HFpEF: Evidence from Recent Clinical Trials and New Perspectives

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Heart failure (HF) is a highly prevalent clinical syndrome affecting more than 10% of the population older than 70 years of age, with a great impact on morbidity and mortality.[1,2] HF is traditionally divided into three categories based on the left ventricular ejection fraction (EF): HF with reduced EF (EF<40%; HFpEF), HF with intermediate EF (EF between 40% and 49%; HFiEF) and HF with preserved EF (EF>50%; HFpEF).[3]

HFpEF represents nearly half of HF cases in developed countries; its pathophysiology is complex and still little understood.[4] The great variety of HFpEF phenotypes, makes its diagnosis and treatment challenging. Unlike HFrEF, before the emergence of SGLT-2 inhibitors, no treatment had been shown effective in reducing the hard outcomes in HFpEF.[5] Also, the wide variability in diagnostic criteria of HFpEF adopted in different clinical trials may have contributed to the difficulty in showing therapeutic effectiveness in reducing mortality.

HFpEF accounts for more than 50% of all cases of HF and is associated with considerable mortality and morbidity.[6] The prognosis of HFpEF patients is dismal, with a one-year mortality rate of 10-30%.[7] The diagnosis is more difficult as compared with HFrEF, since several mechanisms have been implicated in its pathophysiology. Patients with HFpEF, when compared with HFrEF patients, are usually older, of female sex, and have comorbidities such as arterial hypertension, atrial fibrillation, pulmonary hypertension, diabetes mellitus, chronic renal disease, among others. The European Society of Cardiology guidelines recommended three criteria for the diagnosis of HFpEF – signs and symptoms of HF, LVEF ≥ 50%, increased natriuretic peptides and relevant structural heart disease and/or evidence of diastolic dysfunction.[3] However, despite these recommendations, due to the lack of pathognomonic criteria, there are still many uncertainties in the diagnosis of HFpEF.[8]

Several clinical trials have examined the use of proven-effective drugs in HFrEF. However, before the first results of studies on SGLT-2 inhibitors, all clinical trials had failed to demonstrate the benefits of pharmacological treatments in mortality and morbidity. The CHARM-Preserved trial showed that candesartan had an impact in preventing admissions for chronic HF but had no impact in reducing cardiovascular death compared with placebo.[9] Similarly, the PEP-CHF evaluated the effect of perindopril in HFpEF patients and did not show any significant difference in mortality or hospitalization.[10] The study suggested, however, improvement in symptoms and exercise capacity and fewer hospitalizations for HF with perindopril. In the I-PRESERVE, irbesatan did not improve the outcomes of mortality, hospitalization or quality of life.[11] The TOPCAT trial demonstrated that spironolactone significantly reduced hospitalizations for HF. However, a post-hoc analysis revealed that this benefit was more pronounced in the Americas (the United States, Canada, Brazil, and Argentina), while no significant differences were observed in Russia or Georgia.[12] Given the divergence of results between populations, issues about the homogeneity of patients, and likely randomization of less severe patients in the east European countries were raised. Results of the PARAGON HF[13] trial revealed a trend, but not significant, of reduced risk of hospitalization for heart failure or death with the use of the angiotensin receptor–neprilysin inhibitor (ARNI). A subgroup analysis, however, suggested benefit in patients with an EF between 45 and 57% and in women.[13] An interesting subanalysis of this population showed that the presence of HF signs and symptoms, particularly orthopnea and rales, were correlated with a higher risk for adverse CV events in patients with HFpEF.[14] Another important finding was a better blood pressure control in HFpEF patients and resistant hypertension treated with sacubitril–valsartan.[15] This result is particularly important considering the high prevalence of hypertension HFpEF and a close relationship between these clinical conditions.

A meta-analysis of 14 studies with a total of 19,573 demonstrated that none of the drugs tested significantly reduced mortality. However, ARNI and angiotensin converting enzyme inhibitors (ACEIs) were associated with a lower risk of hospitalizations in HFpEF patients (hazard ratio [HR] 0.73, 95%CI 0.60–0.87 and HR 0.64, 95% CI 0.43–0.96, respectively), and ARNIs were superior to angiotensin receptor blockers (ARBs) in reducing admissions for HF (HR 0.80, 95% CI 0.71–0.91).[16] Another meta-analysis including five studies corroborated this hypothesis – the study evaluated different renin-angiotensin-aldosterone system (RAAS) inhibitors and did not find statistically significant differences in cardiovascular mortality between the drugs. Also, ARNI was more effective in reducing hospitalizations compared with the other RAAS inhibitors.[17]

Despite the adoption of a LVEF ≥ 50% for the diagnosis of HFpEF, patients with a LVEF in the range of 40-49% have been included in these studies, which leads to a methodological

Keywords

Heart Failure; Stroke Volume; Mortality

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Manuscript received September 20, 2022, revised manuscript September 30, 2022, accepted September 30, 2022

DOI: https://doi.org/10.36660/abchf.20220071

limitation. Different classifications have been proposed and several inclusion criteria have been used in the clinical trials over the years, contributing to a high heterogeneity of the studied populations.[1,5]

The discrepant results among the clinical trials could be explained by differences in the standardization of LVEF in randomized patients and in atrial natriuretic peptide (BNP) cut-offs used in the studies. These frustrating results call attention to the fact that the known effects of the RAAS blockade and beta-adrenergic blockers in reducing mortality and morbidity in HFeEF have not been demonstrated in HFpEF.

