Title: Sodium-glucose cotransporter 2 inhibitors as a treatment for heart failure

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Learning Objectives

- To review the evidence for sodium-glucose cotransporter 2 inhibitors (SGLT2i) for the prevention of heart failure in patients with type 2 diabetes.
- To review the evidence for SGLT2i as a treatment for heart failure and reduced ejection fraction (HFrEF) irrespective of diabetes status.
- To understand which patients with HFrEF are eligible for treatment with an SGLT2i and review some practical tips for the implementation of SGLT2i into clinical practice.

Abstract

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to prevent the development of heart failure (HF) in patients with type 2 diabetes with established (or at high risk of) cardiovascular disease. The finding that this benefit was independent of any glucose lowering effect prompted the development of a series of clinical trials examining the potential role of SGLT2i as a treatment for HF. In two large, randomised, placebo-controlled trials in patients with chronic HF and reduced ejection fraction (HFrEF), the SGLT2i dapagliflozin and empagliflozin reduced the risk of cardiovascular death and worsening HF, and improved symptoms and quality of life, when added to guideline recommended pharmacological and device therapy. The benefits of SGLT2i in HFrEF were consistent regardless of the presence or absence of type 2 diabetes. These results have established SGLT2i as one of the cornerstones of HFrEF pharmacotherapy along with an angiotensin receptor-neprilysin inhibitor, beta-blocker and mineralocorticoid receptor antagonist. We summarise the evidence for the use of SGLT2i as a treatment for HFrEF, provide practical guidance for their implementation and give insight into ongoing trials with this class of drug across the HF landscape.

Introduction

Despite advances in both the pharmacological and device-based management of heart failure with reduced ejection fraction (HFrEF), patients remain at a high risk of morbidity and mortality. The last decade has seen a new era in the pharmacological management of HFrEF with 4 drug classes affecting 5 distinct physiological pathways now established as cornerstones of HFrEF pharmacotherapy: an angiotensin receptor-neprilysin inhibitor (ARNI) in the form of sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists (MRA) and most recently, sodium-glucose cotransporter 2 inhibitors (SGLT2i). Originally investigated as glucose lowering agents, SGLT2i in randomised, placebo-controlled trials prevented the development of heart failure (HF) in patients with type 2 diabetes with established or at high risk of cardiovascular disease.[1–5] The clinical benefits of SGLT2i were independent of their glucose lowering effect. Subsequently, two large, randomised, placebo-controlled trials have reported that SGLT2i (dapagliflozin and empagliflozin) improved morbidity and mortality in patients with HFrEF, irrespective of diabetes status.[6,7] A further trial has reported on the benefits of sotagliflozin, a combined SGLT1 and SGLT2 inhibitor, in patients with diabetes and hospitalised HF.[8] The purpose of this article is to provide background to the use of SGLT2i in patients with HF, review the evidence for their use, suggest how they may be implemented in clinical practice as a new cornerstone in the management of patients with HFrEF, and discuss ongoing trials of SGLT2i across the HF landscape.

Sodium-glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporters (SGLT) are situated in the proximal convoluted tubule of the kidney and reabsorb approximately 180g/day of filtered glucose.[9] Two main forms of SGLT involved in renal glucose handling have been described; SGLT1 are located in the distal portion of the proximal convoluted tubule (PCT) as well as being present in the intestine and heart among other locations, and account for <5% of renal glucose reabsorption. In contrast, SGLT2, low-affinity, high-capacity transporters, are found predominantly in the proximal PCT and are responsible for over 95% of renal glucose reabsorption.

The initial pharmaceutical development of SGLT inhibitors as glucose lowering agents focused on compounds with high selectivity for SGLT2 over SGLT1 due to gastrointestinal side-effects relating to SGLT1 inhibition. To date, four SGLT2i have marketing authorisation for the management of type 2 diabetes in Europe and the United States of America; canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. A combined SGLT1/SGLT2 inhibitor, sotagliflozin, has approval in Europe as an adjunct to insulin in the management of type 1 diabetes but is not currently available in the United Kingdom.

SGLT2 inhibitors in patients with type 2 diabetes – prevention of heart failure

In 2008, the United States Food and Drug Administration (FDA) mandated that the cardiovascular safety of new glucose lowering therapies be demonstrated in large, prospective, randomised controlled trials. To date, six cardiovascular outcome trials of SGLT2i have reported in patients with type 2 diabetes with varying cardiovascular disease risk profiles; the design of

each trial, baseline characteristics and main results are detailed in Table 1. The first to publish in 2015, the BI 10773 (empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), compared the SGLT2i empagliflozin with placebo in 7020 patients with established cardiovascular disease and reported a 14% relative risk reduction (95% confidence interval [CI] 1-26%; p for superiority 0.04) in the risk of the primary composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke .[1] In addition a significant 35% reduction in the prespecified, adjudicated secondary endpoint of hospitalisation for HF was observed. Of note, the observed 38% reduction in risk of death from cardiovascular causes appeared early in the trial, which, along with no significant treatment effect on the incidence of myocardial infarction or stroke, suggested that the mortality benefits of empagliflozin were unlikely to be due to a reduction in the risk of atherothrombotic events. This effect seemed to predominantly be *prevention* of HF in this high risk population with only 10% of patients having an investigator reported history of HF at baseline (with no further HF phenotyping) and a consistent treatment effect in those patients with and without a history of HF at baseline.[10] It is likely however, given the prevalence of atherosclerotic disease in the trial, that a proportion of patients had subclinical cardiac dysfunction. Taken together, the totality of evidence from the six large, randomised, placebo-controlled trials in 46969 patients (Table 1) points towards a class effect of SGLT2i in preventing the development of HF in patients with type 2 diabetes with a pooled trial-level meta-analysis estimate of a 32% reduction in risk (hazard ratio [HR] 0.68; 95%CI, 0.61-0.76).[11]

