

Heart Failure with Preserved Ejection Fraction: Management Guidelines (From Heart Failure Association of India, Endorsed by Association of Physicians of India)



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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for 15–20% of patients with heart failure (HF) in India. Diagnosis is by clinical features supported by biomarkers and echocardiography. Lifestyle modifications, control of risk factors to optimum levels, and treatment of comorbidities are essential in the management of HFpEF. Spironolactone and sacubitril-valsartan [angiotensin receptor neprilysin inhibitor (ARNI)] are beneficial in subsets of HFpEF, especially with lower range of ejection fraction (EF). Sodium-glucose co-transporter-2 inhibitors (SGLT2i)—empagliflozin and dapagliflozin and probably sotagliflozin are the only currently available drugs which have shown benefits in HFpEF, mostly by reducing hospitalizations. The benefit of SGLT2i is evident in both diabetic and nondiabetic subsets.

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Heart failure with preserved ejection fraction is defined as patients with HF with documented left ventricular ejection fraction (LVEF) equal to or more than 50%.¹

Globally, HFpEF accounts for close to 50% of patients presenting with HF. As per the registry data like Trivandrum Heart Failure Registry² and ASIAN-HF,³ the proportion of HFpEF in our country is approximately 19–25%, which is much lower as compared to that of western population. There is a possibility that many cases go undiagnosed in developing countries like India. The mean age of presentation of patients from India was around 58–68 years, which is about 10 years younger than the data reported from the west.

Heart failure with preserved ejection fraction is characterized by elevated left ventricular filling pressures and/or reduced cardiac output either at rest or on exertion. Cardiac output is maintained at the cost of abnormally elevated filling pressure which is responsible for the symptoms and signs. Neurohumoral activation (sympathetic and renin-angiotensin-aldosterone system activation) is present only in a group of HFpEF patients unlike in patients with heart failure with reduced ejection fraction (HFrEF).⁴

Diagnosis of HFpEF

Unlike HFrEF, the diagnosis of HFpEF is not straightforward. Diagnosis of HFpEF requires the presence of signs and symptoms of HF supported by biomarkers, demonstration of preserved LVEF ($\geq 50\%$), and the documentation of diastolic dysfunction on echocardiogram.

The gold standard for confirming the diagnosis of HFpEF is right heart catheterization which is cumbersome and not easily available. An invasively measured pulmonary capillary wedge pressure of ≥ 15 mm Hg (at rest) or left ventricular end-diastolic pressure ≥ 16 mm Hg (at rest) is generally considered diagnostic in presence of clinical features. If resting echocardiographic findings and laboratory parameters are equivocal, diastolic stress (exercise) test is recommended.⁵

All patients with suspected HFpEF should undergo an electrocardiogram and a chest X-ray along with blood tests including blood cell counts, renal function test, thyroid function test, glycosylated hemoglobin, lipid levels, iron studies, and biomarkers like B-type natriuretic peptide (BNP/NT-proBNP) and troponin. Transthoracic echocardiogram with detailed evaluation for cardiac chamber enlargement, left ventricular hypertrophy, diastolic function assessment, and pulmonary hypertension is essential in the workup. Cardiac magnetic resonance imaging is recommended in patients with suspected infiltrative cardiomyopathy, hemochromatosis, or hypertrophic cardiomyopathy. The proposed diagnostic algorithm for HFpEF based on the universal definition of HF 2021 is attached below. The European Society of Cardiology (ESC) has proposed the PEFF algorithm for the diagnosis of HFpEF, with a score >5 points are diagnostic and if the score is borderline, that is 2–4, we need to do stress testing or have to go for invasive hemodynamic testing (Flowchart 1).⁶

Management of HFpEF

Till recently, no pharmacological therapy had been shown to significantly reduce mortality and morbidity in patients with HFpEF, although improvements had been reported in certain specific phenotypes of patients within the HFpEF spectrum. The recent data on SGLT2i have given hope to patients with HFpEF.

Phenotypes of HFpEF

Patients with HFpEF have varying presentations and clinical trajectories which resulted in categorizing patients based on pathophysiologic phenotypes. It is believed that this strategy may provide more targeted and efficacious therapies.⁷ Different phenogroups are based on clinical presentation, structural and functional alteration of cardiovascular system, hemodynamic patterns, exercise tolerance and capacity, and presence of comorbidities.⁷ While currently there is no consensus in defining the phenogroups, it is expected that it may occur in the near future.

