

Management Strategies for Heart Failure with Preserved Ejection Fraction



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KEYWORDS

• Heart failure • Preserved ejection fraction • LCZ696

KEY POINTS

- The management of HFpEF is challenging and requires an accurate diagnosis. Although currently there is no convincing therapy that can prolong survival in patients with HFpEF, treatment of fluid retention and of comorbidities, such as hypertension, myocardial ischemia, and atrial fibrillation, may improve symptoms and quality of life.
- Spironolactone may be considered in patients with HFpEF with an elevated BNP, and if prescribed, patients require monitoring of potassium levels and renal function.
- Future outcome trials of HFpEF testing the efficacy of promising new agents, such as LCZ696, will have better characterization of patient phenotype to maximize the potential response to therapies.

INTRODUCTION

Epidemiologic studies have shown that approximately half of patients with heart failure (HF) have normal or near normal ejection fraction (EF); this syndrome is referred to as HF with preserved EF (HFpEF).^{1–3} The overall cost of HF was estimated to be more than \$30 billion for 2012,⁴ and the prevalence and cost are predicted to rise with the aging population. The epidemiologic and etiologic profile of HFpEF seems to differ from that of HF with reduced EF (HFrEF), such that HFpEF patients are frequently older, more often women, obese, suffer from hypertension and atrial fibrillation, and less likely to suffer from coronary artery disease.^{1–3} The risk of mortality and readmission is similar to that of HFrEF, although in trials mortality rate seems to be lower.⁵ In contrast to HFrEF, there are no therapies that have been proved to improve mortality and morbidity in patients with HFpEF as acknowledged in international

guidelines.^{6,7} The latter relate to uncertainties surrounding the pathophysiology of HFpEF and lack of consensus of its definition and classification, which at present seems to comprise patients with heterogeneous phenotype. The specific criteria for HFpEF continue to be debated. Although all agree that EF needs to be in the “preserved” range, the cutoff ranges from 40% to 50% in various guidelines and reviews. In addition to EF in the preserved range, most guidelines require evidence of structural or functional abnormality of the heart (eg, enlarged left atrium; left ventricular [LV] hypertrophy; and/or diastolic dysfunction, such as raised E/e’ ratio) in the presence of typical symptoms (eg, breathlessness) and signs (eg, raised jugular venous pressure, edema) of HF. Because these symptoms are nonspecific it is also important to exclude other potential diagnoses that may have a similar presentation.^{6,7} Interestingly, in most recent trials of HFpEF, the cutoff value of EF used is 45%.

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This article provides the reader with the current management strategies available for HFpEF, gives an overview of previous trials that have failed to prove the benefit of therapies to improve outcomes, and highlights promising novel therapies.

MANAGEMENT GOALS

There is no convincing therapy available to prolong survival in patients with HFpEF. Therefore, the goal of therapy is to relieve symptoms and improve quality of life. As recommended by international guidelines^{6,7} this is best accomplished by treating fluid retention; reducing high ventricular rates; maintaining and restoring atrial contraction; and optimizing treatment of comorbidities, such as systemic hypertension, myocardial ischemia, diabetes mellitus, chronic obstructive lung disease, and sleep apnea (**Table 1**).

Treatment of Fluid Retention

Diuretic agents are used to treat pulmonary congestion and peripheral edema, as they are in HFrEF. The main agents used include loop diuretics and thiazide or thiazide-like drugs. The evidence base for the use of diuretics, however, is limited. The DOSE, which was the largest

prospective, double-blind, randomized acute decompensated HF trial to evaluate initial diuretic strategies in patients with acute decompensated HF included a small proportion of patients with HFpEF; however, the mean LVEF was approximately $35 \pm 18\%$. In this trial there no significant differences in either of the coprimary end points of global assessment of symptoms or change in serum creatinine over 72 hours with diuretic administration by bolus or continuous infusion or with a low- versus a high-dose strategy.

A recent study has also shown that ultrafiltration is well tolerated in patients with HFpEF and evidence of fluid retention when compared with those with HFrEF.⁸ The exact role of ultrafiltration in the management of decompensated HF remains unclear, but could be considered as outlined in international guidelines.^{6,7}

In general, careful attention for symptoms and signs (eg, dizziness, syncope, hypotension) of low cardiac output is necessary, because excessive preload reduction with diuretics (or nitrates or calcium antagonist) can lead to underfilling of the LV and also dynamic LV outflow tract obstruction leading to low stroke volume and low cardiac output state and hypotension. This is especially seen in patients with excessive LV hypertrophy with small ventricles and those with hypertrophic cardiomyopathy.

