

Sodium-glucose cotransporter 2 inhibitors: the first universal treatment for heart failure?

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In 2015, publication of the results of the BI 10773 (empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) heralded the beginning of a new era in cardiovascular disease pharmacotherapy.¹ Initially investigated as glucose-lowering agents in patients with type 2 diabetes, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to improve cardiovascular outcomes in a wide range of patients, including those with type 2 diabetes, chronic kidney disease, and in patients with heart failure across the full spectrum of left ventricular ejection fraction (LVEF).^{2–6}

Traditionally, treatments for the syndrome of heart failure have been investigated separately in subgroups of patients with either heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF) generally using a cut-off at LVEF 40%. These two phenotypes of heart failure differ in their aetiology, demographics, and outcomes; therefore, it is perhaps no surprise that until recently, treatments shown to improve outcomes in patients with HFrEF have failed to replicate these benefits when studied in patients with HFpEF. This historical precedent has recently been overturned with the discovery that SGLT2 inhibitors improve outcomes in all patients with heart failure, irrespective of LVEF.^{4–6}

To date, three randomized, placebo-controlled trials of SGLT2 inhibitors have been performed in patients with heart failure: two trials in patients with chronic ambulatory HFrEF (DAPA-HF with dapagliflozin and EMPEROR-Reduced with empagliflozin) and one trial in patients with HFpEF (EMPEROR-Preserved with empagliflozin).^{4–6} A further trial (SOLOIST-WHF) was conducted with the combined SGLT1 and SGLT2 inhibitor sotagliflozin in hospitalized patients with heart failure and type 2 diabetes across the range of LVEF.⁷ In an effort to provide an up-to-date summary of the totality of evidence supporting the use of SGLT2 inhibitors in

heart failure, Ahmad and colleagues present the results of a trial-level estimate meta-analysis of the 15 684 patients enrolled in these four trials (weighted-mean follow-up 20 months).⁸ They report a significant pooled 12% [95% confidence interval (CI) 3–21%] reduction in the risk of cardiovascular mortality, a 30% (23–36%) reduction in the risk of the total number of heart failure hospitalizations, and a 24% (19–29%) reduction in the risk of the composite of cardiovascular mortality or first heart failure hospitalization. The observed absence of heterogeneity between trials is supportive of a class effect of treatment on these endpoints. Subgroup analyses demonstrated a consistent benefit of SGLT2 inhibitors irrespective of chronic kidney dysfunction, diabetes, or treatment with an angiotensin receptor-neprilysin inhibitor (ARNI).

Ahmad and colleagues should be commended for providing a timely synthesis of the contemporary data supporting the benefits of SGLT2 inhibitors in a wide range of patients across the spectrum of heart failure. The present analysis adds to previous analyses, which were limited to patients with HFrEF, thereby providing pooled estimates supporting the role of SGLT2 inhibitors as a treatment for heart failure irrespective of LVEF.⁹

Several aspects of the meta-analysis merit further discussion. First, it is important to highlight that some key patient groups were excluded from the trials included in this analysis, namely patients with type 1 diabetes (due to the risk of ketoacidosis with an SGLT2 inhibitor) and those with significant impairment of kidney function. Each trial differed in its lower limit cut-off of estimated glomerular filtration rate (eGFR), with the most liberal being the EMPEROR trials with an eGFR of ≥ 20 mL/min/1.73 m².^{5,6} Further evidence supporting the use of an SGLT2 inhibitor in patients with chronic kidney disease is provided by the DAPA-CKD trial, which mandated an eGFR at baseline of between 25 and 75 mL/min/m².³ It is worth highlighting that in DAPA-CKD discontinuation of dapagliflozin was not protocol-mandated if eGFR decreased to < 15 mL/min/1.73 m² and in a small subgroup of patients with stage 4 chronic kidney disease at baseline (eGFR < 30 mL/min/1.73 m²), the efficacy and safety of dapagliflozin were consistent with that seen in the overall

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population.¹⁰ Whether the benefits and safety of SGLT2 inhibitors in heart failure patients with an eGFR of <20 mL/min/m² or with stage 5 CKD are similar to those described in the trials reported to date remains to be seen and should be a focus for future research given the lack of treatment options in this high-risk patient population.¹¹

