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Editorial

# The Syndrome of Heart Failure With Preserved Systolic Function

## El síndrome de la insuficiencia cardiaca con función sistólica conservada

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Heart failure with preserved ejection fraction (HFpEF) is now a fully acknowledged syndrome and may represent up to half of the heart failure (HF) population.[1] When compared with HF with reduced ejection fraction (HFrEF), outcomes in HFpEF have not improved over the last decade, highlighting the need for effective therapies for this condition.[2,3] Results from large phase III trials[4,5] have been disappointing and reflect the gap in the understanding of the mechanisms underlying HFpEF. Among HF patients requiring hospitalization, the proportion of HFpEF patients has been rising[6] and the rehospitalization rate of HFpEF is the same as that of HFrEF.[7] Multiple epidemiological studies show that HFpEF patients are predominantly elderly and more likely to be female and have higher rates of comorbid conditions such as hypertension, coronary artery disease, diabetes mellitus, anemia, obesity, chronic kidney disease, chronic obstructive pulmonary disease, and atrial fibrillation.[7,8] Such studies of HFpEF thus indicate its association with heterogeneous causes and multifactorial pathophysiological mechanisms. As HFpEF becomes one of the major public health burdens worldwide, a deeper understanding of its clinical behavior and socioeconomic burden is needed.

In the article published in *Revista Española de Cardiología*, Santas et al.[9] report on the variations in readmission rates between HFrEF and HFpEF populations due to worsening HF after discharge from hospital for acute HF hospitalization. The study used a longitudinal analysis encompassing all readmissions during the follow-up period, instead of time-to-first event. We agree with the idea that the choice of endpoints has to reflect the changing pattern of the disease, especially in the HF population. Hence, all-cause mortality is no longer considered a practical endpoint because it fails to fully reflect the current burden of the disease.[10] Time-to-first event analysis does not consider hospitalizations occurring before cardiovascular death as an endpoint and, hence, does not take into account the true influence of treatments or other factors and their effects on all events or repeat events, such as rehospitalizations. To statistically tackle these shortcomings and take into account multiple events as an endpoint, the investigators used multivariable negative binomial regression analysis. Other analytic methods available include the Anderson-Gill method with robust standard errors and the method of Wei, Lin, and Weissfeld.[11,12]

Although inaccurate in terms of therapy outcomes, most HF trials characterize HF according to left ventricular ejection fraction. This classification becomes challenging with heart failure with midrange ejection fraction (HFmEF), which encompasses individuals with a left ventricular ejection fraction $\geq$ 40% to $<$ 50%. Although Santas et al. have used 50% ejection fraction as a cutoff value, in line with European Society of Cardiology guidelines[1] and some recent results,[13] HFmEF is now also receiving attention,[14] although others call it "midrange" HF or HFmrEF.[1] There is no real pathophysiological basis for the cutoff values but consideration of an ejection fraction of 40% to 50% recognizes this "intermediate group" in studies. The Get With The Guidelines-HF (GWTG-HF) registry is now the largest registry of hospitalized HF patients and includes an HFmEF/HFmrEF cohort.[15] In the future, the data from the entire spectrum of ejection fraction groups may provide deeper insights into the behavior and pathophysiology of HF subgroups.

In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) trial, both HFrEF and HFpEF patients were evaluated for in-hospital and postdischarge characteristics. There were no significant differences between the HFrEF and HFpEF groups in postdischarge mortality from 60 to 90 days (9.8% vs 9.5%, respectively; $P = .459$) or in rehospitalizations (29.9% vs 29.2%, respectively; $P = .591$). Similarly, there was no significant difference in death from any cause and/or rehospitalization: 36.1% in HFrEF and 35.3% in HFpEF ($P = .577$).[7] In a cohort of 19 477 Medicare patients, Loop et al.,[16] found no significant differences in length of stay and 30-day readmission rates between HFpEF and HFrEF patients. Santas et al.[6] reported no significant differences in any of the postdischarge outcomes evaluated, but their results showed modest but significantly higher rates of noncardiovascular readmissions in HFpEF patients (incidence rate ratio, 1.24; 95% confidence interval, 1.04-1.47; $P = .012$). This finding may be due to their higher rates of comorbidities, such as coronary artery disease, atrial fibrillation, obesity, metabolic syndrome, and diabetes mellitus. These chronic comorbidities emphasize the role of the proinflammatory state, which causes widespread endothelial dysfunction that leads to decreased nitric oxide (NO) bioavailability in cardiomyocytes, decreased myocardial cyclic guanosine 3,5-monophosphate (cGMP) concentration, and low protein kinase-G (PKG) activity. However, the proof-of-concept studies performed so far have been

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unable to show a clinical benefit from targeting the NO-cGMP-PKG pathway.[2] Further and better designed studies should examine the role of higher rates of comorbidities in the HFpEF population and their consequent effect on the higher burden of readmission rates.

Several novel approaches, such as phosphodiestrase-5 inhibitors, soluble guanylate cyclase stimulators, mineralocorticoid receptor antagonists, neprilysin inhibitors, ivabradine, statins, calcium-cycling modulators, microRNA, and exercise, have shown benefits in early clinical studies of HFpEF patients and need to be tested further for safety and efficacy in large-scale clinical trials. Although Santas et al. may address some of the issues, such as higher noncardiovascular readmission rates in the HFpEF population, this population has its own challenges, including the complex nature of the HFpEF syndrome and the lack of availability of an effective therapeutic strategy. Thus, the full public health value of these data will not be obtained until we identify and address the unmet needs of the HF population subsets and their associated comorbidities.

## CONFLICTS OF INTEREST

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