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Eligibility of sodium-glucose cotransporter-2 inhibitors in heart failure with preserved ejection fraction: Insights from the Colombian heart failure registry (RECOLFACA)

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ABSTRACT

Background: The value of Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitor) therapy in individuals with heart failure with preserved EF (HFpEF) was unknown until the EMPEROR-Preserved trial. We aimed to assess the proportion of patients with HFpEF that are eligible for empagliflozin therapy within the Colombian Heart Failure Registry (RECOLFACA).

Methods: RECOLFACA enrolled adult patients with a HF diagnosis during 2017–2019 from 60 medical centers in Colombia. Criteria of the EMPEROR-Preserved Trial were used to recruit participants. The main outcome was individual eligibility with N-terminal pro-B-type natriuretic peptide (NT-proBNP) criteria, while the secondary outcome was eligibility without NT-proBNP data.

Results: RECOLFACA had 799 patients with HFpEF (mean age70.7 ± 13.5; 50.7 % males). According to the major selection criteria of the EMPEROR Preserved Trial, 73.7 % patients would be eligible for empagliflozin therapy initiation when considering the NT-proBNP threshold. The NT-proBNP threshold represented the main determinant of ineligibility in patients with this biomarker measure (13.6 %; n = 16). In patients without NT-proBNP data, the main reasons for exclusion were the diagnosis of symptomatic hypotension or a systolic blood pressure below 100 mmHg (7.5 %), having an eGFR < 20 ml/min/1.73 m^2 (4.3 %), and haemoglobin < 9 g/dl (3.1 %). Excluding NT-proBNP criteria increased empagliflozin eligibility to 80.6 %.

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Conclusion: Most patients with HFpEF from RECOLFACA are potential candidates for empagliflozin therapy initiation according to the EMPEROR-Preserved trial criteria. These findings favor the utilization of SGLT-2 inhibitor medications in daily medical practice, which may further decrease morbidity and mortality in HF patients, regardless of their EF classification.

1. Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a special medical condition that comprises most HF cases in a community, commonly affecting females and patients over 65 years of age [1]. Despite exhibiting a preserved EF phenotype, HFpEF is characterized by elevated morbidity and mortality, highlighting a 5-year survival of 65 % after a HF hospitalization, which is comparable to the survival rate of individuals with HF with reduced EF (HFrEF) [2–6]. Even though significant advances have been made in the treatment of this condition, the results obtained have not been favorable, and its benefits may not cover the entire population of HFpEF patients [7].

Recently, the discovery of a significant cardiovascular benefit of sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitor) could enhance the prognosis of individuals with HF [8]. Although, the benefits of SGLT-2 inhibitor were initially proven in individuals diagnosed with HFrEF and type 2 diabetes, the recent publication of the EMPEROR-Preserved trial results, a double-blind, randomized clinical trial, have provided evidenced for the potential efficacy of these molecules in the context of HFpEF [7]. In this trial, patients with HFpEF treated with a SGLT-2 inhibitor (empagliflozin) had a significantly lower incidence of the principal outcome of adjudicated cardiovascular death or hospitalization for HF compared to the placebo group [7]. Regarding this research breakthrough, there is a need to characterize the patients in real-life clinical practice that may benefit from the prescription of this SGLT-2 inhibitor [9,10]. The aim of this research was to assess the proportion of outpatients with HF who meet the inclusion criteria of the EMPEROR-Preserved trial using data from the Colombian Heart Failure Registry (RECOLFACA).

2. Methods

2.1. Study design and population

RECOLFACA is a prospective cohort study, with participants from 60 different medical centers in Colombia. Recruitment began in February 2017 and finished in October 2019. The inclusion criteria in brief were individuals older than 18 years of age, with a diagnosis of HF of every etiology based on standard clinical characteristics, and with at least one HF hospital admission in the year prior to recruitment. Detailed inclusion and exclusion criteria, as well as extended methodologic descriptions of the registry have been described previously [11]. Our study was approved by the Ethics committee of the Fundación Valle del Lili under the act number 174–2017.