A further limitation of the present analysis was the relatively small number of patients enrolled at the time of hospitalization for worsening heart failure. However, the relative risk reduction in SOLOIST-WHF with sotagliflozin on cardiovascular death and heart failure hospitalization was of a similar magnitude to the treatment effect seen in the other trials, suggesting that the benefit seen in ambulatory outpatients extends to this high-risk patient population.⁷ Given that patients with non-fatal episodes of worsening heart failure requiring hospitalization are at high future risk of adverse outcomes, the minimal effects of SGLT2 inhibitors on blood pressure and renal function should make treatment with these drugs relatively safe and effective in these patients and provide an opportunity to overcome the therapeutic inertia that limits widespread uptake of guideline-recommended therapy in heart failure.¹² Additional evidence supporting the safety of initiating an SGLT2 inhibitor in patients stabilized from an episode of worsening heart failure requiring hospitalization is provided by the small EMPA-AHF trial and further outcome data will be provided by the upcoming EMPULSE (ClinicalTrials.gov identifier NCT04157751), DAPA ACT TIMI-68 (NCT04363697), DICTATE-AHF (NCT04298229), and DELIVER (NCT03619213) trials.^{13–15}

Perhaps the most obvious difference among the trials included in the present analysis was that only one recruited exclusively patients with an LVEF >40% (EMPEROR-Preserved).⁶ EMPEROR-Preserved was the first randomized trial to show a significant benefit of a heart failure therapy in reducing the primary composite outcome of cardiovascular death or heart failure hospitalization in patients with an LVEF >40%, an effect that was largely driven by a reduction in heart failure hospitalization. In a subgroup analysis of reduced vs. preserved LVEF, Ahmad and colleagues did not observe any significant interaction of the effect of SGLT2 inhibitors on the composite outcome of cardiovascular mortality or heart failure hospitalization. However, they did not report any similar analyses for the individual all-cause or cardiovascular mortality endpoints, which is an important omission given the lack of significant treatment effect on these two endpoints in EMPEROR-Preserved. Indeed, there was mild heterogeneity seen in the non-significant pooled estimate for all-cause mortality and the pooled estimate was statistically significant when EMPEROR-Preserved was removed from the meta-analysis. Prior meta-analysis of DAPA-HF and EMPEROR-Reduced reported no between-trial heterogeneity with a significant beneficial treatment effect of SGLT2 inhibitors on both all-cause and cardiovascular mortality, suggestive of a class effect in patients with HF_rEF.⁹ Examination of the mortality rates in both EMPEROR trials and DAPA-HF may provide some insight into a potential differential effect of SGLT2 inhibitors on mortality in heart failure patients with reduced and preserved LVEF. In EMPEROR-Reduced and DAPA-HF, the placebo group incidence rate of cardiovascular death was 8.1 and 7.9 per 100 patient-years, respectively, and the corresponding rate in EMPEROR-Preserved was 3.8 per 100 patient-years.^{4–6} A further difference between the trials was the proportion of all deaths that were adjudicated to be due to cardiovascular causes; in DAPA-HF

and EMPEROR-Reduced, 83% and 76% of all deaths were cardiovascular, whereas in EMPEROR-Preserved the proportion of cardiovascular deaths was 55%. The lower event rate and a greater competing risk of death from non-cardiovascular causes may have limited the statistical power of EMPEROR-Preserved to detect a significant treatment effect on cardiovascular mortality. Future meta-analyses including the results of the upcoming trials may provide further insight into the effect of SGLT2 inhibitors on mortality in HF_pEF.¹⁴

The recently updated European Society of Cardiology guidelines for the management of heart failure have afforded a class I, level of evidence A recommendation to SGLT2 inhibitors in patients with HF_rEF to reduce the risk of cardiovascular death and heart failure hospitalization.¹⁶ No recommendation for SGLT2 inhibitors in HF_pEF was made, since the publication of EMPEROR-Preserved followed development of the guidelines. No doubt a guideline update will offer a class I indication for SGLT2 inhibitors in HF_pEF based on the results of EMPEROR-Preserved (and potentially the DELIVER trial), with supporting evidence for their efficacy and safety in hospitalized patients provided by the trials discussed earlier. SGLT2 inhibitors may have an extended role for prevention of heart failure following myocardial infarction following publication of the DAPA-MI (NCT04564742) and EMPACT-MI (NCT04509674) trials, which are examining the potential role of these drugs in high-risk patients following myocardial infarction. The present work by Ahmad and colleagues is a valuable addition to the literature confirming the benefits and safety of SGLT2 inhibitors in heart failure and leaves no doubt that SGLT2 inhibitors should be considered the first treatment to improve morbidity and mortality across the full range of LVEF.

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