Managing Heart Failure with Preserved Ejection Fraction; A Short Review of Latest Evidences

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a clinical dilemma and various clinical trials so far have failed to give a concrete evidence of reducing mortality and major adverse cardiac events (MACE) in this condition. A detailed analysis of the existing evidences and a future plan for a concrete trial design with long duration of follow up is needed to address the dilemma of Heart failure with preserved ejection fraction.

The objective of this short review was to review the latest and major randomized controlled trials and study the primary outcomes. The public database of PubMed, Google Scholar and Cochrane were extensively searched for all randomized controlled trials using keywords of Heart failure with preserved ejection fraction, major adverse cardiac events, Hospitalizations; and studies were included in the review if data were reported for patients with ejection fraction > 40%, did not include congenital heart disease, and demonstrated evidence of diastolic failure on echocardiogram (ECHO), and evaluated hospitalizations, major adverse cardiac events and cardiovascular mortality.

Despite the major trials reporting improved primary composite endpoints with newer drugs the results have to be interpreted cautiously since the primary outcome were mostly driven by heart failure hospitalizations and not mortality reduction.

KEY WORDS

Diastolic dysfunction, Heart failure, Heart failure with preserved ejection fraction, Preserved left ventricular function, SGLT2

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome in which patients have clinical features of heart failure in the presence of normal or near-normal left ventricular ejection fraction, usually defined as ejection fraction at 50% or above.[1]

Making a diagnosis of HFpEF is challenging. A diagnostic score based algorithm has been described to aid HFpEF diagnosis (Fig. 1 and 2).

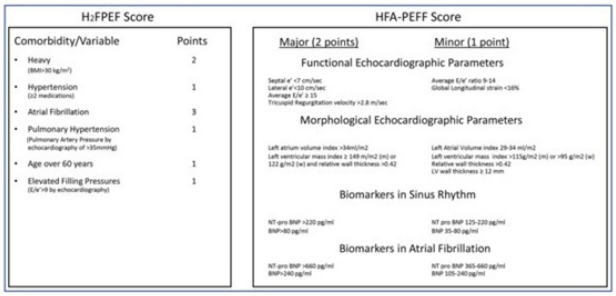
Management of HFpEF ranges from lifestyle interventions (diet, exercise training), management of modifiable risk factors and comorbidities (hypertension, coronary artery disease, atrial fibrillation, obesity, diabetes, cigarette smoking), to pharmacologic therapies, and health services.[2]

Despite years of research and a multitude of drugs being tried and tested for the treatment of HFpEF we still do not have a drug for the reduction of mortality in this patient group, but recently a lot of interest and positive results have been shown with some newer drugs.

The public database of PubMed, Google Scholar and Cochrane were extensively searched for all randomized controlled trials using keywords of HFpEF, major adverse cardiac events (MACE), Hospitalizations; and studies were included in the review if data were reported for patients with EF > 40%, did not include congenital heart disease, and demonstrated evidence of diastolic failure on echocardiogram (ECHO), and evaluated hospitalizations, MACE and cardiovascular mortality.

PREVIOUS TRIALS in HFpEF

The TOPCAT trial was the only trial which showed the benefit of the drug spironolactone for HFpEF in reducing heart failure hospitalizations in select regions of the Americas but not in Russia and georgia, in a post hoc analysis.[3]



Scoring algorithms for HFpEF diagnosis. H 2 FPEF score: Patient gets points based on presence of comorbidity/variable. Low probability of HFpEF (0-1 points), Intermediate Probability of HFpEF (2-5 points), High probability of HFpEF (6-9 points). HFA-PEFF score: Each category is assessed, and patients get points if meeting a major or minor criteria. Intermediate score (2-4 points), High score consistent with HFpEF (≥ 5 points).

- **Image courtesy: Dmitry Abranov, Purvi Parwani DOI:**
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Figure 1. SCORING SYSTEM for HFpEF

Previous trials in HFpEF have largely been neutral. They include the PEP-CHF Trial (perindopril), CHARM-PRESERVED (candesartan), I-PRESERVE (irbesartan), PARAGON (sacubitril-valsartan), DIG-PEF (digoxin), RELAX (sildenafil), ALDO-CHF (spironolactone), and SENIORS (nebovilol) trials.

Beta blockers despite being heavily prescribed in this condition especially due to comorbidities, CAD and AF do not have much evidence of reducing mortality in this patient group, and further trials are needed.