2.2. Data collection

Sociodemographic, clinical, and laboratory data were collected at the beginning of the study. The New York Heart Association (NYHA) classification was used to evaluate the severity of HF. Individuals with a left ventricular EF (LVEF) $>$ 40 % were classified as HFpEF, and individuals with a LVEF $<$ 40 % were classified as having HFrEF. The coexisting conditions evaluated were chronic kidney disease (estimated glomerular filtration rate $<$ 60 ml/min/1.73 m^2 according to the MDRD equation), high blood pressure (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg), atrial fibrillation (diagnosed based on a 12-lead ECG or previous records of this illness), anemia (haemoglobin $<$ 13 g/dL for men and $<$ 12 g/dL for women), and dyslipidemia (total cholesterol $\geq$ 200 mg/dL, or low-density lipoprotein [LDL] cholesterol $\geq$ 100 mg/dL, or triglycerides $\geq$ 150 mg/dL, or receiving lipid-lowering drugs). Clinical scenarios including valvular heart disease, chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus (T2DM), cancer, liver failure, dementia, thyroid disease, and Chagas disease were also registered. For certain individuals, supplementary echocardiographic studies like systolic diameter of the left ventricle were performed.

2.3. Eligibility criteria

Recruited HF patients meet the criteria for the EMPEROR-Preserved trial as follows: age $\geq$ 18 years at the time of screening, diagnosed with chronic HF for at least three months diagnosed with chronic HF for at least three months according to the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC), with NYHA functional classification class II-IV, and with a preserved EF defined as LVEF $>$ 40 % per local reading. In addition, if a NT-proBNP measurement was available at the time of registry enrollment, only individuals with N-terminal pro-B-type natriuretic peptide (NT-proBNP) $>$ 300 pg/mL (without atrial fibrillation, AF), or $>$ 900 pg/mL with AF were included (exclusion criteria in Supplementary Material 1). For patients without NT-proBNP data, the same inclusion criteria as the EMPEROR-Preserved trial were applied, except for the NT-proBNP levels, and a separate eligibility analysis was performed.

2.4. Statistical analysis

Baseline attributes of patients were reported as medians and quartiles in the case of continuous variables. Categorical variables were reported using absolute counts and proportions. All analyses were implemented in the statistical software STATA version 15 [12].

3. Results

The RECOLFACA registry included 2528 patients; from those, 2514 patients (99.45 %) had complete information regarding sociodemographic and clinical variables. The median age was 69 years old (Q1:59; Q3:78), with a higher proportion of males (57.6 %; n = 1447). From the total cohort, 1139 patients (45.3 %) had a diagnosis of HFpEF, while 799 had complete information (Supplementary Material 2).

3.1. Patient characteristics and comparison with the EMPEROR-Preserved trial population

A similar sex and age distribution was observed between the two populations, with a slight majority of males and an average age of approximately 70 years in both groups. Also, a predominance of white patients and NYHA functional class II was found in both populations. Patients in the RECOLFACA had a lower incidence of concomitant disorders such as arterial hypertension, T2DM, and atrial fibrillation, than patients in the EMPEROR-Preserved trial. Additionally, patients in the RECOLFACA experienced a higher heart rate and an inferior systolic blood pressure than participants from the trial. Interestingly, RECOLFACA patients present a lower EF value while reporting increased levels of NT-proBNP in serum, and a higher prevalence of ischemic HF. Finally, the average estimated glomerular filtration rate (eGFR) was similar across the two populations. Table 1 summarizes the baseline characteristics of both groups.

Table 1
Baseline characteristics of patients with a HFpEF diagnosis enrolled in the Colombian Heart Failure Registry (RECOLFACA), compared to patients included in the treatment group of the EMPEROR-Preserved trial.

