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

Heart failure (HF) is common and associated with a poor prognosis, despite advances in treatment. Over the last decade cardiovascular outcome trials with sodium-glucose co-transporter 2 (SGLT-2) inhibitors in patients with type 2 diabetes mellitus (T2DM) have demonstrated beneficial effects for three SGLT-2) inhibitors (empagliflozin, canagliflozin and dapagliflozin) in reducing hospitalisations for HF. More recently, dapagliflozin reduced the risk of worsening HF or death from CV causes in patients with chronic HF with reduced left ventricular ejection fraction, with or without T2DM. A number of additional trials in HF patients with reduced and/or preserved left ventricular ejection fraction are ongoing and/or about to be reported. The present position paper summarises recent clinical trial evidence and discusses the role of SGLT-2 inhibitors in the treatment of HF, pending the results of ongoing trials in different populations of patients with HF.

Key words: heart failure, SGLT2 inhibitors, type 2 diabetes, cardiovascular outcomes, quality of life

Introduction

Heart failure (HF) and type 2 diabetes mellitus (T2DM) often occur together with an associated increased risk of adverse outcomes. HF is one of the most common cardiovascular conditions and one of the major causes of mortality in patients with T2DM [1, 2]. Furthermore, T2DM is frequent in patients with HF, occurring in almost 40% of patients hospitalised for HF and up to 30% of those with chronic HF [3]. Despite numerous available treatments for HF, the prognosis remains poor, with a small increase in survival over the last decade [4]. Concomitant T2DM confers a worse prognosis in HF, as the risks of cardiovascular and all-cause mortality are significantly increased, independent of other factors [5, 6].

Over the last decade, cardiovascular outcome trials have investigated several classes of new glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors, glucagon like peptide-1 receptor agonists and sodium–glucose co-transporter 2 (SGLT2) inhibitors, and all have demonstrated cardiovascular safety in patients with T2DM. Furthermore, some of these agents have been proven to have beneficial effects in reducing both major adverse cardiovascular events (MACE), as well as hospitalisation for HF and a few of these drugs have also reduced cardiovascular mortality (i.e. empagliflozin in EMPA-REG-Outcome [7] and liraglutide in LEADER [8]). Of particular importance has been the consistent finding of a reduction in HF hospitalisations in trials with SGLT2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) in patients with T2DM [9]. Also, there was a consistent finding of renal protection in T2DM with these drugs [10-12]. The safety profile and position of the new glucose-lowering agents in T2DM in general has been described in the 2019 European Society of Cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases [13], The 2019 Heart Failure Association (HFA) position paper on the role and safety of new glucose-lowering medications [14], and the HFA Clinical practice update on HF [15]. These documents suggest that SGLT-2 inhibitors,

empagliflozin, canagliflozin and dapagliflozin can be used to prevent HF hospitalisation in patients with T2DM.

Recently, the DAPA-HF trial reported that dapagliflozin reduced the risk of worsening HF or death from cardiovascular causes in patients with HF, with and without T2DM [16]. The results of this trial put forward the need to further update the role of SGLT-2 inhibitors in the treatment of HF. Hence, the present position paper extends the 2019 documents by providing a summary of evidence from the recent trials and discusses the role of SGLT-2 inhibitors in the treatment of HF.

New clinical trials with SGLT2 inhibitors

In patients with T2DM, SGLT2 inhibitors have been shown to reduce the risk of hospitalization for HF as shown for the first time for empagliflozin, and then for canagliflozin and dapagliflozin [9]. Of note, soon after the results of EMPA-REG-Outcome became known, the executive committee of DECLARE-TIMI-58 changed the trial end-point, from, initially having a primary safety outcome of MACE [17]. This was changed to having two primary efficacy outcomes – MACE and cardiovascular death or hospitalization for HF (with a split of alpha level equally), and no change in the primary safety outcome or the sample size. In the final results, the MACE co-primary outcome was not significantly reduced, but the second co-primary outcome was reduced, being entirely driven by HF hospitalisation, with no effect on cardiovascular mortality [17]. Recently, DAPA-HF has been the first trial to investigate efficacy of dapagliflozin in patients with HF and reduced ejection fraction (HFrEF) regardless of the presence of T2DM. This trial explored whether dapagliflozin 10 mg once daily, compared to placebo, improves morbidity, mortality and quality of life in symptomatic patients with HF and a left ventricular (LV) ejection fraction (LVEF) ≤40%, largely receiving guideline directed medical therapy (GDMT) for HF [16].