SOCIETY GUIDELINES for HFpEF

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure recommends diuretics as class 1 indication for management of HFpEF. SGLT2 inhibitors as CLASS 2A, ARNI, MRAs, ACEI and ARBs as CLASS 2B indications.[4] (Table 1)

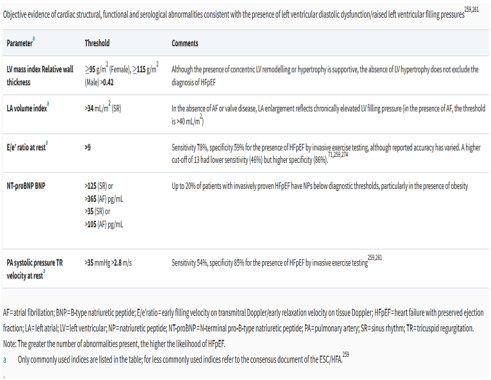
Table 1. 2022 AHA/ACC/HFSA Guideline for the Management of HFpEF

TREATMENT FOR HFpEF	
Symptomatic HF with LVEF >50%	DIURETICS (CLASS 1)
	SGLT 2 inhibitors (CLASS 2a)
	ARNI (CLASS 2b)
	ACEI/ARB (CLASS 2b)
	MRA (CLASS 2b)

2021 ESC guidelines for heart failure management only recommends the treatment of comorbidities and diuretics for the management of volume overloaded patient with HFpEF as a CLASS 1 C indication.[5] (Table 2)

Table 2. 2021 ESC Recommendations for the Treatment of Patients with Heart Failure with Preserved Ejection Fraction

TREATMENT FOR HFpEF		
RECOMMENDATION	CLASS	LEVEL
Screening for and treatment of aetiologies and cardiovascular and non cardiovascular comorbidities	I	C
Diuretics in congested patients to relieve symptoms and signs	I	C



Objective evidence of cardiac structural, functional and serological abnormalities consistent with the presence of left ventricular diastolic dysfunction/raised left ventricular filling pressures[289,261]

Parameter[a]	Threshold	Comments
LV mass index Relative wall thickness	>95 g/m² (Female), >115 g/m² (Male) >0.42	Although the presence of concentric LV remodelling or hypertrophy is supportive, the absence of LV hypertrophy does not exclude the diagnosis of HFpEF
LA volume index[a]	>34 mL/m² (SR)	In the absence of AF or valve disease, LA enlargement reflects chronically elevated LV filling pressure (in the presence of AF, the threshold is >40 mL/m²)
E/e' ratio at rest[a]	>9	Sensitivity 78%, specificity 59% for the presence of HFpEF by invasive exercise testing, although reported accuracy has varied. A higher cut-off of 13 had lower sensitivity (48%) but higher specificity (86%).[1,260,274]
NT-proBNP BNP	>125 (SR) or >365 (AF) pg/mL >35 (SR) or >105 (AF) pg/mL	Up to 20% of patients with invasively proven HFpEF have NPs below diagnostic thresholds, particularly in the presence of obesity
PA systolic pressure TR velocity at rest[a]	>35 mmHg >2.8 m/s	Sensitivity 54%, specificity 85% for the presence of HFpEF by invasive exercise testing[260,261]

AF = atrial fibrillation; BNP = B-type natriuretic peptide; E/e' ratio = early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LV = left ventricular; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PA = pulmonary artery; SR = sinus rhythm; TR = tricuspid regurgitation.
Note: The greater the number of abnormalities present, the higher the likelihood of HFpEF.
a Only commonly used indices are listed in the table; for less commonly used indices refer to the consensus document of the ESC/HFA.[259]

Figure 2. 2021 ESC GUIDELINES for HFpEF DIAGNOSIS

DEVICE THERAPY for HFpEF

It is known that placement of an interatrial shunt device reduces pulmonary capillary wedge pressure during exercise in patients with heart failure and preserved or mildly reduced ejection fraction. But the trials of LAP reduction failed to show any benefit in terms of heart failure events or improve health status (REDUCE – LAP TRIAL).[6]

DISCUSSION

Ever since its arrival and the EMPA REG OUTCOME Trial showing remarkably positive results for the drug, SGLT2 inhibitors have been the topic of discussion in all the recent major cardiovascular and nephrology society meetings.[7]

Due to the vast popularity and theoretical benefits, this group of drugs have been studied in many trials in HFpEF population and have shown some encouraging results. But the results still need to be interpreted cautiously in order to put into clinical practice.