	RECOLFACA (N = 799)	EMPEROR-Preserved (N = 2997)
Sex, Male	405 (50.7 %)	1659 (55.4 %)
Age (years)	70.7 ± 13.5	71.8 ± 9.3
Population		
Asian	1 (0.1 %)	413 (13.8 %)
White	665 (83.2 %)	2286 (76.3 %)
African American	13 (1.6 %)	133 (4.4 %)
Other or missing	120 (15.1 %)	165 (5.5 %)
NYHA classification		
I	85 (10.6 %)	3 (0.1 %)
II	464 (58.1 %)	2432 (81.1 %)
III	226 (28.3 %)	552 (18.4 %)
IV	24 (3 %)	10 (0.3 %)
Heart rate (bpm)	74 ± 15.2	70.4 ± 12
Systolic blood pressure (mmHg)	127 ± 23.2	131.8 ± 15.6
Left ventricular ejection fraction (LVEF)		
Mean LVEF (%)	49.9 ± 8.2	54.3 ± 8.8
- LVEF > 40 % to < 50 %	401 (50.2 %)	995 (33.2 %)
- LVEF ≥ 50 % to < 60 %	251 (31.4 %)	1028 (34.3 %)
- LVEF ≥ 60 %	147 (18.4 %)	974 (32.5 %)
Median NT-proBNP (pg/ml)†	1652 (781; 3736)	994 (501; 1740)
HF etiology		
- Ischemic	343 (42.9 %)	1079 (36 %)
- Nonischemic	456 (57.1 %)	1917 (64 %)
Mean eGFR — ml/min/1.73 m^2	66 ± 31	60.6 ± 19.8
eGFR < 60 ml/min/1.73 m^2	297 (51.5 %)	1504 (50.2 %)
Hypertension	620 (77.6 %)	2721 (90.8 %)
T2DM	193 (24.2 %)	1466 (48.9 %)
Atrial fibrillation	196 (24.5 %)	1543 (51.5 %)

†The NT-proBNP data for RECOLFACA patients was available for only 118 patients with this information available during enrollment in the registry.
eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ml/min/1.73 m^2: milliliters of cleansed blood per minute per body surface; pg/ml: picograms per milliliter; bpm: beats per minute; mmHg: millimeter of mercury; T2DM: Type 2 diabetes mellitus; HF: Heart failure.

3.2. Eligibility for empagliflozin therapy in RECOLFACA patients

From the total of 799 patients with HFpEF enrolled in the RECOLFACA, 681 patients did not have NT-proBNP data. For these patients, the same inclusion criteria as the EMPEROR-Preserved trial were applied, except for the NT-proBNP levels, as mentioned in the Methods section. Moreover, two different assessments were performed to evaluate eligibility: one considering the NT-proBNP criterion (n = 118 patients) and another one not considering the NT-proBNP criterion (n = 681).

Following the inclusion and exclusion criteria guidelines and considering the NT-proBNP criterion, in our HFpEF individuals, 87 (73.7 %) patients would be candidates for initiation of empagliflozin. Also, 80.6 % (n = 549) of the patients without NT-proBNP data would be eligible for empagliflozin therapy when the criterion of this biomarker was not considered (Fig. 1). The main reason behind the ineligibility of patients for empagliflozin in this cohort was not reaching the NT-proBNP threshold in patients with this biomarker measured (13.6 %; n = 16). On the other hand, the main reasons for exclusion in patients without NT-proBNP data were the diagnosis of symptomatic hypotension or a systolic blood pressure below 100 mmHg (7.5 %), having an eGFR < 20 ml/min/1.73 m^2 (4.3 %), followed by a haemoglobin < 9 g/dl (3.1 %). Fig. 2 summarizes the most frequent exclusion criteria observed in the RECOLFACA.

