of candesartan on elderly patients with HFpEF [42]. Candesartan showed no significant reduction of cardiovascular death but showed significant reduction in HF hospitalization. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial was a randomized placebo-controlled trial which evaluated the effect of perindopril on patients with HFpEF [43]. At the end of the study, perindopril showed no significant effect on mortality, but showed significant benefit in unplanned HF hospitalization in 1 year. The Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) investigated the effect of the angiotensin-receptor blocker irbesartan on mortality and cardiovascular morbidity in patients with HFpEF [44]. Treatment with irbesartan did not reduce the risk of death or hospitalization for cardiovascular causes among HFpEF patients nor did it improve any of the secondary clinical outcomes, including disease-specific quality of life.

The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors (SENIORS) with Heart Failure, which consist of both HFrEF and HFpEF patients,

Trial	Year	Intervention	No. of subjects	Key inclusion criteria	Key exclusion criteria	Outcome(s)	Findings
CHARM-preserved	2003	Candesartan versus placebo	3023	Age > 18 years LVEF > 40% NYHA class II–IV	Persistent systolic or diastolic hypertension	Hospitalization Mortality	No effect on mortality Slight reduction in HF hospitalization
PEP-CHF	2006	Perindopril versus placebo	846	>40%		Rehospitalization at 1 year Mortality	No effect on mortality Decreased 1 year rehospitalization and increased exercise capacity
SENIORS	2006	Nebivolol versus placebo	752	>35%		CV-related hospitalization Mortality	No effect on mortality or hospitalization in patients with EF > 40%
I-PRESERVE	2008	Irbesartan versus placebo	4128	Age > 60 years LVEF > 45% NYHA class II–IV and HF hospitalization < 6 months or NYHA class III/IV and abnormal CXR, ECG, or echocardiogram	AF with resting heart rate > 120 beats/min Cor pulmonale Clinically significant pulmonary disease Significant valvular disease Hb < 11 g/dl BP > 160/95 mm Hg despite therapy	Mortality Hospitalization	No effect on mortality or CV hospitalization
ALDO-DHF	2013	Spirolactone versus placebo	422	Age > 50 LVEF > 50% NYHA class II or III Echo evidence of diastolic dysfunction (grade ≥I) Atrial fibrillation at presentation, maximum exercise capacity (peak VO ₂) < 25 mL/kg/min	Significant CAD Significant pulmonary disease GFR < 30 ml/min MI or CABG in past 3 months	Improvement in diastolic function (E/e') And maximal exercise capacity (VO ₂)	Improved diastolic function Induced reverse remodeling Improved neuroendocrine activation but not improve heart failure symptoms or quality of life and slightly reduced 6 min walk distance

Trial	Year	Intervention	No. of subjects	Key inclusion criteria	Key exclusion criteria	Outcome(s)	Findings
TOPCAT	2014	Spirolactone versus placebo	3445	Age > 50 LVEF > 45% ≥1 HF hospitalization in the previous 12 months or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL Controlled systolic blood pressure asystolic blood pressure < 140 mm Hg or 140 to 160 mm Hg if on ≥3 antihypertensive medications	COPD Infiltrative of hypertrophic CMP Significant valve disease AF with resting heart rate >90 beats/min GFR < 30 ml/min MI or CABG in past 3 months PCI in past 30 days	Death from cardiovascular causes Aborted cardiac arrest Hospitalization for HF	No effect on cardiovascular death Reduced HF hospitalization Induced an increase in serum creatinine and potassium levels
PARAMOUNT	2012	LCZ 696 versus valsartan	301	Age > 40 years EF > 45%, NYHA class II and III, Elevations of NT-proBNP > 400 pg/ml	LVEF < 45% Isolated right heart failure owing to pulmonary disease Dyspnea from non cardiac causes GFR < 30 ml/min Primary valvular or myocardial diseases Coronary or cerebrovascular diseases needing revascularization within 3 months	Reduction in NT-proBNP at 12 weeks NYHA functional class and LA dimension at 36 weeks	Reduced natriuretic peptides at 12 weeks Improved NYHA class and improved left atrial dimensions at 36 weeks

Trial	Year	Intervention	No. of subjects	Key inclusion criteria	Key exclusion criteria	Outcome(s)	Findings
RELAX HF	2013	versus placebo	216	LVEF > 45% NYHA II–IV Previous hospitalization for HF Increased pro NT-pro BNP or invasively measured high filling pressure Peak VO ₂ < 60%	Any obstacle for exercise testing Need for nitrate therapy Primary pulmonary Arteriopathy Primary valve disease Other causes of dyspnea	Exercise capacity Clinical status	No effect on exercise capacity or clinical status

All abbreviations are explained in the text of the manuscript.

Table 3. Major clinical trials in patients with HFPEF.

showed that a beta1-blocker with nitric oxide-potentiating vasodilatory effect, nebivolol, reduces hospitalization in older HF patients with preserved and reduced EF but had no effect on mortality [45]. Preserved EF was considered as EF > 35% which constitutes 35% of the overall study population. The proportion of patients with truly preserved EF (>50%) was very small. Therefore, although the overall study suggests a modest benefit of nebivolol, the results can't be extrapolated to true HFpEF patients.