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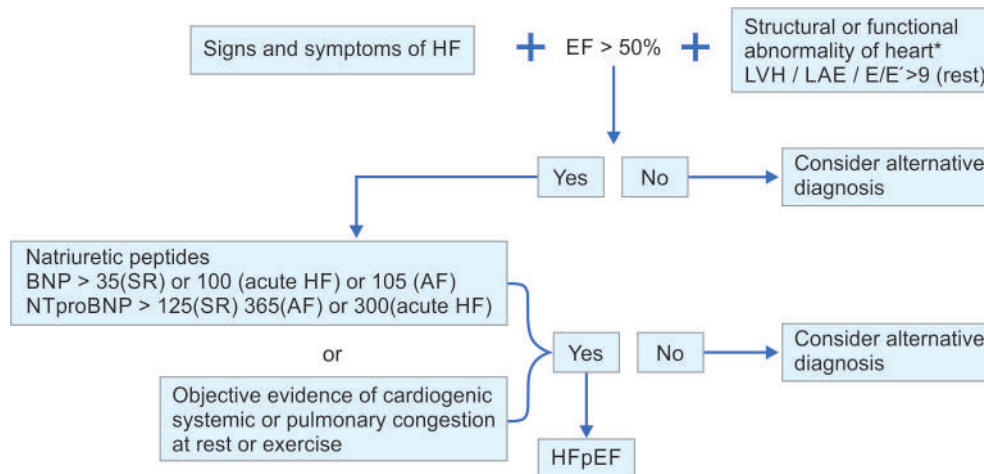
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Flowchart 1: Algorithm for diagnosis of HFpEF. *LV mass index ≥ 95 gm/m² (female), ≥ 115 gm/m² (male), relative wall thickness >0.42 LA volume index >34 mL/m² (SR) >40 mL/m² (AF) PA systolic pressure—TR velocity at rest >35 mm Hg/ >2.8 m/s at rest. On exercise TR velocity >3.4 m/s, E/E' >15 ; BNP, B-type natriuretic peptide; E/E' ratio, early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; SR, sinus rhythm; TR, tricuspid regurgitation



General Measures

Lifestyle modifications are important—structured cardiac rehabilitation and weight loss in the obese have shown to benefit patients. Dietary salt and fluid restriction help to minimize congestion and should be considered in patients who have features of volume overload. Tobacco cessation and restriction of alcohol consumption should be advised. Treatment of comorbidities is essential—control of hypertension, correction of anemia, and heart rate control especially in atrial fibrillation (AF) are very important. Myocardial ischemia should be assessed and treated.

Renal dysfunction is a common accompaniment of HFpEF and pharmacotherapy should be modified according to the renal function. Vaccination for influenza and pneumococcus should be considered whenever appropriate. Sleep pattern should be assessed to look for obstructive sleep apnea.

Use of organic nitrates (except to control angina), phosphodiesterase-5 inhibitors, or digoxin (except for ventricular rate control in AF), beta-blockers (except in relief of angina or rate control in AF) should be avoided in patients with HFpEF.

AF

Urgent cardioversion is recommended for patients with AF and hemodynamic compromise. Restoration of sinus rhythm by catheter ablation is preferred to rate control in HFpEF patients with AF, whenever feasible. Anticoagulation for CHA₂DS₂-VASc ≥ 2 in men and ≥ 3 in women, preferably with novel oral anticoagulant drugs, except in those with a

prosthetic mechanical valve or significant mitral stenosis, is recommended.

Diuretics are needed for reducing congestion and symptoms. Diuretic therapy should be administered with caution to avoid excessive preload reduction and hypotension which can be detrimental in HFpEF. If there is objective evidence of hypervolemia, it should be treated with loop diuretics.

Other Drugs: Possibly Disease-modifying Agents

SGLT2i and HFpEF

Based on the success of SGLT2i in HFrEF⁸ these drugs were tried in HFpEF also. EMPEROR-Preserved trial tested the efficacy of empagliflozin compared with placebo and enrolled 5,988 patients with class II–IV HF and an EF of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy.⁹ Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF regardless of the presence or absence of diabetes. The result was mostly driven by reduction in hospitalizations.