Why did SGLT2i reduce the risk of HF in patients with type 2 diabetes? A glucose-lowering mechanism of HF prevention seems very unlikely. The glucose lowering effects of these drugs

are modest, with a mean reduction in HbA1c of -0.7% in randomised controlled trials compared to placebo and the beneficial effects on HF were found to be independent of any glucose lowering effect.[12–14] Moreover, the glycosuric effect of this class of drugs is attenuated in patients with impaired renal function (eGFR <60 ml/min/1.73m^2) in whom there is clearly no heterogeneity of treatment effect on both cardiovascular and renal outcomes with SGLT2i.[12–14] A variety of other mechanisms of action underlying the clinical benefits observed both in patients with diabetes, and in patients with HFrEF irrespective of diabetes status, have been suggested (Figure 1); these include beneficial effects on diuresis, myocardial fibrosis, left ventricular volumes and myocardial metabolism along with potential reductions in oxidative stress secondary to upregulation of the sirtuin-1 pathway and reduced activity of the Na^+/H^+ exchanger.[15,16] Two cardiac magnetic resonance and one echocardiography-based trials have reported a beneficial reverse remodelling effect of the SGLT2i empagliflozin in patients with HFrEF with and without diabetes.[17–19]

SGLT2 inhibitors in patients with heart failure and reduced ejection fraction – treatment of heart failure

Following on from the substantial body of evidence of benefit with SGLT2i in preventing HF in patients with type 2 diabetes, the question arose whether SGLT2i could improve outcomes in patients with established HFrEF, and most importantly, whether this class of drugs could benefit both patients *with* and *without* diabetes.

<u>DAPA-HF</u>

The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial compared the SGLT2i dapagliflozin 10mg once daily with placebo in 4744 patients with chronic ambulatory HFrEF.[6,20,21] To be eligible for inclusion, patients had to have a left ventricular ejection fraction (LVEF) ≤40%, be in New York Heart Association (NYHA) functional classification II-IV, have elevated levels of natriuretic peptides, an eGFR ≥30 ml/min/1.73m^2 and be optimally treated with pharmacological and device therapy for HFrEF.[20] Key exclusion criteria included type 1 diabetes and symptomatic hypotension or systolic blood pressure <95mmHg. The primary endpoint was a composite of time to first HF hospitalisation, urgent outpatient HF visit requiring intravenous therapy for HF, or cardiovascular death. Of the 4744 randomised patients, the majority had no history of type 2 diabetes (55%) and were NYHA functional class II (68%). Median NT-proBNP was 1437 pg/ml and mean LVEF was 31%.[6,21]

Dapagliflozin, compared with placebo, reduced the risk of the primary composite outcome by 26% (HR 0.74, 95%CI 0.65-0.85).[6] In terms of absolute risk reduction, the number of patients needed to treat over the median follow-up of 18 months to prevent one primary composite endpoint event was 21. A statistically significant effect on the primary outcome was evident and persisted from 28 days following randomisation. The effect of dapagliflozin on the primary outcome was consistent across the prespecified subgroups.[6]

When considered individually, the components of the primary endpoint occurred less frequently with dapagliflozin compared with placebo; the risk of cardiovascular death was significantly reduced by 18% and worsening HF event (HF hospitalisation or urgent HF visit) by

30%. In a prespecified secondary analysis, dapagliflozin significantly reduced total (first and recurrent) HF hospitalisations and cardiovascular death with a rate ratio of 0.75 (95%CI 0.65-0.88). Death from any-cause also occurred less frequently with dapagliflozin compared with placebo (HR 0.83; 95% CI 0.71-0.97). Patients with HFrEF frequently experience worsening of HF in the outpatient setting with the addition of new oral treatments for HF or escalation of existing therapy; dapagliflozin reduced the risk of these events by 26% (95%CI 13%-37%).[22] As well as benefits on clinical outcomes, dapagliflozin markedly improved patient's symptoms, function and quality of life in DAPA-HF as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[6,23] Patients randomised to dapagliflozin were more likely to report a clinically meaningful improvement (≥5-point change) in the KCCQ total symptom score compared with placebo (odds ratio [OR] 1.15; 95%CI 1.08-1.23) and less likely to report a significant deterioration (OR 0.84; 95%CI 0.78-0.90).

Dapagliflozin was well tolerated with no increase (compared with placebo) in the occurrence of volume depletion, renal adverse events, hypoglycaemia or the number of patients discontinuing trial medication due to an adverse event.[6] Cases of diabetic ketoacidosis were adjudicated, with 3 events occurring in the dapagliflozin arm (all in patients with diabetes) and no events in the placebo group.