Maintenance and Restoration of Atrial Contraction

Patients with HFpEF do not tolerate atrial fibrillation, especially when the ventricular rate is high, because loss of atrial contraction can significantly reduce LV filling and therefore cardiac output. Ideally sinus rhythm should be restored and if not possible the focus should be on ventricular rate control with β -blockers, rate-lowering calcium antagonists, or digoxin.⁶ Sinus rhythm may be restored with medications or electrical cardioversion. Radiofrequency ablation may also be considered. Importantly, patients with paroxysmal, persistent, or permanent atrial fibrillation should be anticoagulated if not contraindicated^{6,7} to avoid risk of systemic embolization.

Optimization and Treatment of Comorbidities

The treatment of comorbidities needs to be optimized because the burden of poorly controlled comorbidity increases risk of readmission.⁹ Treatment of elevated systolic and diastolic blood pressure is important, because lowering blood pressure is associated with reduced risk of developing HF in patients with hypertension.^{10,11} The agents that may be used include angiotensin receptor blockers (ARB), angiotensin-converting enzyme

Table 1
Management goals for heart failure with preserved ejection fraction

| Goal | Treatment Options |
|--|---|
| Treat fluid retention | Diuretics Ultrafiltration |
| Maintain and restore atrial contraction and rate control | Medically cardiovert with class I, II, or III antiarrhythmics β -Blocker, digoxin, rate-limiting calcium antagonists DC cardioversion Radiofrequency ablation |
| Optimize and treat comorbidities | Hypertension Myocardial ischemia Obstructive sleep apnea Obesity Diabetes mellitus Renal dysfunction Chronic obstructive pulmonary disease Iron deficiency |
| Entrance into chronic heart failure management program | Patient education Follow-up by health care team |

(ACE) inhibitors, calcium antagonists, thiazide diuretics, and β -blockers. These agents have been associated with regression of LV hypertrophy, which in itself is associated with the development of diastolic dysfunction.¹² Therefore, regression of LV hypertrophy is considered to be an important treatment target; however, in the hypertension population regression of LV hypertrophy has not been linked to a reduction in risk of long-term outcomes. In a meta-analysis of hypertension, the use of ARB (13%), ACE inhibitors (10%), and calcium antagonist (11%) was associated with the greatest reduction in LV mass from baseline compared with diuretics (8%) and β -blockers (6%).¹³ The choice of agent to use, however, is also based on other factors as recommended in the hypertension guidelines.¹⁴

Because myocardial ischemia may worsen HFpEF, its presence should be detected and, if present, treated using anti-ischemic therapies, which include β -blockers, calcium antagonists, and nitrates. Patients with evidence of myocardial ischemia could also be considered for revascularization with percutaneous coronary intervention or by coronary artery bypass graft surgery, especially if they have drug-refractory angina or angina-equivalent symptoms.

Diagnosis and treatment of obstructive sleep apnea, which has been associated with the development of diastolic dysfunction, is also important. Therapy with continuous positive airway pressure may reverse diastolic dysfunction and reduce left atrial size as measured by Doppler echocardiography, although treatment of sleep apnea has not been shown to reverse HFpEF in trials.¹⁵

Treatment of iron deficiency may improve symptoms and quality of life in patients with HFrEF, as demonstrated in the Fair-HF trial, which randomized 459 patients with HFrEF with evidence of iron deficiency with or without anemia to intravenous iron or placebo.¹⁶ Whether intravenous iron is useful in HFpEF will be determined by future studies.

Obesity, diabetes mellitus, and renal dysfunction are associated with ventricular-vascular characteristics that contribute to HFpEF.¹⁷ Optimal treatment of chronic obstructive pulmonary disease is also recommended.

It is recommended that HFpEF patients receive the pneumococcal vaccination and the annual influenza vaccination.

PHARMACOLOGIC STRATEGIES

Most drug trials have failed to improve outcomes in HFpEF (Table 2). This section gives an overview of pharmacologic trials and studies. Several factors may be responsible for the failure of trials to show

a benefit of specific therapies in HFpEF. These include uncertainties surrounding the pathophysiology of HFpEF, the lack of consensus in the definition and classification of HFpEF with resulting inability to clearly define the patient population, and potential use of end points or analyses that may not be ideal in HFpEF. Moreover, patients with this heterogeneous syndrome might in fact respond to different types of therapies, which would require more accurate phenotyping. For example, HFpEF patients with EF of 45% to 50% may with elevated natriuretic peptide levels behave more like patients with HFrEF, responding to renin-angiotensin-aldosterone system antagonism compared with those with EF greater than 50%.

