Meta-analysis of the effects of four factors on the efficacy of SGLT2 inhibitors in patients with HFrEF

Zannad et al. conducted a meta-analysis\(^1\) based on the EMPEROR-Reduced\(^2\) and DAPA-HF\(^3\) trials for the following two purposes. First, they aimed to assess the effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on fatal and non-fatal heart failure events as well as renal endpoints in all randomly assigned patients with heart failure and reduced ejection fraction (HFrEF), while they used time to all-cause death as the primary endpoint. Second, they aimed to assess the effects of SGLT2 inhibitors on the combined risk of hospitalization for heart failure (HHF) or cardiovascular death (CVD) in the clinically important subgroups respectively defined by the following 10 factors: type 2 diabetes status, sex, age, New York Heart Association (NYHA) functional class, angiotensin receptor nephrilysin inhibitor treatment, history of HHF, race, body mass index, estimated glomerular filtration rate, and geographical region. On the contrary, the aforementioned factors assessed in the Zannad et al. meta-analysis\(^2\) did not include cause of heart failure, baseline use of mineralocorticoid receptor antagonist (MRA), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, and left ventricular ejection fraction (LVEF) level. These four factors are so important that both DAPA-HF\(^3\) and EMPEROR-Reduced\(^2\) trials have assessed their effects on the efficacy of SGLT2 inhibitors in reducing the heart failure composite outcome (i.e. a composite of HHF or CVD). However, neither of the two trials\(^2,3\) was powered to characterize the subgroup effects deriving from the four factors. Thus, it is essential to assess these subgroup effects by meta-analysis incorporating the two trials.\(^2,3\)

According to the two study protocols from our research team published in the PROSPERO website (Registration Numbers: CRD42020159584 (Supporting Information, Appendix S1) and CRD42020159567 (Supporting Information, Appendix S2)) on 28 April 2020, we performed this present meta-analysis to evaluate the effects of important baseline characteristics on the efficacy of SGLT2 inhibitors on the heart failure composite outcome in patients with HFrEF. Because many of the relevant subgroup analysis results have been reported in the Zannad et al. study,\(^2\) we only report the results of the subgroup analysis according to cause of heart failure, baseline use of MRA, NT-proBNP level, and LVEF level.

Figure 1 shows that SGLT2 inhibitors versus placebo significantly reduced the composite outcome of HHF or CVD in the subgroups with ischaemic heart failure [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.70–0.89, \(P_{\text{heterogeneity}} = 0.630\)] and with nonischaemic heart failure (HR 0.69, 95% CI 0.60–0.79, \(P_{\text{heterogeneity}} = 0.690\)) in the subgroups with no baseline use of MRA (HR 0.75, 95% CI 0.63–0.89, \(P_{\text{heterogeneity}} = 0.883\)) and with baseline use of MRA (HR 0.74, 95% CI 0.66–0.84, \(P_{\text{heterogeneity}} = 0.910\)), and in the subgroups with NT-proBNP ≤ median (HR 0.66, 95% CI 0.55–0.79, \(P_{\text{heterogeneity}} = 0.580\)) and with NT-proBNP > median (HR 0.72, 95% CI 0.60–0.88, \(P_{\text{heterogeneity}} = 0.127\)). The effects of SGLT2 inhibitors were consistent across relevant subgroups defined by the aforementioned three factors (\(P_{\text{subgroup}} = 0.1545, 0.9027, \) and 0.5176, respectively). Moreover, SGLT2 inhibitors significantly reduced this composite outcome in the subgroup with LVEF ≤ 30% (HR 0.68, 95% CI 0.61–0.77, \(P_{\text{heterogeneity}} = 0.716\)) but not in the subgroup with LVEF >30% (HR 0.88, 95% CI 0.72–1.07, \(P_{\text{heterogeneity}} = 0.253\)) and with baseline use of MRA (HR 0.74, 95% CI 0.66–0.84, \(P_{\text{heterogeneity}} = 0.910\)), and NT-proBNP level (\(P_{\text{subgroup}} = 0.1545\)), baseline use of MRA (\(P_{\text{subgroup}} = 0.9027\)), and NT-proBNP level (\(P_{\text{subgroup}} = 0.5176\)). This finding will further prompt SGLT2 inhibitors to be used in patients with HFrEF to prevent important endpoints associated with heart failure. Second, SGLT2 inhibitors, with a significant subgroup effect (\(P_{\text{subgroup}} = 0.0279\)), showed a significant reduction in the risk of HHF or CVD in patients with HFrEF with LVEF ≤ 30% (HR 0.68, 95% CI 0.61–0.77) but not in patients with HFrEF with LVEF >30% (HR 0.88, 95% CI 0.72–1.07). This finding suggests that patients with HFrEF with LVEF ≤ 30%, but not with LVEF >30%, benefit from SGLT2 inhibitors. This could mean that as LVEF increases, the efficacy of SGLT2 inhibitors in patients with HFrEF may decrease. Therefore, to explore this
issue, future studies are needed. The Zannad et al. meta-analysis revealed that geographical region \((P = 0.037)\), race \((P = 0.0063)\), and NYHA class \((P = 0.0087)\) significantly affected the efficacy of SGLT2 inhibitors in patients with HFrEF, raising the possibility of an attenuated effect of this drug class in patients enrolled in Europe, in White patients, and in patients with NYHA class III–IV. Meanwhile, our meta-analysis revealed that LVEF level \((P = 0.0279)\) was one of the factors significantly affecting the efficacy of SGLT2 inhibitors. However, just like the Zannad et al. meta-analysis, ours also was a trial-level meta-analysis due to the lack of patient-level data, and therefore, in this meta-analysis, we failed to conduct multiple-factor analysis to adjust confounding factors. Thus, whether LVEF level is a real independent impact factor for the efficacy of SGLT2 inhibitors or not requires to be verified by further studies conducting the analysis based on patient-level data.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information

Data S2. Supporting Information
References

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