Arguably one of the most important results of DAPA-HF was the observation, for the first time, that the cardiovascular benefits of dapagliflozin on all of the pre-specified endpoints extended to both HFrEF patients with and without diabetes.[6,24] When examined as a continuous variable

or in tertiles of glycated haemoglobin (HbA1c), the effect of dapagliflozin was consistent across the range of HbA1c in DAPA-HF.[24] The magnitude of treatment effect on HbA1c was small (placebo-corrected difference in patients with diabetes = -0.24% at 8 months).[6] Therefore, it is unlikely that the glucose lowering effect of SGLT2 inhibition was the mechanism of action behind the observed clinical benefits. The placebo corrected change in NT-proBNP at 8 months following randomisation was -303 pg/ml, a relatively modest change which, along with another smaller trial showing no difference in NT-proBNP at 12 weeks with dapagliflozin, suggests that a significant diuretic effect is not the sole driver behind the observed clinical benefits.[6,25] Haematocrit significantly increased with dapagliflozin compared with placebo, whereas weight and systolic blood pressure were significantly lower at 8 months,.[6]

Patients enrolled in DAPA-HF covered a wide age-range (22-94 years), with a mean age of 66 years; approximately a quarter of patients were aged 75 years and older. The beneficial effects of dapagliflozin were consistent across the spectrum of age studied in DAPA-HF.[26] Both adverse events and study drug discontinuation were more frequent with increasing age, however, these occurred at a similar rate in patients treated with dapagliflozin or placebo. The effect of dapagliflozin on the primary composite endpoint was consistent across the range of LVEF studied.[27] Similarly, dapagliflozin had the same beneficial effect on the primary outcome regardless of baseline systolic blood pressure with a mean placebo-corrected reduction at 2-weeks with dapagliflozin of 2.5 mmHg.[28]

There was high use of contemporary guideline-directed pharmacological and device therapy in DAPA-HF with 83% of patients taking a ACE-inhibitor or ARB, 11% an ARNI, 96% a beta-blocker, 71% an MRA, 84% a loop and/or thiazide diuretic and 7.5% of patients had a cardiac resynchronisation therapy (CRT) device and 26% an implantable cardioverter defibrillator (including CRT-D).[6] The benefits of dapagliflozin in improving outcomes compared with placebo were consistent regardless of background use of these pharmacological and device therapies.[29,30] In patients taking a diuretic at baseline no significant interaction with treatment effect was observed across categories of diuretic dose.[31] The majority of patients did not change their diuretic dose during follow-up and there was no significant difference in mean diuretic dose between dapagliflozin and placebo during follow-up.

<u>EMPEROR-Reduced</u>

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) was the second trial to report on the effect of an SGLT2i, empagliflozin at a dose of 10mg once daily, compared with placebo in HFrEF.[7,32] Approximately 1000 fewer patients were included in EMPEROR-Reduced than DAPA-HF. Patients were followed for 2 months less (median follow-up 16 versus 18 months). Differences in the eligibility criteria of the two trials (e.g. higher NT-proBNP thresholds for patients with higher LVEF and a lower eGFR threshold for inclusion [≥20 ml/min/1.73m^2] in EMPEROR-Reduced) resulted in a trial population with a lower mean EF (27%), higher median NT-proBNP level (~1900 pg/ml) and a lower mean eGFR (62 ml/min/1.73m^2) than DAPA-HF.[7] The placebo group event rate of hospitalisation for HF was higher in EMPEROR-Reduced than in DAPA-HF (15.5 versus 9.8 per

100 patient-years) whereas there was no difference in the rate of cardiovascular death (8.1 versus 7.9 per 100 patient-years). Another key difference was the higher background use of sacubitril/valsartan (19% versus 11%), CRT and ICDs in EMPEROR-Reduced compared with DAPA-HF.

Empagliflozin, compared with placebo, reduced the risk of the primary composite endpoint of time to first HF hospitalisation or cardiovascular death by 25% (HR 0.75; 95%CI 0.65-0.86); p<0.001).[7] Both first and recurrent HF hospitalisations were reduced by 31% (95% CI 19-41%) and 30% (15-42%), respectively. The rates of cardiovascular or all-cause death were not statistically lower in the empagliflozin group, compared with placebo. A prespecified analysis of EMPEROR-Reduced examining the same composite outcome as the primary outcome of DAPA-HF reported a significant 24% reduction with empagliflozin (HR 0.76; 95%CI 0.67-0.87;p<0.001).[33] The rate of deterioration in eGFR over time was attenuated by empagliflozin.[7,34] Quality of life measured by the KCCQ Clinical Summary Score at 52-weeks was improved by empagliflozin group compared with placebo (+1.7 [95%CI 0.5-3.0]). Similar changes in haematocrit, weight, systolic blood pressure and NT-proBNP were seen with empagliflozin to those observed with dapagliflozin in DAPA-HF. The effect of empagliflozin on the primary composite outcome was consistent in those with and without diabetes, and in those taking or not taking sacubitril/valsartan at baseline.[7,35] A similar safety profile with empagliflozin was observed as with dapagliflozin in DAPA-HF with no cases of diabetic ketoacidosis reported.