The SOLOIST-WHF trial was a sponsored trial funded by Sanofi and Lexicon Pharmaceuticals, of Sotaglifozin which is a dual SGLT2 and SGLT1 inhibitor. In the trial sotaglifozin showed reduced primary outcome (deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure) in subgroup of 250 patients with type 2 DM and Heart failure with preserved ejection fraction who were recently admitted for worsening heart failure. Early termination of the trial due to stopping of funding from the sponsors and the small sample size of this subgroup makes it difficult to draw any firm conclusion in this regard.[8] Also the actual number of cardiovascular deaths and the reduction of heart failure hospitalizations were not reported separately in the paper so it could be that reduction of heart failure hospitalizations was the key driver for reduction in primary composite outcome.

The SCORED trial of sotagliflozin showed that sotagliflozin has salutary effects on CV outcomes among patients with T2DM and CKD at cardiovascular risk. This trial also had to be stopped early due to stopped funding from trial sponsors and the primary outcome had to be changed to

include CV death, HF hospitalization, urgent visit for HF for sotagliflozin vs. placebo.[9]

The EMPEROR PRESERVED Trials was the largest RCT of SGLT2 inhibitor empagliflozin in HFpEF which enrolled 5988 patients in Class II-IV. It was again a sponsored trial funded by Boehringer Ingelheim and Eli Lilly, and surprisingly in this trial the LVEF cutoff was lowered to include patients with a LVEF of more than equal to 40%. Patients received empagliflozin at a dose of 10 mg daily versus placebo on the background of maximally tolerated dose of Beta blockers, RAAS blockers and statins.

Two thirds of the patient had a LV ejection fraction of more than equal to 50%.

In summary in patients with heart failure and a preserved ejection fraction, SGLT2 inhibition with empagliflozin led to a 21% lower relative risk in the composite of cardiovascular death or hospitalization for heart failure, which was mainly related to a 29% lower risk of hospitalization for heart failure with empagliflozin irrespective of diabetes status.

Treatment with empagliflozin did not appear to affect the number of deaths from cardiovascular or other causes in this trial.

The PRESERVED-HF Trial was designed to test the hypothesis that Dapagliflozin will improve symptoms, physical limitations and exercise function in patients with well-phenotyped HFpEF, both with and without type 2 diabetes (T2D) and it showed that 12 weeks of Dapagliflozin successfully achieved the primary and secondary outcomes. Again in this trial there was no significant difference in mortality and MACE.[10]

CONCLUSION

SGLT2 inhibitors as a class have been a major stepping stone in HFpEF in recent times and is definitely the only drug with hard evidence for benefit in this condition. But still evidences for mortality benefit and MACE reduction is lacking.

It can be argued that achieving symptom reduction and decreased hospitalization is an important landmark in HFpEF management, it will definitely reduce patient symptoms, morbidity, improve the quality of life and reduce financial and healthcare burden.

It can be also argued that given the short duration of follow up in clinical trials the difference in mortality and MACE was not significant and if we were to follow up the patients for a longer duration we would achieve a significant benefit in the hard end points; but such extrapolation should be done with caution.

DAPAGLIFLOZIN TO DELIVER?

Recently a report was published that the Phase III Deliver Trial of Dapagliflozin in Heart Failure with preserved and mildly reduced ejection fraction has been completed and has met its primary endpoint by significantly lowering the risk of cardiovascular death or worsening heart failure. In a press release, Scott Solomon, MD (Harvard Medical School and Brigham and Women's Hospital, Boston, MA), the principal investigator of the DELIVER trial, said the new results "extend the benefit of dapagliflozin to the full spectrum of patients with heart failure".[11]

According to AstraZeneca, the full study results will be submitted for presentation at a forthcoming medical meeting of European Society of Cardiology and regulatory submissions will be made in the coming months.

It will be interesting to see the study results as this trial again included patients with LVEF more than 40%, and it is already known that SGLT2 inhibitors reduce mortality and MACE in patients with lower end of HFpEF spectrum. Also the exact statistical difference in heart failure hospitalizations and cardiovascular mortality has to be studied properly.

FUTURE DIRECTIONS

A multicenter trial 4x4 trial design of MRA, Betablockers, SGLT2 inhibitors and placebo with a longer follow up duration is definitely needed to fill the gap and answer few questions to solve the dilemma of HFpEF management.

Also recently RATE-AF trial favoured digoxin as compared with beta blockers in patients with AF and mostly HFpEF, this finding has to be clarified further in a larfe RCT as it was a small trial done on elderly patients.[12]

There is no further role in evaluating nitrates in HFpEF as evidenced by the NEAT-HFpEF trial and previously the RELAX trials.

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