

The EMPEROR-Preserved Trial: Results that Innovate the Treatment of Heart Failure with Preserved Ejection Fraction

Ricardo Mourilhe-Rocha,^{1,2} Marcelo Imbroinise Bittencourt,^{1,3} Felipe Neves de Albuquerque,^{1,4} Ana Luiza Ferreira Salles,^{1,2} Pedro Pimenta de Mello Spineti,^{1,5} Denilson Campos de Albuquerque^{1,6}

Universidade do Estado do Rio de Janeiro,¹ Rio de Janeiro, RJ – Brazil

Hospital Pró-Cardíaco - Américas Serviços Médicos,² Rio de Janeiro, RJ – Brazil

Grupo DASA,³ Centro, RJ – Brazil

Hospital Samaritano Botafogo – Américas Serviços Médicos,⁴ Rio de Janeiro, RJ – Brazil

Hospital Unimed Rio,⁵ Rio de Janeiro, RJ – Brazil

Instituto D'Or de Pesquisa e Ensino (IDOR),⁶ Rio de Janeiro, RJ – Brazil

The treatment of heart failure with reduced ejection fraction (HFrEF) has been improving by numerous pharmacological and non-pharmacological options, as described in national and international guidelines. However, in the scenario of patients with HF with preserved EF (HFpEF), no therapeutic update has occurred since the last published guideline.¹⁻⁴

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are effective hypoglycemic agents in type 2 diabetes mellitus (T2DM) and are associated with improved glycemic control as well as with reduced body mass and blood pressure. In large-scale randomized trials of patients with diabetes, the use of SGLT2 inhibitors has improved cardiovascular and renal outcomes – including hospitalization for HF (HHF). This benefit was also observed in patients without diabetes who have HFrEF.⁵ That is, the presence of T2DM is not necessary to endorse the clinical benefit of SGLT2 inhibitors in HFrEF.⁵

Recently, the classification of forms of HF according to EF was redefined, but the definition of EF $\geq 50\%$ for HFpEF was maintained.⁶ This is a crucial point, since the EMPEROR-Preserved trial used an EF cutoff of 40% for patient inclusion – that is, it included patients with EFs 41% to 50% classified as HF with slightly reduced EF.⁶ However, the authors were careful to prespecify subgroups according to EF, which allowed the interpretation of specific results for each EF range, thus reinforcing the value of this statistical analysis.⁷

The recently published EMPEROR-Preserved results demonstrate, in an unprecedented way, solid benefits of empagliflozin for patients with HFpEF. It reduced the combined risk of cardiovascular death, HHF, or HF emergency visit. This benefit started at day 18 post-randomization. There was also a reduction in the total number of HHFs (first and recurrent) as well as in hospitalizations for any cause.

Advantages were evinced in all HF severity spectra: in the most severe one, there were fewer HHFs in intensive care and less need for vasopressors or positive inotropes. In the outpatient setting, fewer patients on empagliflozin required increased diuretics and there was a higher likelihood (1.2 to 1.5x) of improvement in the New York Heart Association (NYHA) functional class.⁷ Despite the consistent effect of reducing HHFs in these scenarios, there was no impact on cardiovascular death alone or on total deaths. Therefore, the combined primary outcome proved to be statistically significant at the expense of the impact on hospitalizations, which does not underestimate the beneficial effect of the drug for HFpEF.⁷

As mentioned earlier, in order to study the impact on different EF ranges, the authors analyzed 3 EF subgroups. The benefit of reducing HHFs was similar across the lower EF ranges (40%-50% and 51%-60%), but it was attenuated in the subgroup with higher EFs (above 60%).⁷⁻¹⁰

Another relevant aspect of the EMPEROR-Preserved trial was the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ) to assess the impact on quality of life (QoL). Two results were prominent. First, the benefit of reducing cardiovascular outcomes was independent of the severity of the symptoms presented at the beginning of the follow-up (ie, with a lower KCCQ score). Second, the mean KCCQ score was better in the intervention group over the 26.2 months of follow-up reflecting a gain in QoL – an effect that appeared early and was maintained for at least 12 months. This advantage was seen in all patients, regardless of their KCCQ or NYHA data at baseline. These findings reinforce the importance of early initiation of empagliflozin in HFpEF.^{11,12}

This type of finding is similar to that reported in other randomized trials of HFpEF (such as TOPCAT and PARAGON-HF). It is important to highlight, however, that this impact on QoL was also attenuated in patients with EFs $\geq 60\%$ to 65% (as well as for HHFs).¹¹

In contrast to these favorable effects, empagliflozin did not reproduce this pattern in major renal outcomes – defined as a sustained $\geq 40\%$ reduction in estimated glomerular filtration rate (renal death was not included in this outcome in the EMPEROR-Preserved trial). These disagreements were intriguing because, in previous clinical trials, the effect of SGLT2 inhibitors on HF and renal outcomes was consistent.¹¹