When the results of DAPA-HF and EMPEROR-Reduced are considered together, it is clear that SGLT2i improve outcomes and symptoms in patients with HFrEF, regardless of the presence or absence of type 2 diabetes (Figure 2). A trial-level meta-analysis of both trials reported a pooled estimate of a 26% (95%CI: 18-32%) reduction in the risk of first hospitalisation for HF or cardiovascular death, 31% reduction (95%CI: 22-38%) in the risk of first HF hospitalisation, 14% reduction (95%CI: 2-24%) in the risk of CV death, and 13% reduction (95%CI: 2-23%) in the risk of all-cause mortality.[36] These benefits are incremental to those offered by contemporary HFrEF pharmacological and device therapy including sacubitril/valsartan.[29,30] We suggest that the SGLT2i dapagliflozin and empagliflozin should now be considered as cornerstones of the treatment for HFrEF. The addition of an SGLT2i to current guideline-advocated therapy with an ARNI (sacubitril/valsartan), beta-blocker and MRA, so called 'quadruple-therapy', may result in substantial absolute benefits for patients; compared to treatment with an ACE-inhibitor or ARB and a beta-blocker, quadruple-therapy has been estimated to offer an additional 8.3 years and 2.7 years free from CV death or first HF hospitalisation for a 55 and 80-year old, respectively.[37] The additional expected survival-free time from death from any cause is estimated at 6.3 years (for a 55-year old) to 1.4 years (for an 80-year old). Furthermore, a series of cost-effectiveness analyses have reported favourable costs per quality-adjusted life-year gained below the willingness-to-pay thresholds in a variety of health-care systems.[38–40]

Following on from the results of DAPA-HF, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have both approved dapagliflozin for use in patients with NYHA functional class II-IV HFrEF.[41,42] At the time of writing, the Canadian

Cardiovascular Society, American College of Cardiology and European Society of Cardiology Heart Failure Association have provided updated recommendations supporting the addition of an SGLT2i in patients with HFrEF, with updates to the European Society of Cardiology HF guidelines expected in the next 12 months.[43–45]

SOLOIST-WHF

The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial compared the combined SGLT1/SGLT2 inhibitor sotagliflozin with placebo in 1222 patients with type 2 diabetes who were hospitalised for HF.[8] Sotagliflozin reduced the risk of the primary composite endpoint of the total number of HF hospitalisations, urgent HF visits and cardiovascular death by 33% (95%CI 15-48%). This trial adds to the results of DAPA-HF and EMPEROR-Reduced in two important ways. Firstly, it demonstrates the safety and clinical efficacy of SGLT2i in a group of patients hospitalised with HF. Secondly, there was no upper ejection fraction limit in SOLOIST-WHF with 21% of patients reported to have an LVEF ≥50%. In a prespecified sub-group analysis, there was the suggestion of benefit of SGLT2i in patients with HFpEF with a hazard ratio of 0.48 (95% 0.27-0.86), however this result requires confirmation in larger, adequately powered trials.

Practical guidance for the use of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction

Both dapagliflozin and empagliflozin were studied at a dose of 10mg once daily. Neither trial required uptitration from the starting dose of 10mg, therefore the simplicity of commencing an

SGLT2i at a single dose with no need for uptitration makes it an attractive addition to HF therapy. We will now provide some practical advice relating to the use of SGLT2i in HFrEF and this is summarised in Table 2.

Renal function

Chronic kidney disease (CKD) is a frequent comorbidity in patients with HF and is associated with worse outcomes. With regards to morbidity and mortality outcomes, the benefits of SGLT2i in DAPA-HF and EMPEROR-Reduced were not modified by baseline renal function, meaning that given their high event rates, patients with CKD and HFrEF stand to derive large absolute benefits with SGLT2 inhibition.[6,7,34,46] Both dapagliflozin and empagliflozin attenuated the decline in eGFR compared with placebo during follow-up.[7,46] Furthermore, in EMPEROR-Reduced, the occurrence of the prespecified renal endpoint of chronic dialysis or renal transplantation or a sustained reduction of ≥40% in the eGFR or a sustained eGFR of <15 ml/minute/1.73m^2 in patients with a baseline eGFR of ≥30 ml/minute/1.73m^2 or a sustained eGFR of <10 ml/minute/1.73m^2 in those with a baseline eGFR of <30 ml/minute/1.73m^2 was reduced by 50% compared with placebo (HR 0.50; 95% CI 0.32-0.77).[7] The occurrence of a similar renal composite outcome in DAPA-HF occurred less frequently with dapagliflozin compared with placebo (1.2% versus 1.6%), however was not statistically significant possibly reflecting that DAPA-HF mandated a 50% or greater decrease in eGFR (rather than 40% in EMPEROR-HF) and the higher baseline eGFR.[6] Further evidence supporting the use of SGLT2i in patients with CKD with and without diabetes has been provided by the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney

Disease (DAPA-CKD) trial which reported substantial improvements in cardiovascular and renal outcomes as well as all-cause mortality in this high-risk patient group; the findings of DAPA-CKD and the observed safety profile in this trial and both DAPA-HF and EMPEROR-Reduced should offer reassurance to cardiologists when using this class of medication in patients with concomitant HFrEF and renal dysfunction.[47]

In line with the DAPA-HF inclusion criteria, the FDA and EMA labelling approves dapagliflozin 10mg once daily for use in HFrEF patients with an eGFR of ≥30 ml/min/1.73m^2, regardless of diabetes status. The details of the labelling for empagliflozin are awaited, however these are likely to reflect the inclusion criteria of EMPEROR-Reduced, i.e. use in patients with an eGFR of ≥20 ml/min/1.73m^2. There is no evidence for the use of SGLT2i in patients on renal replacement therapy.

