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Editorial: Cochrane Heart Corner

Beta-blockers and renin–angiotensin–aldosterone system inhibitors in HFpEF. An urgent need for precision medicine☆

Bloqueadores beta e inhibidores del eje renina-angiotensina-aldosterona en la ICFEc. Una necesidad urgente de medicina de precisión

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Despite modern improvements in preventing and treating cardiovascular risk factors and diseases, heart failure (HF) with preserved ejection fraction (HFpEF) is a syndrome with elevated and increasing prevalence.[1] It is associated with a significant morbidity burden and a significant decrease in life expectancy.[1–3] To date, the main neurohormonal inhibitors drugs that have shown a substantial benefit in HF with reduced ejection fraction (HFrEF) have individually failed to demonstrate a robust clinical benefit in HFpEF.[4] Only a sodium-glucose cotransporter 2 (SGLT2) inhibitors trial in HF and left ventricular ejection fraction (LVEF) ≥ 45% recently met the primary endpoint by showing that empagliflozin reduced the composite risk of cardiovascular death or HF hospitalization, mainly by reducing worsening HF events.[5]

In a recent Cochrane systematic review, Martin et al.[6] evaluated the effect of adverse clinical events of neurohormonal inhibitors on those patients with HF and mildly systolic dysfunction and preserved ejection fraction. For this purpose, the authors included 41 randomized controlled trials with 23 492 participants with HF and LVEF > 40%, with an age of participants ranging from 30 years to 81 years and a median follow-up ranging from 6 months to 49.5 months. The authors evaluated the effects of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs).[6]

Regarding beta-blockers, the authors reported a possible reduction in cardiovascular mortality (risk ratios [RR] = 0.78;

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95% confidence interval [95%CI], 0.62–0.99; in 10 studies), with no effect on all-cause mortality or HF hospitalization. However, only 3 clinical trials and 1046 participants were included for cardiovascular mortality analysis. We must point out that the 3 studies enrolled patients with mildly systolic function and different baseline risk profiles (study 1: only 58 patients with ischemic heart disease, New York Heart Associaton class II or III and LVEF ≥ 40%;[7] study 2: 245 patients with the previous diagnosis of HF and LVEF > 40%;[8] study 3: 643 patients with a prior admission for HF and LVEF > 40%[9]). Furthermore, the authors concluded that the certainty of the evidence was low (due to unclear selection bias in most studies and concerns about the smaller study being more precise than the larger one).[6]

Pooled analyses for ACEIs and ARBs treatment revealed no effect on prognosis, (cardiovascular mortality, RR = 0.93; 95%CI, 0.61–1.42 and RR = 1.02; 95%CI, 0.90–1.14; all-cause mortality, RR = 1.04; 95%CI, 0.75–1.45 and RR = 1.01; 95%CI, 0.92–1.11; and heart failure hospitalization, RR = 0.86; 95%CI, 0.64–1.15 and RR = 0.92; 95%CI, 0.83–1.02, respectively). Conversely, MRAs and ARNIs exhibited a modest reduction in HF hospitalization with moderate-certainty evidence (RR = 0.82; 95%CI, 0.69–0.98; 3714 participants, and RR = 0.89; 95%CI, 0.80–1.00; 7362 participants, respectively), with no effect on mortality.[6]

Overall, the present analysis results are consistent with the previous meta-analysis in ACEIs,[10] ARBs,[10] and MRAs.[11] However, findings regarding beta-blockers and ARNIs differ from previous evidence. Regarding beta-blockers, a recent individual-patient level analysis of randomized clinical trials across the full spectrum of LVEF[12] reported that the reduction of cardiovascular mortality was observed only for those HF patients in sinus rhythm with a LVEF of less than 50%. Similarly, an individual patient-level pooled analysis of ARNIs use across the full spectrum of LVEF showed that the highest benefit in terms of HF hospitalization and cardiovascular mortality was for patients with a LVEF less than 50% (40–49%).[13] Overall, most evidence endorses a beneficial effect of neurohormonal inhibition in patients with HF and mildly reduced ejection fraction. However, the uncertainty is increasing at higher LVEF.[14]

This study provides the broadest evaluation of the previous evidence to date in using neurohormonal inhibitors drugs in HFpEF.[6] However, the current analysis does not dissipate the doubt about the role of neurohumoral inhibition in HFpEF. Several limitations deserve to be pointed out. First, most trials included evaluated patients with LVEF > 40% as a whole. Along this line, some evidence suggests that patients with LVEF ranging from 40 to 49% have a clinical and prognosis profile similar to patients with HFrEF.[4] Indeed, the current European Society of Cardiology 2021 Heart Failure Guidelines[4] recommend that these patients with LVEF ranging from 40 to 49% should manage as HFrEF.[4] Second, the heterogeneity in inclusion criteria is problematic. It is especially true for trials in which the current diagnosis accuracy of HFpEF is in question (lack of B-type natriuretic peptides or scarce echocardiographic data). Finally, external validation of randomized clinical trials in HFpEF to daily clinical practice is limited given the essential differences in the baseline risk profile (higher proportion of elderlies and greater comorbidities and geriatric syndromes, among others).

It seems imperative to carry out dedicated studies that evaluate patients with HF and truly preserved ejection fraction in its different phenotypes. Additionally, as a syndrome with complex and heterogeneous pathophysiology, we envision heterogeneous rather than neutral effects observed in most studies. Thus, further studies should focus on unraveling the different pathophysiological phenotypes of HFpEF and, once identified, test different treatment alternatives in each dedicated phenotype, leaving behind the analysis of HFpEF as a whole.

Conflicts of interest

J. Núñez reports personal fees from AstraZeneca, Novartis, Boehringer-Ingelheim, Eli Lilly, Rovi, NovoNordisk, and Vifor Pharma (outside the submitted work). P. Palau and E. Domínguez do not have any conflicts of interest to disclose.

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