Nevertheless, the heterogeneity of clinical, morphometric and laboratory data of these studies, in addition to the lack of well-established diagnostic criteria of HFpEF stresses the need of establishing stricter inclusion criteria in HFpEF studies addressing not only clinical but also morphological and neuro-humoral aspects.

Throughout this long journey in search of pharmacological interventions, recent studies that tested sodium-glucose cotransporter-2 (SGLT2) inhibitors have generated great enthusiasm in the treatment of HF, as these medications reduced both cardiovascular death and hospitalization for HF in both HFrEF and HFpEF. The first clinical trial on this drug class was the EMPEROR Preserved, that included patients with EF > 40% and NT-proBNP ≥ 300 pg (≥ 900 pg in patients with atrial fibrillation) and showed the superiority of empagliflozin versus placebo. The primary outcome (cardiovascular death or hospitalization for HF) occurred in 415 (13.8%) of patients in the empagliflozin group vs 511 (17.1%) patients in the placebo group, *i.e.*, 6.9 vs. 8.7 events per 100 patient-years; (hazard ratio, 0.79; 95% CI, 0.69 – 0.90; p<0.001). The secondary outcome, hospitalization for HF, occurred in 8.6% in the empagliflozin group and in 11.8% in the placebo group (p<0.001).[18] Subgroup analyses showed that patients aged older than 70 years and NYHA functional class II seemed to respond better to therapy. Results of the DELIVER trial were recently published; the study compared the effects of dapagliflozin with placebo in 6263 patients with HF and mildly reduced LVEF (40-49%) or HF with LVEF < 40% (recovered HF), with median NT-proBNP of 1011pg/mL. Patients were randomly assigned to receive dapagliflozin (at a dose of 10 mg once daily) or placebo. The primary outcome was cardiovascular death or worsening HF (hospitalization for HF or an urgent visit for HF). After a median follow-up of 2.3 years, dapagliflozin reduced the primary outcome by 18%; it occurred in 16.4% in the dapagliflozin group and 19.5% in the placebo group; HR 0.82; 95%CI 0.73-0.92; p < 0.001). When the components of the primary outcome were analyzed individually, the benefit was mostly due to the reduction in worsening HF (HR 0,79; IC 95% 0,69-0,91), 0.88; 95% CI, 0.74 to 1.05). In addition, individuals treated with dapagliflozin showed an improvement in quality of life (Kansas City Cardiomyopathy Questionnaire). There was no increase in the incidence of adverse events (acute renal failure, hypoglycemia, or volume depletion) with dapagliflozin. The results of the primary outcome were consistent among the subgroups, including patients with and without diabetes, patients with EF greater or lower than 60%, and even in those with recovered EF.[19]

A recently published, pre-specified meta-analysis of the DELIVER and the EMPEROR-Preserved trials, with data of the 12251 participants of these studies, showed that SGLT2 inhibitors reduced the composite outcome of cardiovascular death or first hospitalization for HF in 20% (HR 0.80 [95%CI 0.73-0.87]), with a decrease in both components: cardiovascular death (0.88 [0.77–1.00]) first hospitalization for HF (0.74 [0.67–0.83]). These data reflect a change of paradigm in the treatment of HFpEF, in which, for the first time, significant reductions in mortality or hospitalization were observed in HFpEF.

Altogether, the studies evaluating the use of SGLT-2 inhibitors in HF, in a continuous spectrum of EF, have suggested a reduction in the risk of cardiovascular death and hospitalization for HF in a wide range of patients. Such benefit in the continuum of EF contributes to the understanding of common pathophysiological mechanisms in different phenotypic profiles.

In conclusion, SGLT-2 inhibitors have emerged as a new therapeutical option in HF, an alternative to the well-known, gold standard triple therapy. In addition to reducing hard outcomes, SGLT-2 inhibitors improved the quality of life of HF patients and become a mandatory therapeutic approach in this population.[20]

With the increasing understanding of the pathophysiology of HF and targeting several steps in the neurohumoral and inflammatory pathways, many molecules have been tested in robust clinical trials. These molecules include mineralocorticoid antagonists, single- and dual-acting glucagon-like peptide-1 (GLP-1), and inflammatory markers. It is hence expected that advances in the blockade of the complex mechanisms involved in HFpEF will reduce the morbidity and mortality of HFpEF and its increasing prevalence.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Saraiva JFK, Moraes NR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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

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