Routine monitoring of renal function in patients prescribed SGLT2i is recommended in a similar fashion to renin-angiotensin-aldosterone-system antagonists. A small initial decline in eGFR (approximately 3-5 ml/min/1.73m^2) following SGLT2i initiation has been observed in all trials, but as highlighted above, this class of drugs offer long-term beneficial renal effects and the initial expected small dip in eGFR should not dissuade clinicians from continuing SGLT2i therapy.

Volume depletion and hypotension

One potential concern about the use of SGLT2i in HFrEF was the theoretical risk of volume depletion and symptomatic hypotension secondary to a potentially additive diuretic effect in patients who are often prescribed at least one other medication with a diuretic effect such as diuretics and sacubitril/valsartan. As reported in both DAPA-HF and EMPEROR-Reduced, there was no significant excess risk of volume depletion or hypotensive adverse events with an SGLT2i compared with placebo.[6,7] Routine reduction of diuretic therapy with initiation of SGLT2i is not required. A small percentage of patients (around 5%) may require a reduction of loop diuretics and this should be assessed in the weeks and months following initiation.

Hypoglycaemia

The risk of hypoglycaemia with SGLT2i is low due to their insulin-independent mechanism of action. In DAPA-HF and EMPEROR-Reduced episodes of hypoglycaemia were not increased. SGLT2i do not cause hypoglycaemia in patients without diabetes. Routine reduction in the dose of insulin or sulphonylureas is not recommended but can be considered in patients with tight glycaemic control.

Ketoacidosis

Diabetic ketoacidosis (DKA) or euglycaemic ketoacidosis (DKA with normoglycaemia or mildly elevated glucose levels) are rare but recognised side-effects of SGLT2i in patients with type 2 diabetes.[48] There were three episodes of DKA in DAPA-HF and none in EMPEROR-Reduced. SGLT2i do not cause DKA in patients who do not have diabetes. Potential triggers for ketoacidosis include intercurrent illness, dehydration or prolonged fasting, beta-cell

insufficiency (e.g. in long-standing type 2 diabetes or latent autoimmune diabetes of adulthood [LADA]), reductions in insulin dose, and alcohol use. To reduce the risk of ketoacidosis, it is recommended that patients are instructed to temporarily discontinue SGLT2i when very unwell and/or unable to eat or drink (e.g in advance of scheduled major surgery).[49] Patients who have had a recent reduction in insulin dose are also at risk of DKA. Furthermore, type 1 diabetes was an exclusion criterion in both trials, therefore SGLT2i are not recommended for use in this group of patients. Collaboration with diabetologist colleagues is encouraged if cardiologists are uncertain how to manage concomitant glucose lowering therapy.

Mycotic genital tract infections

Patients treated with SGLT2i are at an increased risk of genital tract infections (GTI) (vaginitis/balantitis) due to glycosuria promoting the colonisation of the genitourinary tract with *Candida.* The risk of GTI is higher in patient with type 2 diabetes compared to those without, and GTI occur approximately twice more frequently in women than in men. In EMPEROR-Reduced, GTI were reported in patients with diabetes in 1.9% and 0.4% of those randomised to empagliflozin and placebo, respectively.[35] The corresponding numbers in patients without diabetes were 1.4% and 0.9%. The majority of infections are responsive to a course of topical antifungals and/or oral fluconazole. When commencing patients on an SGLT2i, education on genital hygiene and self-monitoring for symptoms of genital/perineal tenderness, redness, or swelling should be provided. The risk of urinary tract infections is not increased by treatment with SGLT2i.[50]

The future for SGLT2 inhibitors in heart failure

Following the benefits in patients with HFrEF, focus has moved to investigating the potential benefit of SGLT2i across HF landscape including in patients with HF and preserved ejection fraction (HFpEF), hospitalised patients with decompensated HF, and following acute myocardial infarction (complicated by left ventricular systolic dysfunction or HF). Ongoing randomised placebo-controlled outcome trials are summarised in Table 3.

Conclusion

The results of two large, randomised, placebo-controlled trials in HFrEF have established the incremental benefit of SGLT2i on top of guideline-recommended pharmacological and device therapy in reducing morbidity and mortality, and improving symptoms. Further evidence now supports their use in patients hospitalised HF. SGLT2i are no longer considered to be simply glucose-lowering therapies but as a treatment for HFrEF in patients with and without diabetes. Guideline recommendations are forthcoming, however given their clinical benefits (and the early onset of these) alongside their tolerability and safety profile they are now one of the cornerstones of HFrEF pharmacotherapy along with an ARNI, beta-blocker and MRA – i.e. 'quadruple therapy'. Ongoing and future trials will provide further insight into the potential benefits of SGLT2i in hospitalised patients, in HFpEF, and in patients at high risk of HF following acute myocardial infarction.