ACE Inhibitors and ARBs

The rationale for the use of ACE inhibitors and ARBs in HFpEF is to block the neurohormonal pathways that lead to progression of HF and poor outcomes, as seen in HFrEF.¹⁸

There have been three key outcome trials using these agents in patients with HFpEF. The first, the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM Preserved) trial,¹⁹ randomized 3023 patients with an EF of greater than 40% to candesartan (up to 32 mg/day) or placebo. The trial showed a significant reduction in HF hospitalization after a median of 38 months of follow-up, but failed to demonstrate a reduction in cardiovascular (CV) mortality.

The second outcome trial, Perindopril for Elderly People with Chronic Heart Failure trial (PEP-CHF), randomized 850 elderly patients with EF greater than 40% and evidence of diastolic dysfunction on echocardiography to perindopril (titrated to 4 mg/day) or placebo.²⁰ This trial failed to demonstrate any reduction in the composite of all-cause mortality and HF hospitalization (the primary end point of the study) with perindopril. However, in a post hoc analysis, there was trend toward benefit with perindopril after a year follow-up.

In the third outcome trial, 4128 elderly patients with HF with EF greater than 45% were randomized to irbesartan or placebo (I-PRESERVE).²¹ After 50 months of follow-up, irbesartan did not reduce the risk of the composite outcome of all-cause mortality and CV hospitalization.

Currently, guidelines do not recommend the use of ACE inhibitors or ARBs for HFpEF unless they are being used to treat comorbidities, such as hypertension.^{6,7}

β -Blockers

β -blockers may have role in treating comorbidities in patients with HFpEF. Slowing an elevated heart

Table 2
Key outcome trials for heart failure with preserved ejection

| Trial | Year | N | Ejection Fraction | Primary Outcome Hazard Ratio (95% Confidence Interval) | Comments |
|---|------|------|--|--|---|
| CHARM-PRESERVED Candesartan vs placebo | 2003 | 3023 | >40% | Composite of CV death and HF hospitalization 0.86 (0.74–1.0); <i>P</i> = .051 | Significant reduction in HF hospitalization |
| PEP-CHF Perindopril vs placebo | 2006 | 850 | Wall motion index of <1.4 equivalent to EF 40% | All-cause mortality or unplanned HF hospitalization 0.69 (0.47–1.01); <i>P</i> = .055 at 12 months | Post hoc analysis showed a trend toward benefit with perindopril at 12 mo |
| I-PRESERVE Irbesartan vs placebo | 2008 | 4128 | >45% | All-cause mortality or hospitalization for CV cause 0.95 (0.86–1.05); <i>P</i> = .35 | None |
| DIG Digoxin vs placebo | 2006 | 988 | >45% | Composite of HF hospitalization and HF mortality 0.82 (0.63–1.07); <i>P</i> = .136 | Trend toward reduction in HF hospitalization |
| SENIORS Nebivolol vs placebo | 2005 | 2128 | >35% | All-cause mortality or hospitalization for CV cause 0.86 (0.74–0.99); <i>P</i> = .039 | Cut off of EF of 35% makes it difficult to extrapolate these data to HFpEF population |
| TOPCAT Spironolactone vs placebo | 2014 | 3445 | >45% | Composite of death from CV causes, aborted arrest, or hospitalization for HF 0.89 (0.77–1.04); <i>P</i> = .14 | HF hospitalization was reduced by 17% relative to placebo group Prespecified subgroup analysis demonstrated that patients enrolled with elevated natriuretic peptides as opposed to previous history of hospitalization had a significant reduction in primary outcome |

rate can prolong LV filling time in abnormally stiff LV and also prolong coronary perfusion. Therefore, rate limitation and maintenance of atrial fibrillation with β -blockers is beneficial.²² However, there is also a high prevalence of chronotropic incompetence in patients with HFpEF, which may already be a contributing factor to symptoms because of limited increase in cardiac output with exertion,^{23–25} and in these circumstances the use of β -blocker is not recommended. The evidence base for clinical efficacy for the use of β -blocker therapy in HFpEF is inconclusive. The SENIORS trial, which randomized 2128 patients older than 70 years of age with EF \leq 35% to placebo or nebivolol, resulted in significant reduction of all-cause

mortality and CV hospitalization after 21 months of follow-up.²⁶ A prespecified post hoc analysis of the trial demonstrated that the effect of nebivolol on outcomes was similar in those with preserved and impaired LVEF.²⁷ However, the definition of HFpEF used a low cutoff EF of greater than 35% therefore making it difficult to extrapolate these findings to most patients with HFpEF who have a higher EF. Registry data have been controversial, because the OPTIMIZE-HF study did not show any benefit with β -blockers.²⁸ However, the COHERE registry (Carvedilol Heart Failure Registry) demonstrated that carvedilol use was associated with lower mortality and need for rehospitalization in those with EF of greater than

