

Flowchart for Treatment of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) manifests as a heterogeneous syndrome, with pathophysiological variety, often associated with other comorbidities. Furthermore, the therapy performed in these patients is related to the treatment of correlated comorbidities. In this context, the specific pharmacological treatment of HFpEF is a challenge, given the lack of evidence from studies that would prove a significant reduction in mortality outcomes. In this article, we will analyze the management for the control of arterial hypertension and atrial fibrillation as well as evidence from studies on the use of the main classes of medications recommended for the treatment of patients with HFpEF, such as sodium-glucose cotransporter 2 inhibitors, renin-angiotensin system inhibitors, neprilysin inhibitors, and nitrates.

Introduction

Heart failure with preserved ejection fraction (HFpEF), which is defined as left ventricular ejection fraction (LVEF) $\geq 50\%$, accounts for at least 50% of all patients with heart failure (HF). In addition to the fact that its prevalence is increasing, it is associated with significant morbidity and mortality.¹

HFpEF is a heterogeneous disorder with contribution from comorbidities such as hypertension, diabetes, obesity, coronary artery disease (CAD), chronic kidney disease, and specific causes such as cardiac amyloidosis.²⁻⁴ Patients with HFpEF are older, and they are more frequently women. Furthermore, it is more common to observe non-cardiovascular comorbidities, chronic kidney disease, and atrial fibrillation (AF) in these patients.⁵

Clinical trials have used varying definitions of HFpEF (for example, LVEF $\geq 40\%$, 45% , or 50%). In any case, diagnosis should include the following: (1) signs and symptoms of HF; (2) LVEF $\geq 50\%$; (3) objective evidence of structural

and/or functional cardiac abnormalities consistent with the presence of left ventricular diastolic dysfunction/increased left ventricular filling pressures, including increased natriuretic peptides.^{6,7}

To date, no specific drug therapy has demonstrated a reduction in cardiovascular mortality in trials on HFpEF. Therefore, the recommended management is the same as that for HF in general, with the use of diuretics, especially loop diuretics, to reduce congestion. Additionally, weight loss and physical exercise can improve symptoms and functional capacity; therefore, they should be considered in appropriate patients.^{8,9} It is necessary to identify symptoms and treat specific causes, such as amyloidosis, in addition to management of contributing comorbidities, such as hypertension, CAD, and AF.

Control of arterial hypertension

The role of blood pressure control is well established in preventing HF, as well as in reducing other cardiovascular events and mortality from HF in patients without baseline HF.¹⁰⁻¹⁶

The SPRINT (Systolic Blood Pressure Intervention Trial) and meta-analyses have established that patients at high cardiovascular risk benefit from more intense blood pressure control, as this significantly reduces HF and other cardiovascular outcomes.^{11,12,17} That said, recent guidelines on the clinical management of hypertension have established blood pressure targets in HFpEF that extrapolate those for the treatment of patients in general.¹⁸

However, optimal targets for blood pressure and antihypertensive regimens are not known for patients with HFpEF. Renin-angiotensin-aldosterone system (RAAS) antagonists, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists, and possibly neprilysin receptor antagonists, may be first-line agents, given the experience with their use in trials on HFpEF.^{3,19-23} For adults with HFpEF who have persistent hypertension after treatment of volume congestion with diuretics, ACEIs or ARBs and titrated beta blockers should be prescribed to achieve systolic blood pressure below 130 mmHg.¹⁸

Beta blockers can be used to treat hypertension in patients with a history of acute myocardial infarction,²² symptomatic CAD, or AF with rapid ventricular response. This medication interferes with chronotropism and, therefore, needs to have its effects balanced, with possible exercise intolerance in some patients.²⁴

Keywords

Heart Failure; Diastolic Heart Failure; Medication Therapy Management

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Sodium-glucose Cotransporter 2 Inhibitors

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) demonstrated a significant benefit of the sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin in patients with symptomatic HF with LVEF > 40% and elevated natriuretic peptides.²⁵

Empagliflozin led to a 21% lower relative risk of the composite outcome of cardiovascular death or hospitalization for HF, which was mainly related to a 29% lower risk of hospitalization for HF with the use of the medication; lower cardiovascular death was not significant (hazard ratio, 0.91; 95% confidence interval, 0.76 to 1.0), with no benefit in all-cause mortality. The effects were observed consistently across all pre-specified subgroups, including patients with or without diabetes.²⁶

Although the benefit in the primary outcome did not have a significant difference between the pre-specified LVEF subgroups (< 50%, 50% to 60%, and > 60%),²⁵ in another study with subgroup analysis by ejection fraction, there was less benefit in the reduction of total hospitalizations (first and recurrent) due to HF heart failure with higher LVEF > 60%.²⁶

Empagliflozin, in addition to resulting in a decrease in total hospitalizations for HF, promoted a reduction in the estimated glomerular filtration rate (eGFR) and a modest improvement in quality of life at 52 weeks.²⁵

Management of atrial fibrillation

Large randomized clinical trial data are not available to guide a specific therapy in patients with AF and HFpEF. Currently, the comprehensive care of AF in this context is extrapolated from guidelines on clinical practice for AF, but with individualization strategies to control rhythm or frequency in these patients.