4. Discussion

The current research revealed that more than 70 % of the individuals with HFpEF from the RECOLFACA registry are potentially eligible for SGLT-2 inhibitor therapy according to the EMPEROR-Preserved trial criteria, with similar results for patients with and without NT-proBNP data. This study represents the initial efforts to assess the eligibility of individuals with HFpEF for SGLT-2 inhibitor therapy published in the literature, and the first to evaluate the potential use of these medications in a Latin American population with HF.

Evidence about the use of SGLT-2 inhibitor therapy has rapidly evolved in recent years, deriving in substantial changes in the approach of patients with T2DM and HF [13–15]. Results from several clinical trials have revealed a unique and strong benefit regarding the implementation of these types of medication in individuals with HFrEF, as it has been associated with a reduction in all-cause and cardiovascular

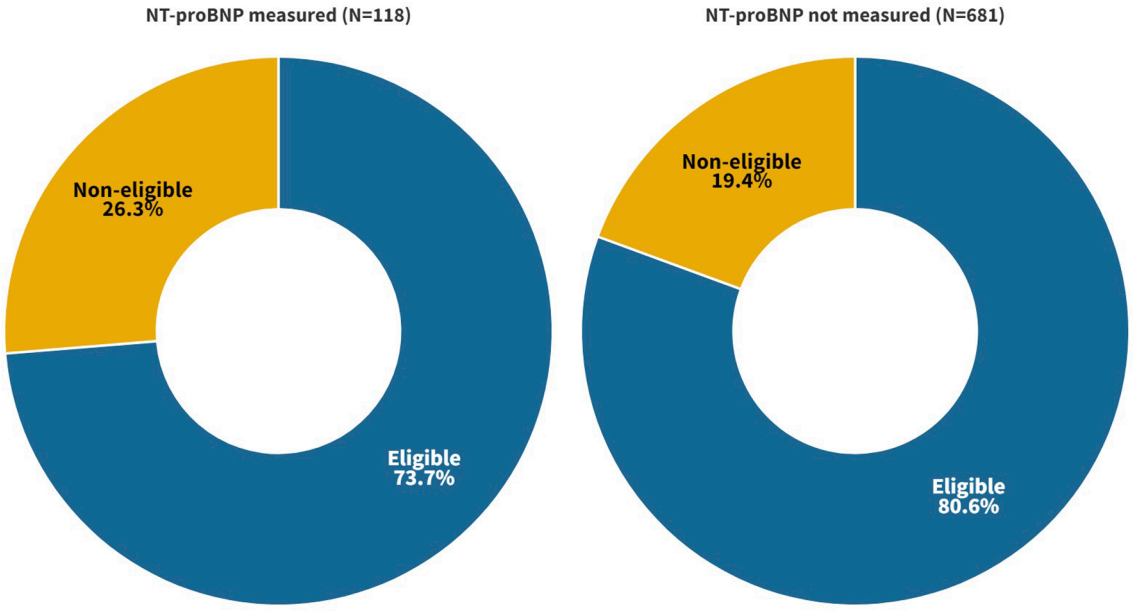

Fig. 1. Eligibility according to EMPEROR-Preserved criteria. Eligibility of patients with left ventricular ejection fraction (LVEF) > 40 % from the Colombian Heart Failure Registry (RECOLFACA), according to the N-terminal pro-B-type natriuretic peptide (NT-proBNP) criterion of the EMPEROR-preserved trial.