Conflicts of Interest

KFD reports that his employer, the University of Glasgow, has been paid by AstraZeneca for his work relating to the DAPA-HF trial and he has received honoraria from AstraZeneca and Eli Lilly. MCP reports research support or consultancy from Boehringer Ingelheim, Astra Zeneca, Novartis, Novo Nordisk, Medtronic, Boston Scientific, Vifor, Pharmacosmos, Abbvie, Bayer, Takeda, Cardiorentis, Siemens. MCP is supported by The British Heart Foundation grant RE/18/6/34217.

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References

1 Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117–28.

2 Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 644–57.

3 Wiviott SD, Raz I, Bonaca MP, *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; **380**: 347–57.

4 Perkovic V, Jardine MJ, Neal B, *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; **380**: 2295–306.

5 Cannon CP, Pratley R, Dagogo-Jack S, *et al.* Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med* 2020; **383**: 1425–35.

6 McMurray JJV, Solomon SD, Inzucchi SE, *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **21**: 1995–2008.

7 Packer M, Anker SD, Butler J, *et al.* Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**: 1413–24.

8 Bhatt DL, Szarek M, Steg PG, *et al.* Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021; **384**: 117–28.

9 Ferrannini E. Sodium-Glucose Co-transporters and Their Inhibition: Clinical Physiology. *Cell Metab* 2017; **26**: 27–38.

10 Fitchett D, Zinman B, Wanner C, *et al.* Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME trial. *Eur Heart J* 2016; **37**: 1526–34.

11 McGuire DK, Shih WJ, Cosentino F, *et al.* Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol* 2021; **6**: 148–58.

12 Vasilakou D, Karagiannis T, Athanasiadou E, *et al.* Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes. *Ann Intern Med* 2013; **159**: 262.

13 Cannon CP, Perkovic V, Agarwal R, *et al.* Evaluating the Effects of Canagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes Mellitus and Chronic Kidney Disease According to Baseline HbA1c, Including Those With HbA1c <7%. *Circulation* 2020; **141**: 407–10.

14 Inzucchi SE, Kosiborod M, Fitchett D, *et al.* Improvement in Cardiovascular Outcomes With Empagliflozin Is Independent of Glycemic Control. *Circulation* 2018; **138**: 1904–7.

15 Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 2020; **17**: 761–72.

16 Packer M. Cardioprotective Effects of Sirtuin-1 and Its Downstream Effectors: Potential Role in Mediating the Heart Failure Benefits of SGLT2 (Sodium-Glucose Cotransporter 2) Inhibitors. *Circ Heart Fail* 2020; **13**: e007197.

17 Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, *et al.* Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. *J Am Coll Cardiol* 2021; **77**: 243–55.

18 Lee MMY, Brooksbank KJM, Wetherall K, *et al.* Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). *Circulation* 2021; **143**: 516–25.

19 Omar M, Jensen J, Ali M, *et al.* Associations of Empagliflozin With Left Ventricular Volumes, Mass, and Function in Patients With Heart Failure and Reduced Ejection Fraction: A Substudy of the Empire HF Randomized Clinical Trial. *JAMA Cardiol* 2021; published online Jan 6. DOI:10.1001/jamacardio.2020.6827.

20 McMurray JJV, DeMets DL, Inzucchi SE, *et al.* A trial to evaluate the effect of the sodium–glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019; **381**: 665–75.

21 McMurray JJV, DeMets DL, Inzucchi SE, *et al.* The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. *Eur J Heart Fail* 2019; **21**: 1402–11.

22 Docherty KF, Jhund PS, Anand I, *et al.* Effect of Dapagliflozin on Outpatient Worsening of Patients With Heart Failure and Reduced Ejection Fraction. *Circulation* 2020; **142**: 1623–32.

23 Kosiborod MN, Jhund PS, Docherty KF, *et al.* Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction. *Circulation* 2020; **141**: 90–9.

24 Petrie MC, Verma S, Docherty KF, *et al.* Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. *JAMA* 2020; published online March 27. DOI:10.1001/jama.2020.1906.

25 Nassif ME, Windsor SL, Tang F, *et al.* Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction.

Circulation 2019; **140**: 1463–76.

26 Martinez FA, Serenelli M, Nicolau JC, *et al.* Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age: Insights From DAPA-HF. *Circulation* 2020; **141**: 100–11.

27 Dewan P, Solomon SD, Jhund PS, *et al.* Efficacy and safety of sodium-glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF. *Eur J Heart Fail* 2020; **22**: 1247–58.

28 Serenelli M, Böhm M, Inzucchi SE, *et al.* Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). *Eur Heart J* 2020; **41**: 3402–18.

29 Docherty KF, Jhund PS, Inzucchi SE, *et al.* Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J* 2020; **41**: 2379–92.

30 Solomon SD, Jhund PS, Claggett BL, *et al.* Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan. *JACC Hear Fail* 2020; **8**: 811–8.

31 Jackson AM, Dewan P, Anand IS, *et al.* Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. *Circulation* 2020; **142**: 1040–54.