In 4744 patients enrolled in DAPA-HF, the primary endpoint of cardiovascular death or worsening HF (defined as a HF hospitalization or urgent outpatient visit for the treatment of HF) was significantly reduced (hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.65 to 0.85, p<0.001) [16]. The number-needed-to-treat in order to prevent one event was 21 over the median follow up of 18.2 months. Reductions in the risk of other outcomes were also observed, including cardiovascular mortality (HR 0.82; 95% CI, 0.69 to 0.98). Beneficial effects were evident in patients mostly receiving optimal GDMT; namely, 94% were treated with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin-1 receptor blockers (ARB) or sacubitril/valsartan (of note, 11% received the latter at baseline), 96% with a beta-blocker and 71% with a mineralocorticoid receptor antagonist (MRA). Furthermore, patients who received dapagliflozin were more likely to have a clinically relevant improvement in their quality of life after 8 months of treatment as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). Importantly, there was no difference in pre-specified serious adverse events between the dapagliflozin and placebo groups. There was no evidence of heterogeneity in the efficacy of dapagliflozin in any of the pre-specified subgroups, except possibly for the New York Heart Association (NYHA) functional class, given that patients with NYHA class III-IV appeared to derive less benefit compared to patients with NYHA class II. However, there were no heterogeneities in other subgroups of patients, including those with lower LVEF or higher NT-proBNP levels, or in patients with more advanced renal insufficiency, which suggests that dapagliflozin may be similarly effective in patients with more severe HF [16]. Most importantly, there was no difference in the efficacy of dapagliflozin in patients with and without T2DM. An exploratory analysis of DAPA-HF demonstrated that the efficacy of dapagliflozin was similar over the entire spectrum of glycosylated haemoglobin A_{1c} values [18]. These findings suggest that the SGLT2 inhibitor dapagliflozin exerts beneficial effects in HFrEF irrespective of T2DM status and it appears that the mechanism of action of dapagliflozin in HFrEF extends beyond a simple glucose-lowering effect.

In addition to the DAPA-HF trial, another trial of interest to learn lessons as to how to prevent HF development was the CREDENCE trial [12]. In this trial, 4401 patients with T2DM and an estimated glomerular filtration rate (GFR) of 30 to <90 ml/min/1.73 m^2 and albuminuria (ratio of albumin (mg) to creatinine (g), >300 to 5000) were randomized to canagliflozin or placebo [12]. Of the included patients, 15% had a history of HF at baseline, but these patients are not well characterised. Canagliflozin substantially reduced the risk of the primary composite endpoint of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death (HR 0.70; 95% CI, 0.59 to 0.82; P < 0.001) [12]. There was also a significant reduction in the secondary outcome of HF hospitalizations (HR 0.61; 95% CI, 0.47 to 0.80; P<0.001) [12], indicating that HF prevention is possible also in the setting of high-risk patients with T2DM and concomitant CKD. The preventive role of SGLT2 inhibitors for HF also pertains to other high-risk patients such as those with T2DM and established atherosclerotic cardiovascular disease, in whom cardiovascular outcome trials have consistently shown lower risk for HF hospitalisation with SGLT2 inhibitors [9].

In addition to clinical outcomes, a potential for an improvement in functional status has been recently explored with SGLT2 inhibitors. The effect of SGLT2 inhibitors on exercise tolerance in patients with HFrEF with and without T2DM is still under debate as the DEFINE-HF trial has not shown a significant effect of dapagliflozin on the mean N-terminal pro-B-type natriuretic peptide levels (NT-proBNP), but increased the proportion of patients achieving a combined endpoint of improved functional status (as measured by the KCCQ), or ≥20% reduction in NT-pro-BNP [19]. The results of DEFINE-HF trial could be considered as hypothesis generating. In contrast to these results, according to the recent press release, the EMPERIAL Reduced and Preserved trials failed to demonstrate an effect of empagliflozin on functional status in patients with HFrEF and HFpEF, with and without T2DM over a period of 3 months [20]. After these disappointing head-line results became known, the DETERMINE

Reduced and Preserved trials (testing the impact of dapagliflozin vs placebo on quality of life and functional capacity over 3 months) changed their primary endpoint to be quality of life-focused (rather than relying on 6-min-walking test distance as originally planned) and they were somewhat increased in size to improve power. Quality of life improvement may, however, need longer periods of time to become apparent (i.e. 8 months in DAPA-HF), but if achieved, would lend support to a possibility of decreasing the burden of HF symptoms with SGLT2 inhibitor treatment.