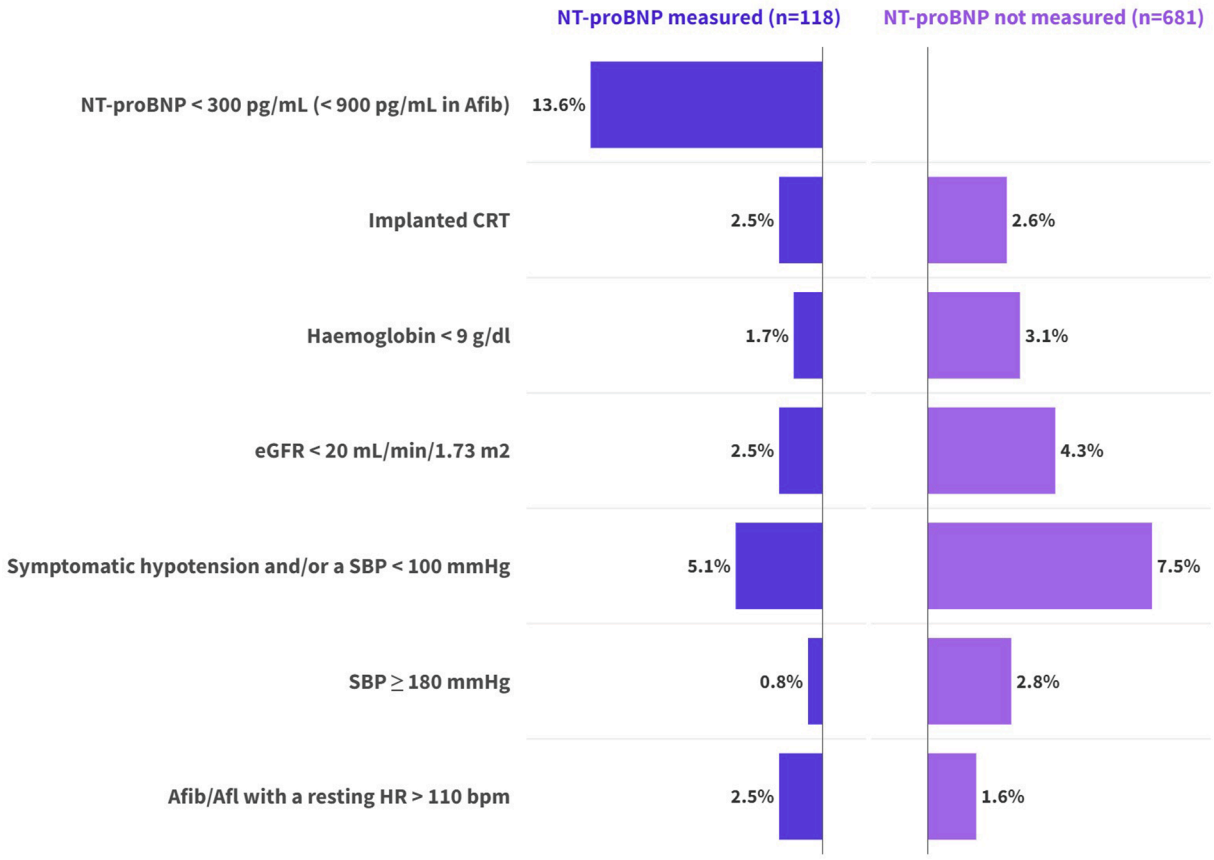

Fig. 2. Prevalence of the most frequent exclusion criteria among patients with left ventricular ejection fraction (LVEF) > 40 % from the Colombian Heart Failure Registry (RECOLFACA).

death, HF medical admissions, and severe negative renal outcomes [8,16].

Nevertheless, until the EMPEROR-Preserved trial results, no study had provided evidence regarding the use of SGLT-2 inhibitor therapy in the context of HFpEF. In this double-blind, randomized trial, 5988 HFpEF individuals were allocated to receive empagliflozin (10 mg once daily) or a placebo [7]. After an average follow-up of 26 months, patients receiving empagliflozin presented a significantly decreased risk of reaching the primary outcome of adjudicated cardiovascular death or hospitalization for HF related to patients in the placebo group. Nonetheless, similar mortality risk in both groups was observed, being the result of the SGLT-2 inhibitor on the primary outcome incidence mainly related to a decreased risk of medical admission due to HF. This benefit was comparable to the one observed for empagliflozin in HFrEF individuals, suggesting that the effect of SGLT-2 inhibitor therapy on HF outcomes may not widely vary across HF phenotypes [7].

