

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

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