Biological mechanisms and effects of SGLT2 inhibitors in heart failure

At present, the mechanisms underlying protective cardiovascular and renal effects of SGLT2 inhibitors in patients with and without T2DM are not completely understood, and several, not mutually exclusive, mechanisms have been proposed [21, 22], as summarised in **Figure 1.**

SGLT2 inhibitors lower the threshold for glycosuria (60-90 g/day) by lowering the maximum renal transport capacity for glucose reabsorption [23]. This effect attenuates at low glucose levels, explaining the low risk of hypoglycaemia with SGLT2 inhibitors. In addition to glycosuria, SGLT2 inhibitors promote natriuresis and uricosuria [7, 17, 24-26]. Their favourable metabolic effects include increased insulin sensitivity and glucose uptake in the muscle cells [27], decreased gluconeogenesis and increased ketogenesis [28, 29]. These drugs also stimulate weight loss due to the renal caloric loss in glycosuria [7, 17, 24], and have a favourable impact on the body fat distribution [30, 31]. Recent findings also suggest a reduction in liver steatosis and the accompanying hepatocellular injury [32-35] Of note, SGLT2 inhibitors provide nephron protection, most likely through a tubulo-glomerular feedback-mediated vasoconstriction of the afferent arteriole and the reduction in intra-glomerular pressure [11, 36-38]. This effect is important to reduce glomerular hyperfiltration in T2DM, which may decrease the risk of subsequent nephropathy [11, 12]. These favourable metabolic and reno-protective effects may provide long-term benefits for outcomes, however, a relatively early separation of

treatment curves for worsening HF or cardiovascular mortality seen in DAPA-HF, suggests that more rapid mechanisms may be involved (e.g. improvement in haemodynamic status, direct metabolic or vascular effects) [39].

The favourable haemodynamic effects are mediated by a number of mechanisms including osmotic diuresis, natriuresis and plasma and interstitial fluid volume reduction, leading to a reduction in ventricular preload and afterload [23, 40, 41]. Furthermore, a mathematical model has been used, coupled with clinical data on water an electrolyte excretion, to illustrate that, unlike diuretics, SGLT-2 inhibitors seem to exert a greater reduction in interstitial fluid compared with plasma volume (mediated by peripheral sequestration of osmotically inactive sodium), which may prevent plasma volume depletion and subsequent hypoperfusion occasionally observed with diuretics [42]. An increasing body of evidence suggests that SGLT2 inhibitors may less likely induce electrolyte disturbances, neurohormonal activation and a decline in renal function that can occur with diuretics [43, 44]. Indeed, they prevent a decline in kidney function, which may have a favourable impact on HF prevention [12, 44].

Interestingly, a mediation analysis exploring the contribution of different factors to the cardiovascular mortality reduction seen with empagliflozin in the EMPA-REG OUTCOME trial, identified an increase in haemoglobin and haematocrit (i.e. likely due to a decrease in plasma volume) as the largest contributors, supporting the above described haemodynamic hypothesis [45, 46]. This is consistent with further observations from the EMPA-REG OUTCOME trial demonstrating that the cardiovascular effects of empagliflozin were independent of glycaemic control [47].

In addition to haemodynamic effects, other mechanisms may be involved in the increase in haematocrit. Given that an increase in haematocrit lasts longer compared with the increase in urine output after an SGLT2 inhibitor initiation, it has been suggested that an increase in renal erythropoietin

production could be a potential mechanism for the change in haemoglobin and haematocrit levels [48, 49].

Another proposed mechanism for the beneficial effect of SGLT2 inhibitors is inhibition of the sodium-hydrogen-exchanger (NHE-1) activity, which is upregulated both in T2DM and HF [50]. By inhibiting the NHE-1 receptors, SGLT-2 inhibitors may protect the heart from toxic intracellular Ca^{2+} overload [51, 52]. SGLT-2 inhibitors may also exert direct effects on myocardial metabolism [40, 53] and decrease myocardial oxidative stress [54]. Similar to T2DM, HF is characterized by a state of insulin resistance [55]. In the insulin resistant heart, fatty acids (FFA) are favoured as an energy source over glucose [56]. This metabolic shift results in decreased cardiac metabolic efficiency (i.e. insufficient ATP production). In an experimental model, empagliflozin prevented a decrease in cardiac function and increased cardiac ATP production without changing overall metabolic efficiency [57]. This increase in cardiac energy production was the result of increased glucose oxidation, lower FFA oxidation, without changes in ketone body oxidation. Additionally, overall rates of ketone body oxidation were decreased and remained unchanged with empagliflozin treatment, although ketone body supply to the heart was increased. This suggests that the ability of STGL2 inhibitors to increase circulating ketone body levels may provide an additional source of energy to sustain cardiac contractile function. This was supported by another experimental study showing that empagliflozin ameliorated LV remodelling in pigs, an effect mediated by a greater uptake of ketone bodies, FFA and branched-chain amino acids [53].