Although beta blockers and non-dihydropyridine calcium channel blockers are often considered first-line agents for heart rate control in patients with HFpEF, recently, a smaller, open-label study, RATE-AF,²⁷ was conducted in elderly patients with AF and symptoms of HF (the majority with preserved LVEF). This study compared the use of the beta blocker bisoprolol to digoxin, and the primary quality of life outcome was similar between both groups at the end of 6 months. In both groups, there was a similar decrease in heart rate, but adverse events such as dizziness, lethargy, and hypotension occurred more with the beta blocker than with digoxin. Moreover, several secondary endpoints of quality of life, functional capacity, and reduced NT-proBNP at the end of 12 months also favored digoxin.

Mineralocorticoid receptor antagonists

The TOPCAT study investigated the effects of spironolactone in patients with HFpEF. In this study, a small reduction (hazard ratio, 0.89) was observed in the analysis of the composite outcome involving death, aborted cardiac death, and hospitalization for HF. However, this reduction

was not statistically significant, although hospitalization for HF was reduced (hazard ratio, 0.83). Furthermore, the group that received the treatment had more adverse effects, such as hyperkalemia and increased creatinine levels.²⁸ Regarding the effects of breast pain and related gynecomastia that led to treatment discontinuation, they were equal between the different regions of the study.²⁹

Careful monitoring of potassium, renal function, and diuretic dosing at baseline and follow-up are fundamental to minimizing the risks of hyperkalemia and worsening renal function.

A post hoc analysis²⁹ showed efficacy in the Americas (hazard ratio, 0.83), but not in Russia-Georgia (hazard ratio, 1.10). In the Americas, linked to efficacy, more frequent occurrence of hyperkalemia and renal involvement was also observed. In Russia-Georgia, the same benefits were not observed, as was the case with the adverse effects.²⁹ In the latter population, a sample in the active treatment arm showed no detectable levels of a spironolactone metabolite.

Post hoc analyses have limitations, but they do suggest a possible benefit in appropriately selected patients with symptomatic HFpEF (LVEF ≥ 45%, elevated BNP level, or admission for HF at 1 year, eGFR > 30 mL/min/1.73 m², creatinine < 2.5 mg/dL, and potassium < 5.0 mEq/L).

Furthermore, another post hoc analysis suggested that the potential efficacy of spironolactone was greater at the lower end of the LVEF spectrum.³⁰

Renin-angiotensin-aldosterone system inhibitors

Although RAAS inhibition strategies have been successful in the treatment of heart failure with reduced ejection fraction, and RAAS activation is suggested in HFpEF, clinical trials with RAAS inhibition have not shown great benefits in patients with HFpEF. For example, in a meta-analysis of 7,694 patients with HFpEF, comprising 4 studies evaluating ARB, there was no sign of benefit regarding hospitalization for HF (hazard ratio, 0.92; 95% confidence interval, 0.83 to 1.02) or in cardiovascular or all-cause mortality (hazard ratio, 1.02).^{31,32}

The CHARM-Preserved trial (Candesartan in patients with chronic HF and preserved left-ventricular ejection fraction) evaluated patients with LVEF > 40%, who were randomized to an ARB, candesartan, or placebo.¹⁹

The primary outcome (cardiovascular death or hospitalization for HF) was not significantly different between the 2 groups (hazard ratio, 0.89; 95% confidence interval, 0.77 to 1.03, *p* = 0.118; hazard ratio adjusted for covariates, 0.86; *p* = 0.051).

Cardiovascular mortality was identical in both groups, whereas hospitalizations for HF were lower in the candesartan arm. However, this result was observed only in the covariate-adjusted analysis, and it was still borderline in relation to statistical significance (hazard ratio, 0.84; 95% confidence interval, 0.70 to 1.00; *p* = 0.047; unadjusted *p* = 0.072).

With respect to individuals hospitalized for HF (reported by the investigator), the results obtained with the candesartan group were better than with placebo

(230 versus 279; $p = 0.017$). Furthermore, another improvement observed in the CHARM studies was identified through a post hoc analysis, in which these results with candesartan were found to be better at the lower end of the LVEF spectrum.³³

Angiotensin receptor blockers and neprilysin inhibitors

The PARAMOUNT-HF (Prospective Comparison of ARNi with ARB on Management of Heart Failure with Preserved Ejection Fraction) study, a phase II randomized clinical trial in patients with HFpEF (LVEF $\geq 45\%$), compared sacubitril-valsartan with the ARB valsartan. They observed a lower level of NT-proBNP after 12 weeks of treatment with the neprilysin and angiotensin receptor inhibitor.³⁴

The PARAGON-HF study (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction) was carried out with 4,822 patients with HFpEF (LVEF $\geq 45\%$, admission for HF at 9 months or elevated natriuretic peptides and eGFR ≥ 30 mL/min/m²). In this study, the comparison between sacubitril-valsartan and valsartan did not achieve a significant reduction in the primary composite outcome of cardiovascular or total death or in first and recurrent hospitalizations for HF (rate ratio, 0.87; 95% confidence interval, 0.75 to 1.01; $p = 0.06$).²⁰

In the sacubitril-valsartan group, 15% of patients had an improvement in New York Heart Association class at 8 months; 76.3% had no change, and 8.7% had a worsening of New York Heart Association class, in comparison with 12.6%, 77.8%, and 9.6%, respectively, in the valsartan group (odds ratio for improvement, 1.45; 95% confidence interval, 1.13 to 1.86).