The DELIVER trial tested dapagliflozin 10 mg once daily in patients with HFpEF. The results appear promising.¹⁰

In a pooled analysis from the SOLOIST-WHF¹¹ and SCORED¹² clinical trials, sotagliflozin which is a dual (SGLT1 and SGLT2 blocker) was also found to benefit patients with HFpEF. But we must wait and see whether it is a class effect of SGLT2 inhibition or an effect of the dual blockade.

A subanalysis of the data of 4,005 subjects with LVEF $>50\%$ in the EMPEROR-Preserved cohort was presented in the American Heart

Association Scientific Sessions 2021.¹³ There was a relative risk reduction of primary endpoint composite of cardiovascular death or hospitalization by 17% ($p = 0.024$) and first HF hospitalization by 22% ($p = 0.013$). There was also a significant improvement in quality of life and the slope of decline in glomerular filtration rate over time (difference vs placebo 1.24 mL/min/1.73 m² per year). This large-scale data will have clinical implications in patients of HFpEF with LVEF $>50\%$.

Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid receptor antagonists (spironolactone and eplerenone) prevent cardiac fibrosis, limit inflammation, and decrease left ventricular mass. We know that all these three abnormalities are common in HFpEF. Treatment with spironolactone was tested in the TOPCAT¹⁴ trial of 3,445 patients with symptomatic HF with EF $\geq 45\%$, which showed no difference in primary endpoints, but some subgroups showed benefits. In patients with symptomatic HFpEF and recent decompensation or elevated natriuretic peptide (NPs), MRAs may be initiated. Spironolactone or eplerenone can be started at dosages of 12.5 and 25 mg, respectively, and titrated up to 25–50 mg, while monitoring for hyperkalemia. There is no head-to-head comparison between spironolactone and eplerenone.¹⁵ Eplerenone has lesser side effects like gynecomastia but is much costlier.

ARNI—Sacubitril-valsartan

Angiotensin receptor neprilysin inhibitor is found to benefit patients with HFrEF without any doubt. The PARAGON-HF trial¹⁶ compared clinical outcomes with sacubitril-valsartan vs

valsartan in 4,796 HFpEF patients with New York Heart Association class II–IV HF, LVEF $\geq 45\%$, and elevated natriuretic peptide levels. The study did not meet its primary endpoints, but benefit was shown in a few subgroups of HFpEF like women, those with recent HF admission, and those with LVEF $< 57\%$. ARNI can be recommended in patients with HFpEF who are already on MRA and who require additional medication for blood pressure control, particularly female patients with an LVEF less than 57%.

Angiotensin-converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB) in HFpEF

ACEI therapy has not shown any benefits in patients with HFpEF in reducing mortality or morbidity. Prospective, randomized, placebo-controlled clinical trials using ARBs—candesartan, perindopril, and irbesartan in patients with HFpEF failed to decrease cardiovascular mortality although there was some decrease in hospitalization for HF with candesartan largely in those patients who had HF with mildly reduced EF (HFmrEF, EF 41–49%). Based upon the CHARM trial,¹⁷ angiotensin receptor blocking agents are recommended for treatment of HFpEF with a lower level of evidence and weaker recommendation.

Management of Distinct Phenotypes

Conditions like hypertrophic cardiomyopathy and cardiac amyloidosis have specific management pathways. Septal reduction therapies like surgical myectomy and alcohol septal ablation can help in hypertrophic obstructive cardiomyopathy. Myosin inhibitor like mavacamten has shown promise in hypertrophic cardiomyopathy.¹⁸ For the management of cardiac amyloidosis (especially the transthyretin variety), we have the drugs like tafamidis and patisiran. Tafamidis is recommended in the ESC Guidelines

2021 for patients with genetic testing proven hereditary transthyretin cardiac amyloidosis and wild-type cardiac amyloidosis.⁵ It is going to be introduced into India shortly, but the cost of therapy could be an issue.

Summary

Heart failure with preserved ejection fraction contributes to nearly 20% of patients with HF in India, though it is likely to be an underestimate. Diagnosis can sometimes be difficult and requires detailed evaluation with echocardiography and biomarkers. Lifestyle modifications and control of risk factors are very important in the management of HFpEF. Treatment of comorbidities is essential. Spironolactone and ARNI are beneficial in some subsets of HFpEF with lower range of EF. SGLT2i—empagliflozin, dapagliflozin and probably sotagliflozin are the only currently available drugs which have shown benefit, mostly by reducing hospitalizations in both diabetic and nondiabetic patients with HFpEF.

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