32 Packer M, Butler J, Filippatos G, *et al.* Evaluation of the effect of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. *Eur J Heart Fail* 2019; **21**: 1270–8.

33 Packer M, Anker SD, Butler J, *et al.* Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced

Trial. *Circulation* 2021; **143**: 326–36.

34 Zannad F, Ferreira JP, Pocock SJ, *et al.* Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. *Circulation* 2021; **143**: 310–21.

35 Anker SD, Butler J, Filippatos G, *et al.* Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. *Circulation* 2021; **143**: 337–49.

36 Zannad F, Ferreira JP, Pocock SJ, *et al.* SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020; **396**: 819–29.

37 Vaduganathan M, Claggett BL, Jhund PS, *et al.* Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet* 2020; **396**: 121–8.

38 Savira F, Wang BH, Kompa AR, *et al.* Cost-effectiveness of dapagliflozin in chronic heart failure: an analysis from the Australian healthcare perspective. *Eur J Prev Cardiol* 2020; published online July 14. DOI:10.1177/2047487320938272.

39 Krittayaphong R, Permsuwan U. Cost-utility analysis of add-on dapagliflozin treatment in heart failure with reduced ejection fraction. *Int J Cardiol* 2021; **322**: 183–90.

40 McEwan P, Darlington O, McMurray JJV, *et al.* Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *Eur J Heart Fail* 2020; **22**: 2147–56.

41 Food and Drug Administration. Farxiga (Dapagliflozin) prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s020lbl.pdf (accessed Oct 21, 2020).

42 European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) post authorisation summary of opinion: Forxiga (dapagliflozin). 2020. https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-forxiga-ws-1737_en.pdf (accessed Oct 21, 2020).

43 O'Meara E, McDonald M, Chan M, *et al.* CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis. *Can J Cardiol* 2020; **36**: 159–69.

44 Seferović PM, Fragasso G, Petrie M, *et al.* Heart Failure Association of the European Society of Cardiology update on sodium–glucose co-transporter 2 inhibitors in heart failure. *Eur J Heart Fail* 2020; **22**: 1984–6.

45 Maddox TM, Januzzi JL, Allen LA, *et al.* 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol* 2021; **77**: 772–810.

46 Jhund PS, Solomon SD, Docherty KF, *et al.* Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. *Circulation* 2021; **143**: 298–309.

47 Heerspink HJL, Stefánsson B V., Correa-Rotter R, *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; **383**: 1436–46.

48 Tang H, Li D, Wang T, Zhai S, Song Y. Effect of sodium-glucose cotransporter 2 inhibitors on diabetic ketoacidosis among patients with type 2 diabetes: A meta-analysis of randomized controlled trials. Diabetes Care. 2016; **39**: e123–4.

49 Handelsman Y, Henry RR, Bloomgarden ZT, *et al.* AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF SGLT-2 INHIBITORS AND DIABETIC KETOACIDOSIS. *Endocr Pract* 2016; **22**: 753–62.

50 Puckrin R, Saltiel M-P, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2018; **55**: 503–14.

Figures

Figure 1: Proposed mechanisms of benefit of SGLT2 inhibitors

Figure 2: Summary of the benefits of SGLT2 inhibitors in patients with HFrEF

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; HFrEF, heart failure and reduced ejection fraction; IV, intravenous; LV, left ventricle; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Table 1: Evidence for prevention of heart failure with SGLT2i in patients with type 2 diabetes

	EMPA-REG OUTCOME[1]	**CANVAS Program (CANVAS and CANVAS-R)[2]**	**DECLARE-TIMI 58[3]**	**CREDENCE[4]**	**VERTIS-CV[5]**
Investigational drug	Empagliflozin 10mg or 25mg once daily	Canagliflozin 300mg or 100mg once daily	Dapagliflozin 10mg once daily	Canagliflozin 100mg once daily	Ertugliflozin 5 or 15mg once daily
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Number of patients	7020	10142	17160	4401	8246
Median follow-up	3.1 years	3.6 years (mean)	4.2 years	2.6 years	3.5 years (mean)
Established cardiovascular disease at baseline	99.2%	65.6%	40.6%	50.4%	100%
Heart failure at baseline	10.0%	14.4%	10.0%	14.8%	23.7%
Primary outcome	MACE: HR 0.86; 95% CI 0.74, 0.99	MACE: HR 0.86; 95% CI 0.75, 0.97	MACE: HR 0.93; 95% CI 0.84, 1.03	Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml/min/1.73m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes: HR 0.70; 95% CI 0.59, 0.82	MACE: HR 0.97; 95% CI 0.85, 1.11
Heart failure hospitalisation	HR 0.65; 95%CI 0.50, 0.85	HR 0.67; 95%CI 0.52, 0.87	HR 0.73; 95%CI 0.61, 0.88	HR 0.61: 95%CI 0.47, 0.80	HR 0.70; 95%CI 0.54, 0.90

Heart failure hospitalisation or cardiovascular death	HR 0.66; 95%CI 0.55, 0.79	HR 0.78; 95%CI 0.67, 0.91	HR 0.83; 95%CI 0.73, 0.95	HR 0.69; 95%CI 0.57, 0.83	HR 0.88; 95%CI 0.75, 1.03

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular events.

