Heart Failure Association of the European Society of Cardiology Update on Sodium Glucose Co-transporter-2 Inhibitors in Heart Failure

(an update on the Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. The position paper of the Heart Failure Association of the European Society of Cardiology)

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Abstract

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has recently issued a position paper on the role of sodium-glucose co-transporter 2 (SGLT2) inhibitors in heart failure (HF). The present document provides an update of the position paper, based of new clinical trial evidence. Accordingly, the following recommendations are given:

Canagliflozin, dapagliflozin empagliflozin, or ertugliflozin have consistently demonstrated to be effective for the prevention of HF hospitalisation in patients with T2DM and established CV disease or at high CV risk. The specifically listed agents are recommended.

Dapagliflozin or empagliflozin are recommended to reduce the combined risk of HF hospitalisation and CV death in symptomatic patients with HF and reduced ejection fraction, already receiving guideline directed medical therapy, regardless of the presence of T2DM.

Key words: heart failure, SGLT2 inhibitors, type 2 diabetes, cardiovascular outcomes, renal function,

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has recently issued a position paper on the role of sodium-glucose co-transporter 2 (SGLT2) inhibitors in heart failure (HF) [1]. This document was published awaiting the results of ongoing clinical trials that have since become available. Hence, the present document provides an HFA update of the position paper on the role of STGL2 inhibitors in the prevention and treatment of HF [1] in light of new evidence from clinical trials.

Recently, the VERTIS-CV (Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes) trial demonstrated that ertugliflozin vs. placebo reduces the risk of HF hospitalisation in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular (CV) disease (23.7% with a history of HF), with a hazard ratio (HR) of 0.70 (95% confidence interval (CI), 0.54-0.90, p value not provided in accordance with the prespecified hierarchical statistical testing plan) [2]. The benefit was similar in patients with or without a history of HF. These findings are consistent with those of empagliflozin, canagliflozin and dapagliflozin, described in the previous document [1], and solidify the evidence that SGLT2 inhibitors have a beneficial effect in reducing the risk of hospitalisations for HF in patients with T2DM and CV risk factors or established CV disease.

Furthermore, in 3,730 patients with symptomatic HF and reduced ejection fraction (HFrEF), with or without T2DM, the EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) demonstrated a significant risk reduction with empagliflozin 10 mg daily vs. placebo in the primary combined endpoint of CV death or hospitalisation for HF (HR 0.75; 95% CI, 0.65 to 0.86, p<0.001) during a median follow-up of 16 months [3]. The trial included ~50% of patients without T2DM, 73% had left-ventricular ejection fraction <30%, 79% had N-terminal-B type natriuretic peptide level ≥1000 pg/mL and almost a half of patients had significant renal disfunction at baseline (estimated glomerular filtration rate, eGFR, ≥20 to 60 mL/min/1.73m^2) The benefit was

observed regardless of the presence of T2DM, baseline renal function, or the use of medications for HFrEF treatment, including sacubitril/valsartan (~20% of the trial patients). Risk reduction was primarily driven by a substantial decrease in HF hospitalisations (HR 0.69; 95% CI, 0.59 to 0.81, p<0.001). The trial has also shown a significant reduction in the two prespecified secondary outcomes, namely, the total number of HF hospitalisations (first and recurrent events; HR 0.70; 95% 0.58 to 0.85, p<0.001) and a decline in renal function (defined as a mean slope of change in eGFR, mL/min/1.73 m^2 per year).

A meta-analysis which used study-level data from DAPA-HF (A Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and patient level data from EMPEROR-Reduced further explored the effect of SGLT2 inhibition with dapagliflozin or empagliflozin in a broader spectrum of HF patients from both trials [4]. The meta-analysis demonstrated a reduction in both CV (HR, 0.86; 95% CI, 0.76–0.98, p=0.027) and all-cause mortality (HR, 0.87; 95% CI, 0.77–0.98, p=0.018) with SGLT2 inhibition, without any evidence of a statistical heterogeneity between dapagliflozin and empagliflozin. Similarly, SGLT2 inhibition reduced the risk of the combined endpoint of HF hospitalisation or CV death (HR, 0.74; 95% CI, 0.68–0.82, p<0.0001), as well as the first HF hospitalisation (HR, 0.69; 95% CI, 0.62–0.78, p<0.0001), the total number of HF hospitalisations or CV mortality (HR, 0.75; 95% CI, 0.68-0.84, p<0.0001) and worsening renal function (HR, 0.62; 95% CI, 0.43–0.90, p=0.013). The results were consistent in patients with or without T2DM. Data on the safety profile of both agents were reassuring given that no excess risk in adverse events was noted compared with placebo, including renal adverse events, volume depletion, severe hypoglycaemia, bone fractures, amputations or Fournier's gangrene [4]. In particular, ketoacidosis was uncommon with only 3 cases in DAPA-HF (all in patients with T2DM) and 0 cases observed in EMPEROR-Reduced [4].

In addition, a secondary analysis of the DAPA-CKD trial (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic

Kidney Disease) in patients with chronic kidney disease (eGFR, 25 to 75 mL/min/1.73 m^2 of and a urinary albumin-to-creatinine ratio, 200 to 5000 mg/g) with or without T2DM, revealed a significant risk reduction in hospitalisations for HF or CV death (HR, 0.71; 95% CI 0.55 to 0.92; p=0.0089) with dapagliflozin vs. placebo [5].

Assessing the landscape for the use of SGLT2 inhibitors in the prevention and treatment of HF, it can be concluded:

- Canagliflozin, dapagliflozin empagliflozin, or ertugliflozin have consistently demonstrated to be effective for the prevention of HF hospitalisation in patients with T2DM and established CV disease or at high CV risk. The specifically listed agents are recommended.
- Dapagliflozin or empagliflozin are recommended to reduce the combined risk of HF hospitalisation and CV death in symptomatic patients with HF and reduced ejection fraction, already receiving guideline directed medical therapy, regardless of the presence of T2DM.

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