Sodium Glucose Co-transporter 2 (SGLT2) inhibitors in Heart Failure with Preserved Ejection Fraction: A systematic review and meta-analysis

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Whilst Heart Failure with preserved Ejection Fraction (HFpEF) is increasingly studied, the search for a single pharmacotherapeutic agent that will improve hard endpoints like hospitalisation and mortality still continues [1]. Given the various subphenotypes of HFpEF [2], this makes it difficult for a single agent to be universally beneficial. The recent publication of EMPEROR-PRESEVED [3] was an instrumental time for an updated meta-analysis focused on sodium glucose co-transporter 2 inhibitors (SGLT2i) use in HFpEF.

We systematically searched PubMed, Embase, Cochrane and Web of Science databases from inception to August 27, 2021. The key terms used for the search were "SGLT2" *or* "Sodium-glucose cotransporter-2 inhibitors" *or* "canagliflozin" *or* "dapagliflozin" *or* "empagliflozin" *or* "ertugliflozin" *and* "heart failure" with at least six months follow up. The inclusion criteria and the detailed study selection process are shown in Supplementary Figures 1 and 2. Our primary endpoint was cardiovascular death and hospitalisation for heart failure (HHF). From 9,493 articles, 167 studies underwent full-text screening, a total of 5 studies and 9,726 patients were included [3–7]. Of those, 5,046 patients received an SGLT2i, and 4,680 placebo. The characteristics of the studies included are demonstrated in Table 1. The hazard ratios and 95% CI given in each study were used for the meta-analysis. A random-effects model with inverse-variance weights was used to combine the effect measures from all studies on a logarithmic scale. Statistical heterogeneity was assessed using the I^2 statistic. The statistical analyses were conducted using the Review Manager (RevMan) software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The use of SGLT2 inhibitors was associated with a significant reduction in CV death or HHF (HR=0.78, 95%CI: 0.69, 0.87; I^2 0%) (Figure 1) and in HHF (HR=0.71, 95%CI: 0.61, 0.84; I^2 0%) (Supplementary Figure 3) compared with placebo. There were no significant differences between the two groups of patients in terms of CV death (HR=1.01, 95%CI: 0.80, 1.28; I^2 23%) (Supplementary Figure 4) and all-

cause mortality (HR=1.01, 95%CI: 0.89, 1.14; I^2 0%) (Supplementary Figure 5). However, as some studies included patients with Left Ventricular Ejection Fraction (LVEF) 40-50%, not fulfilling the definition of HFpEF according to the recent ESC Heart Failure guidelines[8], we also undertook a focused pre-specified subanalysis for those studies with available data for patients with LVEF>50% [3,6,7]. This comprised 5,928 patients and showed a 23% reduction in CV death or HHF (HR=0.77, 95%CI: 0.66, 0.91; I^2 22%) in the SGLT2 group (Supplementary Figure 6). This value remained significant even after sensitivity analysis removing each study sequentially. The funnel plots for all the meta-analyses performed can be found in Supplementary Material (Supplementary Figures 7 – 11).

We confirm that the use of SGLT2i is associated with a substantial decrease in the risk of CV death or HHF in patients with heart failure and ejection fraction >40%. Importantly, in this first and largest meta-analysis reviewing LVEF>50%, we show that this benefit is maintained, albeit to a lesser degree, in the cohort of patients with LVEF≥50%. SGLT2i become in this way the first medication with potential for prognostic benefit in HFpEF. However, overall mortality was not improved in HFpEF, indicating that the other comorbidities associated with HFpEF play a significant role. In order to draw robust conclusions safely regarding these efficacy outcomes, further large trials need to evaluate the effect of the SGLT2 inhibitors in a sufficient number of patients with HFpEF.

The various subphenotypes of HFpEF and its management have puzzled physicians for several years. The high rates of morbidity and mortality that it carries, along with the diagnostic and treatment challenges, have transformed it in one of the most challenging clinical entities. SGLT2i appear to provide some light and positivity, as their cardiometabolic profile impacts favourably on the complex pathophysiological mechanisms involved in HFpEF [9]. However, the quest to untangle the complexity of treating HFpEF is certainly not over. We show conclusively that for LVEF 40-50% included as HFpEF in previous studies (but no longer considered HFpEF in the guidelines) there is a strong benefit from SGLT2i translating to reduced cardiovascular mortality and HHF, but not overall mortality. This also extended to the LVEF>50% but with a smaller effect. Additionally, while the vast majority of the

patients included in this meta-analysis were individuals with diabetes at baseline, the cardioprotective benefits of the SGLT2i have been shown to occur via mechanisms independent of baseline diabetes status[10]. Furthermore, the effect of SGLT2i in patients with reduced EF without diabetes is well documented[9,10] and EMPEROR-Preserved also included patients without diabetes, therefore their effect is applicable to patients without diabetes. Nonetheless, the DELIVER trial currently recruiting (NCT03619213), will provide additional data in HFpEF patients without diabetes. The journey for an optimal and effective medication for HFpEF still continues. One many argue that with SGLT2i the target destination is now visible, and Ithaca is closer than it has even been.

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Author contribution

VT and VSV conceived the study idea. VT, HE, RC and OA reviewed the literature and extracted data. VT, RC, NA, AC interpreted the data. AC provided statistical support and analysis. PG and VSV provided supervision. VT wrote the first draft and all co-authors revised it.

Declaration of interest

All authors declare no conflict of interest

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