40%.²⁹ Current guidelines do not recommend the use of β -blockers solely for HFpEF, unless it is used to optimize treatment of comorbidity, such as controlling ventricular rate in atrial fibrillation or tachyarrhythmia, treating angina, or hypertension.^{6,7}

Digoxin

The Digitalis Investigation Group (DIG) ancillary trial, randomized 988 patients with EF greater than 45% to digoxin or placebo.³⁰ After a median of 37 months of follow-up, digoxin resulted in a trend toward reduction in HF hospitalization but it did not result in a reduction in all-cause mortality, HF, or CV mortality, or the composite outcome of HF death or hospitalization. Similar to β -blockers, guidelines do not recommend the use of digoxin solely for HFpEF, unless it is used to optimize treatment of comorbidity, such as controlling ventricular rate in atrial fibrillation or tachyarrhythmia.^{6,7}

Calcium Antagonists

Data regarding the use of calcium antagonist are restricted to small studies that have shown that rate-limiting calcium antagonists, such as verapamil, may lead to improved symptoms and exercise tolerance.³¹ There are no outcome studies using calcium antagonists. Current guidelines do not recommend the use of calcium antagonists solely for HFpEF, unless it is used to optimize treatment of comorbidity, such as controlling ventricular rate in atrial fibrillation or tachyarrhythmia, treating angina, or hypertension.^{6,7}

Aldosterone Antagonist

A potential rationale for aldosterone antagonist therapy for HFpEF comes from animal studies suggesting that aldosterone contributes to cardiac hypertrophy and fibrosis.³² By blocking aldosterone these processes may be prevented or reversed.^{33,34} The first key study using aldosterone was Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-HF),³⁵ in which 422 patients were randomized to spironolactone, 25 mg per day, or placebo. After 12 months of follow-up, spironolactone was associated with improved diastolic dysfunction (assessed by e/e' ratio by Doppler echocardiography), reduced LV mass, and reduced N-terminal pro brain natriuretic peptide (NT-proBNP). However, spironolactone did not improve the coprimary outcome of peak VO_2 or for measures of quality of life.

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial³⁶ randomized 3445 patients with HFpEF, EF greater than 45%, to placebo or

spironolactone, 45 mg per day. There was no difference in rates of the primary outcome of death from CV causes, aborted cardiac arrest, or hospitalization for HF over a mean follow-up of 3.3 years. However, HF hospitalization was significantly reduced (17% relative reduction) in patients receiving spironolactone. Of note, patients on spironolactone had double the risk of developing hyperkalemia and a higher rate of increased serum creatinine levels but a lower rate of hypokalemia compared with the placebo group. Prespecified subgroup analyses showed that patients enrolled according to elevated natriuretic peptides criteria as opposed to hospitalization for HF criteria did have a reduction in the primary outcome. However, this entry measure was highly confounded by region and post hoc analyses revealed that patients from the Americas (United States, Canada, Argentina, and Brazil) had a substantially higher event rate than those enrolled in Russia and the Republic of Georgia. Although TOPCAT did not meet its primary end point, and thus spironolactone cannot be recommended based on these results, clinicians who decide to use it in their patients with HFpEF should carefully monitor potassium and renal function.

Studies of Novel Therapies

Several key proof-of-concept studies have focused on the new paradigm of the pathophysiology of HFpEF, which targets the disrupted nitric oxide-cGMP-PKG pathway, which is associated with endothelial dysfunction caused by lack of nitric oxide availability, which is implicated in the development of concentric remodeling, increased stiffness of cardiomyocytes, and increased myocardial collagen deposition in patients with HFpEF.