A benefit on ventricular remodelling was also demonstrated in patients with T2DM and coronary artery disease in EMPA-HEART CardioLink-6 study, which showed a reduction in LV mass index (as measured by cardiac magnetic resonance) and an improvement in diastolic function without changes in LV systolic function after 6 months of treatment with empagliflozin [58]. Furthermore, a significant reduction in LV mass in patients with T2DM was observed with

dapagliflozin in DAPA-LVH trial, suggesting a possibility of reverse LV remodelling [59]. However, this was not corroborated by a recent REFORM trial, in which dapagliflozin had no impact on any of the parameters of LV remodelling over 12 months of treatment [60]. These issues might be resolved by ongoing clinical studies utilizing advanced echocardiographic techniques (e.g. speckle tracking and RT3DE) and cardiac magnetic resonance imaging to assess the effects of SLGT2 inhibition on cardiac structure and function (**Table 1**).

Another currently unproven hypothesis about the cardiovascular effect of STGL2 inhibitors includes possible cardiac anti-fibrotic effects [40, 61]; and an improved balance in adipokine secretion [62]. Beneficial effects on endothelial function [63], blood pressure, central pulse pressure [7, 17, 24], and parameters of arterial stiffness and vascular resistance [64], as well as a reduction in sympathetic nervous system activity [65], may also play an important role in the prevention of HF. Furthermore, it has been hypothesised that a favourable change in the trajectory of cellular responses to environmental stressors may be yet another mechanism of cardiorenal protection with SGLT2 inhibitors that needs to be explored [66].

The role of SGLT-2 inhibitors in prevention and treatment of heart failure

Currently, DAPA-HF is the only published trial demonstrating a reduction in clinical endpoints with an SGLT2 inhibitor, dapagliflozin, in patients with HFrEF, with and without T2DM [16]. Hence, a role of SGLT-2 inhibitors in the treatment of HFrEF can only be documented for dapagliflozin, pending the results of ongoing trials with other SGLT-2 inhibitors.

Two points need to be noted when discussing the place of dapagliflozin in the treatment of HFrEF. First of all, the benefit of dapagliflozin on reducing important clinical events was seen within weeks of its initiation [16]. Given that HF is associated with severely impaired survival, a timely initiation of an agent with a proven benefit on outcomes is of a crucial clinical importance.

Secondly, a sub-analysis of the DAPA-HF trial demonstrated that dapagliflozin can produce a significant improvement in quality of life as assessed by KCCQ in patients with HFrEF [67], which is of high clinical value [19]. Furthermore, dapagliflozin appears safe and effective in vulnerable elderly patients, as well as in those with impaired renal function (excluding patients with estimated glomerular filtration rate <30 mL/min/1.73 m^2), in whom up-titration of GDMT may be challenging [68, 69]. A post-hoc analysis of the DAPA-HF trial demonstrated similar risk reductions in HF hospitalisation and mortality with dapagliflozin, irrespective of background HF therapy, including ACEi/ARB, beta-blockers, MRAs, ivabradine, sacubitril/valsartan, cardiac resynchronisation therapy and implantable cardioverter-defibrillators [70]. Furthermore, the results were consistent regardless of whether patients received ≥50% or <50% of guideline-directed target doses of ACEi/ARBs, beta-blockers or MRAs [70]. These observations indicate a complementary value of dapagliflozin in addition to the established GDMT for HF, and further support its use in ambulatory patients with symptomatic HFrEF in order to improve clinical outcomes.

