Lessons from the EMPEROR Preserved

Ivna Girard Cunha Vieira Lima[1] *and Edimar Alcides Bocchi*[1]

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (UNTCI – InCor – HC-FMUSP),[1] *São Paulo, SP – Brazil*

In randomized clinical trials, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown effective in reducing the risk of cardiovascular (CV) death and hospitalization for chronic heart failure (CHF), as well as renal outcomes, regardless of the presence of diabetes. Despite these findings in patients with heart failure (HF) with reduced ejection fraction (EF) (HFrEF), retrospective subanalyses of patients with type 2 diabetes have suggested that many of preventable events have occurred in patients with a left ventricular (LV) EF (LVEF) greater than 40%.[1] In this regard, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) was carried out to evaluate the safety and efficacy of empagliflozin in patients with HFpEF. A total of 5988 patients with LVEF > 40% were randomized (Empagliflozin or placebo) and followed up for a median of 26.2 months; 45% of participants were women, symptomatic, with class II–IV heart failure, one hospitalization in the last year and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels of more than 300 pg/mL if in sinus rhythm or > 900 pg/mL if in atrial fibrillation NT-PRO-BNP. The primary outcome – composite outcome of CV death or hospitalization for heart failure (HF) – occurred in 13.8% in the empagliflozin group and in 17.1% in the placebo group, with a hazard ratio of 0.79; 95% confidence interval (CI) of 0.69 to 0.90; p<0.001. No significant difference was found in CV death (HR 0.91, 95%CI 0.76-1.09), but a significant difference was observed in hospitalization for HF (HR 0.71, 95%CI 0.60-0.83), regardless of the presence of diabetes. However, this beneficial effect of empagliflozin was not detected in patients with EF>60% (HR 0.87, 95%CI 0.69-1.1) in a subgroup analysis and its limitations.[2]

When the outcomes were stratified by EF, 33% of patients had EF between 41 and 49% and the others an EF>50%. No difference in the effect of the medication was seen between patients with EF > 50% and patients with EF<60% or 41-49% (Table 1). Empagliflozin was superior to placebo in improving the combined outcome regardless of the presence of diabetes in patients with HFpEF. The effect was strengthened especially by the reduction in hospitalization for CHF rather than in CV mortality, which seems to be independent of baseline EF, even among patients with EF between 50% and 60%.[2] With these results, empagliflozin was approved for the treatment of patients with this profile, and generated enthusiasm in the scientific community. Previous medications such as candesartan, spironolactone and sacubitril-valsartan have shown no or modest beneficial effect, and predominantly in populations with lower EF.[3]

Although the mechanism of action of empagliflozin has not been elucidated, the marked reduction in hospitalizations for a condition with an increasing incidence in the world and high health care costs in public and private services seems quite relevant. Another issue to be discussed is the historical classification of CHF by EF cut-offs. Comparison of studies using different medications has shown that different ranges of EF are associated with distinguishable responses to the drugs; while in the lower strata (HFrEF) a reduction in mortality stands out, in the higher strata (HFpEF) a reduction in hospitalization is predominant.

When these data are put into perspective, despite potential differences between populations and outcomes, there are three main trials that evaluated the classes of drugs used in the treatment of HFpEF: the PARAGON[4] (neprilysin inhibitors), the EMPEROR-Preserved[2] (SGLT2i) and the TOPCAT[5] (mineralocorticoid receptor antagonists). In the PARAGON-HF[4] (patients with EF>45%), no benefit was found for the combined outcome, for hospitalization or for CV death. Analysis of subgroups raised the hypothesis, to be confirmed, that the composite outcome of hospitalization and CV death would be reduced by sacubitril–valsartan in the EF <57% stratum and in women. This hypothesis was also suggested by an exploratory analysis of the pool of patients of the PARAGON-HF and PARADIGM-HF trials. In the TOPCAT trial (patients with EF > 45%), spironolactone was shown to have a modest effect on hospitalization for HF, which was a component of the primary outcome, together with CV death and aborted cardiac arrest. There was a higher incidence of hyperkalemia and increased creatinine levels. A subgroup analysis (without an interaction test) suggested that patients with EF lower than the median (but not lower than 50%) would benefit the most from the drug.

Despite the differences for the outcome hospitalization for IC, exploratory and subgroup analyses that need confirmation, suggest the hypothesis that patients with EF between 40% and 60% would benefit from sacubitril-valsartan or spironolactone. However, so far, empagliflozin was the only medication that has been shown to reduce hospitalization for HF both in patients with EF ≤40%

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Mailing Address: Ivna Girard Cunha Vieira Lima •
HCFMUSP – UNTCI – Av. Dr. Enéas de Carvalho, 44. Postal Code 05403-000, Cerqueira Cesar, São Paulo, SP – Brazil
E-mail: ivna_cunha@hotmail.com
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Table 1 – Results of empagliflozin by ejection fraction strata

Outcome	% of events with empagliflozin EF ≥50%	% of events with placebo EF ≥50%	p	% of events with empagliflozin EF 41-49%	% of events with placebo EF 41-49%	p	Interaction p-value
Combined	6.7%	8.0%	0.02	7.2%	10%	0.002	0.27
All cause-mortality	6.1%	6.1%	0.84	7.7%	8.0%	0.72	> 0.05
Total hospitalization rate	4.5%	5.7%	0.013	3.8%	6.5%	<0.001	0.06
Quality of life (KCCQ)	4.24	2.78	0.006	4.86	3.3	0.043	0.92

EF: ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; data extracted from the Emperor-Preserved[2]

and in patients with EF >40%, as reported in the EMPEROR-REDUCED and EMPEROR-PRESERVED studies, respectively. These results give rise to discussion about patient classification based on EF cut-offs and creates an evidence gap for the subgroup of patients with EF>60%, in which the benefits obtained in the subgroup analysis are not maintained.[6,7]

In conclusion, although the mechanism of action of SGLT2i are not fully understood, these drugs reduce hospitalizations for HF regardless of the presence of diabetes and apparently of EF also. Among the therapeutic options available, this class of drugs seems to offer the greatest benefit. Nevertheless, unanswered questions remain, like how and when will medications that effectively affect CV and all-cause mortality in HFpEF patients be available, and why apparently none of these medications are effective in patients with EF>60%.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Lima IGC

Potential Conflict of Interest

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