Revista Portuguesa de Cardiologia 41 (2022) 863–864

Portuguese Society of CARDIOLOGY

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Medical therapy for heart failure with preserved ejection fraction: Still a minefield, but with new hope

Terapêutica médica na insuficiência cardíaca com fração de ejeção preservada: ainda um campo minado, mas com novas esperanças!

Matteo Pagnesi, Antonio M. Sammartino, Marco Metra*

Institute of Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy

Available online 14 July 2022

In this issue of the *Journal*, Formiga et al. present an analysis of the Spanish multicenter prospective RICA registry assessing the impact of beta-blocker therapy prescribed at discharge in a cohort of 1078 elderly patients with heart failure (HF) with preserved ejection fraction (HFpEF) who were admitted for acute HF and were in sinus rhythm at hospital admission.[1] In brief, the national RICA registry, coordinated by the Heart Failure Working Group of the Spanish Society of Internal Medicine, enrolled consecutive patients admitted for acute HF to internal medicine wards at 52 Spanish hospitals. In this study, use of beta-blockers at discharge was not associated with a lower risk of one-year all-cause mortality (adjusted hazard ratio [HR] 0.83; 95% confidence interval [CI] 0.61-1.13; p=0.236) or of the one-year composite endpoint of all-cause death or HF rehospitalization (adjusted HR 0.98; 95% CI 0.79-1.23; p=0.882) in patients with acute HFpEF and sinus rhythm.[1] The strengths of this study are the prospective and multicenter design of the real-world RICA registry and its large sample size. The main limitation is the observational nature of the study, which was potentially affected by residual unmeasured or confounding bias despite the adjusted analyses that were performed by the authors.

The results of this study are in line with available evidence demonstrating the lack of benefit of beta-blockers in HFpEF. In a large individual patient data meta-analysis of 10 trials including 18 254 patients with HF, the benefit of beta-blocker therapy versus placebo in terms of reduction in all-cause mortality was observed only in patients in sinus rhythm, and not in those with atrial fibrillation.[2] In a subsequent large individual patient data meta-analysis of 11 trials including 14 262 patients with HF and in sinus rhythm, beta-blockers improved left ventricular ejection fraction (LVEF) and prognosis in patients with HF with reduced ejection fraction (HFrEF), but not in those with HFpEF.[3] Use of beta-blockers reduced all-cause or cardiovascular mortality compared to placebo only in patients with LVEF <40% and in those with LVEF 40-49%.[3] Although the non-randomized observational design of this study prevents definitive conclusions from being drawn, Formiga et al. also confirmed these findings in a real-world population of patients who were hospitalized for acute HF and had evidence of HFpEF and sinus rhythm.

Considering the high burden of comorbidities in patients with HFpEF, including atrial fibrillation, chronic kidney disease, obesity, and other non-cardiovascular comorbidities that are more common in HFpEF than in HFrEF,[4,5] focusing on the treatment of comorbidities remains of paramount importance in these patients. In the absence of robust evidence from available randomized trials supporting a prognostic

* Corresponding author.
E-mail address: metramarco@libero.it (M. Metra).

https://doi.org/10.1016/j.repc.2022.06.013

benefit of most HFrEF drugs in the treatment of HFpEF, the recent European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF recommend reducing symptoms and signs of congestion with diuretics and treating cardiovascular and non-cardiovascular comorbidities, including hypertension, obesity, coronary artery disease, amyloidosis, atrial fibrillation and valvular heart disease, in patients with HFpEF.[6] Beta-blockers therefore remain a relevant therapeutic option for the treatment of comorbidities in patients with HFpEF, such as hypertension or coronary artery disease.[6]

Of note, after several randomized trials conducted in HFpEF failed to achieve their primary endpoints,[6] the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) and the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials have recently reported positive results in these patients.[7,8] SOLOIST-WHF, however, enrolled only diabetic patients hospitalized for HF.[8] By contrast, EMPEROR-Preserved enrolled diabetic and non-diabetic patients with HF and New York Heart Association class II to IV symptoms and increased N-terminal pro-B-type natriuretic peptide levels.[5,7] In EMPEROR-Preserved, the sodium-glucose cotransporter 2 inhibitor empagliflozin led to a significant 21% reduction in the primary composite endpoint of cardiovascular death or HF hospitalization in 5988 patients with HF and LVEF >40% (mean LVEF 54.3%), regardless of the presence or absence of diabetes.[7] This positive trial has raised the real possibility of finding a treatment for all patients with HFpEF, in fact for all patients with HF, independently of LVEF.[9] Beyond the use of gliflozins, detailed phenotyping, treatment of comorbidities and personalized patient approaches remain the mainstay of treatment in HFpEF. Machine learning techniques and identification of phenotype clusters are not often advocated as tools to better characterize patients with HFpEF.[10–12] Further progress in our understanding of the pathophysiology of HFpEF is now required to refine HFpEF management and potentially find more effective medical therapies for this challenging and difficult-to-treat patient population.

Conflicts of interest

Prof. Metra received personal consulting honoraria from Abbott, Amgen, Bayer, Edwards Therapeutics, LivaNova and Vifor Pharma for participation to advisory board meetings and executive committees of clinical trials. All the other authors have no conflicts of interest to declare.

References

1. Formiga F, Chivite D, Nuñez J, et al. Beta-blocker use in patients with heart failure with preserved ejection fraction and sinus rhythm. Rev Port Cardiol. 2022;41:853–61.
2. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet. 2014;384:2235–43.
3. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018;39:26–35.
4. Pieske B, Tschöpe C, Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40:3297–317.
5. Anker SD, Butler J, Filippatos G, et al. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. Eur J Heart Fail. 2020;22:2383–92.
6. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
7. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–61.
8. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384:117–28.
9. Pagnesi M, Butler J, Metra M. Ejection fraction in heart failure: just become Emperor's new clothes? Eur J Heart Fail. 2022;24:351–2.
10. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation. 2015;131:269–79.
11. Uijl A, Savarese G, Vaartjes I, et al. Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction. Eur J Heart Fail. 2021;23:973–82.
12. Woolley RJ, Ceelen D, Ouwerkerk W, et al. Machine learning based on biomarker profiles identifies distinct subgroups of heart failure with preserved ejection fraction. Eur J Heart Fail. 2021;23:983–91.