Table 2: Practical advice for use of SGLT2 inhibitors in HFrEF

What dose of dapagliflozin/ empagliflozin?	**10mg once a day**
What to tell the patient?	**1) decreases hospitalisation for heart failure and death due to cardiovascular causes**
	2) improves quality of life
	3) beneficial renal effects
	4) increase in genital tract infections **- occurs at the start of treatment** **- prevention by good genital hygiene** **- treatable with topical or oral therapy** **- usually do not recur**
	5) very small increase in diabetic ketoacidosis (only in patients with type 2 diabetes) **- be vigilant if unable to eat or drink, major infections or when insulin dose is reduced**
Does the dose of loop diuretic need to be routinely reduced?	**No – assess at 2 weeks – around 5% of patients will require a reduction in loop diuretic dose.**
Do glucose-lowering therapies need to be routinely adjusted?	**No – modest lowering of HBA1c**
What level of eGFR can SGLT2 inhibitors be started at?	**eGFR≥20 ml/min/1.73m^{2*}**
What level of blood pressure can SGLT2 inhibitors be started at?	**Systolic blood pressure ≥95 mmHg** **(SGLT2 inhibitors cause a small [mean 2.5mmHg at 2-weeks] decrease in systolic blood pressure)**

***Current licensing for dapagliflozin mandates an eGFR ≥30 ml/min/1.73m^2. Evidence from EMPEROR-Reduced supports use of empagliflozin at eGFR ≥20 ml/min/1.73m^2 however regulatory approval for this indication is awaited at the time of writing.**

Table 3: Ongoing large morbidity and mortality outcome randomised placebo-controlled trials with SGLT2 inhibitors

Trial	Investigational treatment	Key inclusion criteria	Primary endpoint	Number of patients	Results expected
Heart failure with preserved ejection fraction					
DELIVER (NCT03619213)	Dapagliflozin	• NYHA II-IV • LVEF>40% and evidence of structural heart disease • ↑ NT-proBNP levels • Ambulatory and hospitalised patients (Patients currently hospitalised for HF, must be off intravenous HF medications for ≥24 hours before randomisation)	Time to first event of CV death, hospitalisation for HF or urgent HF visit (e.g., emergency department or outpatient visit)	6100	Q4 2021
EMPEROR-Preserved (NCT03057951)	Empagliflozin	• NYHA II-IV • LVEF>40% • Structural heart disease or HF hospitalisation within the last 12 months • ↑ NT-proBNP levels	Time to first event of CV death or hospitalisation for HF	5988	Q2 2021
Hospitalised heart failure					
DAPA ACT HF-TIMI 68 (NCT04363697)	Dapagliflozin	• Hospitalised for acute HF and stabilised • LVEF ≤40% within last 12 months • ↑ NT-proBNP or BNP levels	Time to first event of CV death or worsening HF (decompensation during index admission, rehospitalisation for HF or urgent HF visit)	2400	Q4 2022
EMPULSE (NCT04157751)	Empagliflozin	• Hospitalised for the acute HF (de novo or decompensated chronic HF), regardless of ejection fraction and stabilised • ≥ 24 hours and ≤ 5 days after admission • ↑ NT-proBNP or BNP levels	Net clinical benefit assessed by the win-ratio: • All-cause mortality • Number of HF events (including hospitalisations, urgent HF visits and unplanned patient visits) • Time to first HF event • Change from baseline in KCCQ-CSS	500	Q3 2021
Acute myocardial infarction					
DAPA-MI (NCT04564742)	Dapagliflozin	• Confirmed acute myocardial infarction • LVEF <50% or Q wave myocardial infarction	Time to first event of CV death or hospitalisation for HF	6400	Q3 2023

		• Haemodynamically stable at randomisation (no episodes of symptomatic hypotension, systolic blood pressure < 95 mmHg or arrhythmia with haemodynamic compromise in the last 24 hours)			
EMPACT-MI (NCT04509674)	Empagliflozin	• Confirmed acute myocardial infarction • High risk of HF; either symptoms or signs of congestion requiring IV therapy, or LVEF <45% • At least one of a series of risk factors (listed on clinicalttrials.gov)	Time to first event of all-cause death or hospitalisation for HF	3312	Q4 2022

All trials in patients with and without diabetes unless specifically stated.
Trial acronyms are presented with ClinicalTrials.gov unique identifier: DELIVER, Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; EMPEROR-Preserved, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; DAPA-ACT TIMI 68, Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure -Thrombolysis in Myocardial Infarction 68; EMPULSE, A Multicentre, Randomised, Double-blind, 90-day Superiority Trial to Evaluate the Effect on Clinical Benefit, Safety and Tolerability of Once Daily Oral EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart faiLure (de Novo or Decompensated Chronic HF) Who Have Been StabilisEd; DAPA-MI, Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack; EMPACT-MI, A Streamlined, Multicentre, Randomised, Parallel Group, Double-blind Placebo-controlled Superiority Trial to Evaluate the Effect of EMPAgliflozin on Hospitalisation for Heart Failure and Mortality in Patients With aCuTe Myocardial Infarction.
Abbreviations; HF, heart failure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classification; IV, intravenous; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score.