Given that the primary outcome was not met, further analyses are exploratory. That said, there was no benefit of sacubitril-valsartan regarding cardiovascular death (hazard ratio, 0.95) or total mortality (hazard ratio, 0.97), but there was a sign of a benefit with the angiotensin receptor-neprilysin inhibitor for hospitalizations due to HF (rate ratio, 0.85; 95% confidence interval, 0.72 to 1.00; $P = 0.056$). The use of sacubitril-valsartan was less associated with hyperkalemia and increased serum creatinine, but a higher incidence of hypotension and angioedema was observed in this group.²⁰

In pre-specified subgroup analyses, a differential effect was observed for LVEF and sex. The benefits of sacubitril-valsartan compared to valsartan were seen in patients with LVEF below the median (45% to 57%; rate ratio, 0.78; 95% confidence interval, 0.64 to 0.95) and in women (rate ratio, 0.73; 95% confidence interval, 0.59 to 0.90).^{20,35,36}

Nitrates

Nitrate therapy may reduce pulmonary congestion and improve exercise tolerance in patients with heart failure with reduced ejection fraction. With respect to HFpEF, data from previous studies indicate that 15% to 50% of patients are treated with nitrates.^{19,21,37,39}

Nonetheless, the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) study³⁹ randomized 110 patients with LVEF $\geq 50\%$ on stable HF therapy for comparison between isosorbide mononitrate and placebo. This analysis included patients who did not use nitrate and who had activities limited by dyspnea, fatigue, or chest pain. In the results of this study, no beneficial effects were observed regarding activity levels, quality of life, exercise tolerance, or NT-proBNP levels. In fact, daily activities showed a dose-dependent reduction effect among patients who received isosorbide mononitrate.³⁹

Although routine use of nitrates in patients with HFpEF does not appear to be beneficial, patients with HFpEF and symptomatic CAD can still receive symptomatic relief with nitrates.

With respect to phosphodiesterase-5 inhibition, it increases the nitric oxide system, positively regulating cyclic guanosine monophosphate activity. The RELAX study (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction)⁴⁰ randomized 216 patients with LVEF $\geq 50\%$ on stable HF therapy with reduced exercise tolerance (peak oxygen consumption $< 60\%$ predicted) for the use of sildenafil or placebo. However, this study observed a lack of improvement in oxygen consumption and exercise tolerance.

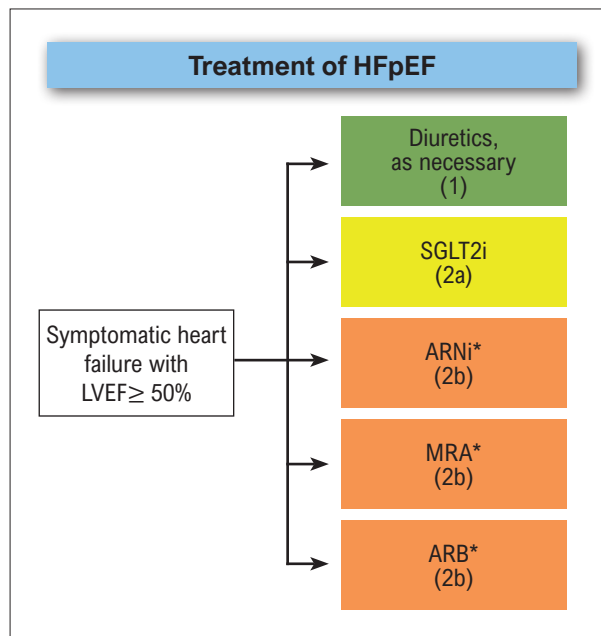


Figure 1 – Recommendations for patients with LVEF ($\geq 50\%$). Adapted from Heidenreich, P. A. et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines Circulation. 2022;145:e895–e1032.

Medication recommendations for HFpEF are exhibited. ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

*Greater benefit in patients with LVEF closer to 50%.

Conclusion

Studies related to approaches to treatment of HFpEF have shown advances. In this context, SGLT2i have showed a favorable result in terms of reducing cardiovascular death or hospitalization. For the first time, there is a medication that has demonstrated significant benefits in patients with preserved ejection fraction (Figure 1). This evolution in the study of HFpEF provides an opportunity to choose a therapy with a better cardiovascular outcome for patients.

Author Contributions

Analysis and interpretation of the data and Critical revision of the manuscript for important intellectual content: Figueiredo Neto JA; Writing of the manuscript: Figueiredo Neto JA, Santos JVS, Figueiredo VMS, Galvão NG.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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