Besides, significant renal protection observed with canagliflozin in the CREDENCE trial of T2DM patients with CKD and albuminuria (also noted in outcome trials with other SGLT2 inhibitors in the general population of T2DM patients) needs to be taken into account when discussing the role of SGLT2 inhibitors in HF [12]. Recently, a press release reported that the DAPA-CKD trial, enrolling 4245 patients with CKD, with and without T2DM, was prematurely stopped because of efficacy [71]. Since CKD is prevalent and associated with high mortality in HF [72, 73], prevention of the progression and/or worsening of CKD needs to be considered as an important goal that may translate into improved outcomes in HF.

Emerging data from EMPA-RESPONSE-AHF suggest potential safety of an early introduction of an SGLT2 inhibitor, empagliflozin, in acute HF patients, with and without T2DM

[74]. Pending confirmation from a larger trial, these results could be promising in advancing the treatment of acute HF.

Ongoing trials will further elucidate the role of SGLT2 inhibitors in the treatment of HF, as well as the underlying mechanisms by which SGLT2 inhibitors impact on cardiac structure, physiology and metabolism (**Table 1**).

Conclusions

Based on the available evidence, SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin), could be recommended to reduce the risk of HF hospitalisation in T2DM patients with either established cardiovascular disease, or at high cardiovascular risk. Currently available data suggest that dapagliflozin could be considered in the treatment of HFrEF patients, with and without T2DM. Further mechanistic studies and ongoing large-scale clinical trials will provide a more comprehensive overview of the role in the treatment of HF with other SGLT2 inhibitors and will also extend our knowledge on their potential for the treatment of acute HF and HFpEF.

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FIGURE LEGEND

Figure 1. Proposed biological mechanisms and effects of SGLT2 inhibitors

Table 1. Ongoing clinical trials with SGLT2 inhibitors

Cardiovascular outcomes in patients with HFrEF or HFpEF
EMPEROR-Reduced (NCT03057977) ▪ Empagliflozin in patients with HFrEF with/without T2DM; ▪ Primary outcome: cardiovascular death or HF hospitalization.
EMPEROR-Preserved (NCT0305795) ▪ Empagliflozin in patients with HFpEF with/without T2DM; ▪ Primary outcome: cardiovascular death or HF hospitalization.
DELIVER (NCT03619213) ▪ Dapagliflozin in patients with HFpEF with/without T2DM; ▪ Primary outcome: composite of cardiovascular death, hospitalisation for HF or urgent HF visit.
SOLOIST-WHF (NCT03521934) ▪ Sotagliflozin in patients with T2DM and HF (following hospitalisation for worsening HF); ▪ Primary outcome: cardiovascular death or hospitalisation for HF in patients with LVEF <50%, as well as in the total patient population (regardless of LVEF); ▪ Prematurely discontinued.
Symptoms and functional status
DETERMINE-Reduced (NCT03877237) ▪ Dapagliflozin in patients with HFrEF with/without T2DM; ▪ Primary outcome: change from baseline in KCCQ and 6-minute walk distance at Week16.
DETERMINE-Preserved (NCT03877224) ▪ Dapagliflozin in patients with HFpEF with/without T2DM; ▪ Primary outcome: change from baseline in KCCQ and 6-minute walk distance at Week16.
Outcomes in patients with chronic kidney disease
EMPA-KIDNEY (NCT03594110) ▪ Empagliflozin in patients with chronic kidney disease with/without T2DM; ▪ Primary outcome: kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or cardiovascular death.
DAPA-CKD (NCT03036150) ▪ Dapagliflozin in patients with chronic kidney disease with/without T2DM; ▪ Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESKD or cardiovascular death or renal death. ▪ Prematurely discontinued for efficacy
Cardiac physiology and metabolism
EMPA-VISION (NCT03332212) ▪ Empagliflozin in patients with HFrEF or HFpEF with/without T2DM; ▪ Primary outcome: effect on cardiac physiology and metabolism as assessed by cardiac magnetic resonance spectroscopy.
EMPA-TROPISM (NCT03485222) ▪ Empagliflozin in patients with HFrEF (LVEF <50%) without T2DM; ▪ Primary outcome: effect on LV systolic and diastolic volumes as assessed by cardiac magnetic resonance imaging.
EmDia (NCT02932436) ▪ Empagliflozin in patients with T2DM; ▪ Primary outcome: effect on LV diastolic function as assessed by echocardiography.

HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; eGFR – estimated glomerular filtration rate; ESKD – end-stage kidney disease; KCCQ – Kansas City Cardiomyopathy Questionnaire; LVEF – left ventricular ejection fraction; T2DM – type 2 diabetes mellitus