The mineralocorticoid receptor antagonists spironolactone and eplerenone have been shown to reduce total and cardiovascular mortality across the spectrum of HFrEF and in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure [46–48]. By reducing cardiac fibrosis and hypertrophy, aldosterone antagonists have the potential to be beneficial in heart failure with preserved ejection fraction (HFpEF) [49]. In the Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial, the effect of spironolactone on diastolic function and exercise capacity in patients with HFpEF was tested [50]. The left ventricular end-diastolic filling, left ventricular remodeling (LV mass index decreased but LA diameter not changed) and neurohumoral activation (NT pro-BNP decreased) were improved with spironolactone, demonstrating aldosterone effect on improving diastolic function and reversing cardiac remodeling. However, spironolactone had no effect on functional exercise capacity in this trial. Upon positive findings with spironolactone on diastolic function and cardiac remodeling, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial was planned to investigate whether treatment with spironolactone would reduce morbidity and mortality in patients with HFpEF [51]. The TOPCAT trial found that, compared to placebo, spironolactone did not reduce the composite of cardiovascular death, aborted cardiac arrest or heart failure hospitalization in patients with HFpEF but reduced the individual component of heart failure hospitalization. However, there was a significant interaction between treatment effect and patient recruitment strategy (natriuretic peptides vs. hospitalization with HF). In patients recruited based on previous hospitalization, spironolactone had no effect on outcome, whereas in patients recruited based on high BNP, spironolactone showed a benefit. This difference highlights the importance of patient selection criteria and recruitment of patients with true HFpEF for future trials. The efficacy of eplerenone on 6 min walking distance was evaluated in a single-center, randomized study. It was found that after 24 weeks of eplerenone treatment, there was no change in 6 min walk distance [52]. Another randomized, clinical study evaluated the effect of eplerenone on the primary outcome comprising of death from cardiovascular causes, nonfatal reinfarction, hospitalization for unstable angina, or decompensation of heart failure [53]. Eplerenone was found to have no significant effect on the primary outcome.

Phosphodiesterase-5 (PDE-5) metabolizes the nitric oxide and natriuretic peptide systems' second messenger cyclic guanosine monophosphate and thus may limit beneficial nitric oxide and natriuretic peptide actions in the heart, vasculature and kidneys. Phosphodiesterase type 5 inhibitors (PDE5I) increase cGMP levels by blocking their catabolism. PDE5I may reduce ventricular-vascular stiffening, antagonize maladaptive chamber remodeling, improve endothelial function, reduce pulmonary vascular resistance and enhance renal responsiveness to natriuretic peptides [54, 55]. Phosphodiesterase type 5 inhibitor, sildenafil, was proved to improve hemodynamic parameters in HFrEF patients [56]. The Phosphodiesterase-5

Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial was conducted to investigate the effect of the PDE-5 inhibitor, on exercise capacity in HFpEF [57]. At the end of 24 weeks, long-term PDE-5 inhibition in HFpEF had no effect on maximal or submaximal exercise capacity, clinical status, quality of life, left ventricular remodeling, diastolic function parameters, or pulmonary artery systolic pressure.

It is known that in both the failing heart and in case of ischemia, the late sodium current is increased, leading to an Na^+ accumulation in cardiac myocytes [58]. The increased Na^+ concentration reverses the mode direction of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, contributing to a Ca^{2+} overload in the cell. Increased diastolic Ca^{2+} impairs relaxation leading to diastolic dysfunction. By inhibiting the late Na^+ channel, ranolazine is theoretically expected to prevent (or reduce) sodium accumulation in the myocyte. This should improve calcium extrusion through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and thereby improve relaxation of the myocardium. The Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) study was designed to evaluate the effect of ranolazine versus placebo on hemodynamics, measures of diastolic dysfunction and biomarkers in 20 patients with HFpEF [59]. After 30 min of infusion, significant decreases from baseline were observed in LVEDP and PCWP in the ranolazine group, but not in the placebo group. However, ranolazine had no effect on invasively determined relaxation parameters and the noninvasive E/E' ratio.

In the recent PARADIGM-HF trial, the patients taking LCZ 696 showed steep reduction in the primary endpoint of CV death/heart failure hospitalization [60]. McMurray et al. noted that a subgroup of patients in the reduced EF spectrum's high end, i.e., LVEF approaching 40%, also benefits to the same extent as the overall study group [61]. Solomon et al. conducted prospective comparison of Angiotensin Receptor Neprilysin Inhibitor (ARNi) with Angiotensin Receptor Blocker (ARB) on Management of heart failure with preserved ejection fraction, PARAMOUNT trial, a double-blind randomized trial in 301 patients with heart failure with HFpEF, which compared LCZ696 with valsartan [62]. The primary endpoint, the decline in NT-proBNP, was significantly greater in the LCZ696 group than in the valsartan group. After 36 weeks, both left atrial volume and dimension, which reflect left ventricular filling pressure, also declined more with LCZ696 and there was greater improvement in the New York Heart Association (NYHA) functional class with LCZ696 than with valsartan.

These encouraging results with LCZ696 have provided the rationale for a large outcomes trial in HFpEF. Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) will use a similar overall study design to that of PARAMOUNT to determine whether LCZ696 can reduce cardiovascular death or total HF hospitalizations in patients with HFpEF. PARAGON-HF will enroll 4,300 patients with HFpEF until the end of 2016.

7. Future perspectives

Diagnosis of HFpEF should only be made after complete workup and if noninvasive diagnostic data comprising of LA dilation, diastolic dysfunction and high natriuretic peptide levels,

or invasively measured high LVEDP or PCWP proves indisputably the presence of high LV filling pressure. Only when more specific diagnostic criteria have emerged over time and started to be used in the clinical trials for patient recruitment, we will see improvements in outcome for this common and growing form of cardiac disease. The strategy of a tailored “precision” approach considering both the comorbidities concomitant with HFpEF and underlying pathophysiologic mechanism of reduced cardiac and vascular reserve will lead to improvement in prognosis of HFpEF.

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