One promising new agent is LCZ696, a first in class angiotensin receptor neprilysin inhibitor, which consists of a molecular complex of the ARB valsartan and the neprilysin inhibitor precursor AHU377 in a 1:1 ratio. After ingestion, the two components separate and AHU377 is converted to the active neprilysin inhibitor, LBQ377. Neprilysin degrades several vasoactive peptides including the biologically active natriuretic peptides ANP, BNP, and CNP, which in turn exert their effects by raising intracellular cGMP.

In the PARAMOUNT study, 301 patients with HFpEF were randomized to valsartan or LCZ696 and followed up for 36 weeks.³⁷ The primary end point of the study was a change in NT-proBNP at 12 weeks from baseline, which was significantly lower in the LCZ696 arm. At 36 weeks, left atrial volumes were reduced and New York Heart Association class was improved in the LCZ696 arm. A

large outcome trial, PARAGON-HF, will assess the efficacy and safety of LCZ696 in patients with HFpEF ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01920711) NCT01920711).

An initial small clinical study of sildenafil, a phosphodiesterase-5 inhibitor that can lead to increased levels of cGMP, in 44 patients with HFpEF (EF \geq 50%) and pulmonary hypertension resulted in improved LV diastolic function, reduced pulmonary pressures, and improved right ventricular systolic function after treatment for a year.

However, these benefits were not reported in the placebo-controlled RELAX trial, which assessed the effects of sildenafil in 216 elderly patients with HFpEF without pulmonary hypertension.³⁸ After 24 weeks of treatment, there were no improvements in exercise capacity measured by 6-minute walk distance or on quality of life; also there were no improvements in diastolic function or LV remodeling. The lack of benefit of sildenafil in the RELAX trial could be because the patients enrolled did not have pulmonary hypertension and as suggested by very high NT-proBNP levels had advanced HF and were therefore less likely to respond to sildenafil treatment.

Another group of agents being studied are stimulators of the soluble guanylate cyclase. The latter acts as a receptor for nitric oxide. Stimulation of soluble guanylate cyclase can lead to increased activity of the cGMP-PKG pathway. The oral soluble guanylate cyclase stimulator, BAY1021189, is currently being investigated in patients with worsening HFpEF (SOCRATES-PRESERVED; [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01951638) NCT01951638).

In the SHIFT trial, heart rate reduction with ivabradine, an inhibitor of the I_f channel within cardiomyocytes of the sinoatrial node, resulted in a significant relative reduction in the primary end point of hospitalization for HF and CV mortality by 18% in patients with HFrEF, mainly driven by a reduction in HF hospitalization.³⁹ The use of ivabradine in patients with HFpEF is limited to a recent trial of 61 patients with HFpEF, randomized to placebo or ivabradine, 5 mg twice a day. The ivabradine arm had improved exercise capacity caused by improved LV filling pressures.⁴⁰ A larger multicenter placebo-controlled trial enrolling 400 patients will evaluate the effects of ivabradine on exercise capacity, NT-proBNP levels, and echocardiographic parameters of LV diastolic function, such as e/e' ([www.clinicaltrialsregister.eu-EUCTR2012-002742-20-DE](http://www.clinicaltrialsregister.eu/EUCTR2012-002742-20-DE)).

NONPHARMACOLOGIC STRATEGIES

Nonpharmacologic strategies for the management of HFpEF include the potential use of exercise training. In the EX-DHF-Pilot study,⁴¹ 64 patients

with HFpEF were randomized to exercise training and usual care or usual care alone. After 3 months, patients who had regular supervised exercise had an increase in peak VO_2 , improved self-reported physical functioning (as assessed by the Short Form-36 health questionnaire), and improved diastolic function and reverse atrial remodeling. A larger trial of exercise training is underway.

The recent COMPASS trial showed that wireless monitoring of pulmonary arterial pressure using an implantable device was safe and resulted in reduced hospitalization in patients with HF.⁴² This trial included patients with HFpEF. However, the device is currently not available for clinical use, but is potentially very promising. The results of trials of remote monitoring using such parameters as weight, heart, and blood pressure monitoring have been mixed and controversial.

SUMMARY

The management of HFpEF is challenging, requiring an accurate diagnosis. Although currently there is no convincing therapy that can prolong survival in patients with HFpEF, treatment of fluid retention and of comorbidities, such as hypertension, myocardial ischemia, and atrial fibrillation, may improve symptoms and quality of life. Spirolactone may be considered in patients with HFpEF with an elevated BNP, and if prescribed, patients require monitoring of potassium levels and renal function. Future outcome trials of HFpEF testing the efficacy of promising new agents, such as LCZ696, will have better characterization of patient phenotype to maximize the potential response to therapies.

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