Keywords

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Mailing Address: Ricardo Mourilhe-Rocha •

Rua Voluntários da Pátria, 445/1402. Postal Code 22270-000, Botafogo, Rio de Janeiro, RJ – Brazil

E-mail: ricardomourilhe@gmail.com

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An explanation for the lack of “renal protection” in the EMPEROR-Preserved trial may be the definition of renal outcomes. A meta-analysis demonstrated agreement between the effects of SGLT2 inhibitors on HF and renal outcomes when using a more conventional definition of renal outcomes, a finding in line with observations of the effects of this drug class in other large-scale studies of patients with T2DM.¹³

A perplexing factor in the interpretation of HFpEF studies is the heterogeneity of the EF thresholds adopted to define it. Inclusion criteria were $\geq 40\%$ in PEP-CHF, $>40\%$ in CHARM-Preserved, and $\geq 45\%$ in I-PRESERVED, TOPCAT, and PARAGON-HF. Note that, as in the EMPEROR-Preserved trial, all patients with slightly reduced EF were included, not just those diagnosed with HFpEF according to the latest universal classification (EF $\geq 50\%$). This seems to be a relevant and weak point, as the greatest benefits in the primary outcomes of these studies were recorded for a left ventricular EF of 40% to 50%, whereas the same treatments were ineffective for patients with an EF $>60\%$. The same pattern was observed in the EMPEROR-Preserved subgroup analysis.¹⁴

When analyzing the characteristics of the EMPEROR-Preserved population, there was a higher percentage of patients with T2DM in the EMPEROR-Preserved trial (49% vs 33% TOPCAT vs 43% PARAGON), which may have contributed to the overall benefits of empagliflozin in addition to standard therapy. Furthermore, only 2% of patients received sacubitril/valsartan, and the combined use of these drugs in the management of HFpEF warrants further investigation.¹⁴

A comparison of the effects reported in 2 randomized trials of patients with HFpEF evaluating the benefits of neprilysin inhibition and SGLT2 inhibition using the same EF cutoffs in comparable patient populations would be ideal. Currently, we can use indirect comparisons between PARAGON (sacubitril-valsartan) and EMPEROR-Preserved (empagliflozin) to infer which drug provides the greatest clinical benefit in HFpEF. Thus, in the outcomes that include HHF, the effect size appears to be larger for empagliflozin in most EF subgroups. We highlight the odds ratio (OR) of one of these outcomes, time to first HHF, to illustrate these findings in the table below.¹⁵

The magnitude of the reduction in the risk of serious HF outcomes appears to be greater with SGLT2 inhibition than with neprilysin inhibition for most patients with HFpEF.¹⁵

Although the EMPEROR-Preserved results may indicate a long-awaited advance in the approach to HFpEF, the heterogeneous patient profile motivates the design of studies based on a more accurate phenotypic characterization. This

scenario would allow us to take advantage of the predominant mechanism of action of the different agents available in individually appropriate clinical phenotypes.

Additionally, evidence is still lacking on how to treat patients with EF $\geq 60\%$ -65%, and we need to wait for the results of other ongoing studies using SGLT2 inhibitors in HFpEF to know how to act in this scenario.

Finally, we can say that we have left ground zero and, in the current context of scientific knowledge, the use of SGLT2 inhibitors in HFpEF seems to be the best therapeutic option for these individuals.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Mourilhe-Rocha R; Critical revision of the manuscript for intellectual content: Mourilhe-Rocha R, Albuquerque DC.

Potential Conflict of Interest

Dr. Ricardo Mourilhe-Rocha - advisor and speaker for: Boehringer-Lilly, Astrazeneca, Novartis, Bayer, Servier, Daichi Sankyo, Pfizer, Proadi-SUS.

Dr. Marcelo Imbroinise Bittencourt - advisor and speaker for: Bristol-Myers Squibb e Sanofi Genzyme.

Dr. Felipe Neves de Albuquerque - advisor and speaker for: Novartis e Boehringer-Lilly.

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Table 1 – Odds Ratio for Time to First Hospitalization for Heart Failure: Comparison between PARAGON-HF vs EMPEROR-Preserved according to ejection fraction subgroups

EF subgroup	PARAGON-HF	EMPEROR-Preserved
$>42.5\%$ to $\leq 52.5\%$	0.83 (0.65-1.06*)	0.65 (0.50-0.85*)
$>52.5\%$ to $\leq 62.5\%$	0.87 (0.71-1.07*)	0.68 (0.51-0.89*)

EF: ejection fraction, Odds ratio: Hazard rate, *95% confidence interval

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