In the present study, RECOLFACA patients had similar sociodemographic and clinical characteristics compared to the EMPEROR-Preserved trial population in the empagliflozin group. However, patients with HFpEF from the RECOLFACA registry had lower median EF values and higher NT-proBNP levels, highlighting a potentially worse disease status. On the other hand, individuals enrolled in the RECOLFACA registry had a distinctly lower prevalence of arterial hypertension, atrial fibrillation, and T2DM. Although the benefit of SGLT-2 inhibitor in HFpEF was consistent among patients with or without T2DM, the differences in comorbidity prevalence in the RECOLFACA patients need to be considered when assessing the benefit of SGLT-2 inhibitor therapy [7].

Furthermore, differences in baseline pharmacological therapy need to be considered, highlighting the use of angiotensin receptor-neprilysin inhibitors (ARNIs), which was prescribed in 8.6 % of patients eligible for SGLT-2 inhibitor in the RECOLFACA. Although no data is yet available regarding the proportion of participants in the EMPEROR-Preserved trial using ARNIs, previous trials such as the EMPEROR-Reduced and DAPA-HF reported a low rate of sacubitril/valsartan prescription [17,18]. According to recent evidence, SGLT-2 inhibitor therapy in patients with HFrEF taking sacubitril/valsartan is equally effective as in patients without this ARNIs, suggesting that dual ARNI-SGLT-2 inhibitor therapy has the potential to further reduce morbidity and mortality in patients with HFrEF [19]. Considering that sacubitril/valsartan has shown significant benefits for patients with HFpEF and was recently approved by the FDA for this population, additional evidence about the benefit of SGLT-2 inhibitor therapy in individuals with HFpEF receiving ARNIs is required [20].

Finally, the relevance of NT-proBNP inclusion thresholds in HFpEF patients might be even higher than in HFrEF patients. In our study, the NT-proBNP criteria was the primary ineligibility factor for SGLT-2 inhibitor treatment in the group of patients with NT-proBNP data, which goes in line with other studies assessing the eligibility for SGLT-2 inhibitor treatment in HFrEF patients. Although NT-proBNP thresholds could help identify patients with higher risk of short-term adverse cardiovascular outcomes, their utility in assessing therapeutic response in HF remains unknown. Moreover, the residual potential for harmful outcomes in individuals with HFpEF and NT-proBNP levels below the actual threshold needs to be considered, since these patients may also potentially benefit from SGLT-2 inhibitor therapy [21]. In the present analysis, eligibility for SGLT-2 inhibitor therapy increased from 74 % to 80.6 % when the NT-proBNP criteria was not considered, highlighting the need of assessing the benefit of SGLT-2 inhibitor therapy in individuals with HFpEF below the actual proposed NT-proBNP threshold. Additionally, we highlight that the potential implications of our findings on healthcare costs and resource allocation should be further explored in

future studies.

5. Study limitations

One of the limitations of our study is the high proportion of individuals without NT-proBNP data, which represented a relevant inclusion criteria for the EMPEROR Preserved trial. However, our main aim was to evaluate the eligibility of patients from a real-world registry, using the EMPEROR-Preserved trial criteria as a reference point. In clinical practice, especially in acute settings, the lack of repeated NT-proBNP measurements poses a significant challenge in our country and region. Consequently, we deemed it prudent to include patients without this biomarker measurement in our analysis, as this scenario reflects the real-life constraints and provides valuable insights into our clinical context. Moreover, as the information analyzed in this study is derived from a national registry database that involves more than 60 HF centers, echocardiographic LVEF estimations may present significant variation.

6. Conclusions

Most patients with HFpEF enrolled in the RECOLFACA are potential candidates for empagliflozin therapy initiation according to the EMPEROR-Preserved trial criteria. The insights from this population highlight the possible extensive utilization of SGLT-2 inhibitor medications in daily medical practice, which may further decrease morbidity and mortality in the population HF patients, regardless of their EF classification.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101448.

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