Optimising the heart failure treatment pathway: The role of SGLT2 inhibitors

Running heading: The role of SGLT2 inhibitors in heart failure

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were first developed as glucose-lowering therapies for the treatment of diabetes. However, these drugs have now been recognised to prevent worsening heart failure events, improve health-related quality of life and reduce mortality in people with heart failure with reduced EF (HFrEF), including both those with and without diabetes.

Despite robust clinical trial data demonstrating favourable outcomes with SGLT2 inhibitors for patients with HFrEF, there is a lack of familiarity with the HF indication for these drugs, that have been the remit of diabetologists to date.

In this article we have used consensus expert opinion alongside the available evidence and label indication to provide support for the healthcare community treating people with HF regarding positioning of SGLT2 inhibitors within the treatment pathway. By highlighting appropriate prescribing and practical considerations, we hope to encourage greater, and safe, use of SGLT2 inhibitors in this population.

Key Points

- SGLT2 inhibitors should no longer be considered only as glucose-lowering therapy and cardiologists and heart failure specialists should familiarise themselves with their use, and begin to prescribe an appropriate SGLT2 inhibitor as a new pillar of therapy for heart failure.
- Clarity around appropriate prescribing and practical considerations for the use of SGLT2 inhibitors in people with heart failure with and without diabetes, is likely to encourage greater, and safe, use of SGLT2 inhibitors in this population.
- The SGLT2 inhibitors are well-tolerated in people with heart failure, with a low risk of serious adverse effects that should not overshadow the significant cardioprotective benefits.
- Increased use of SGLT2 inhibitors in patients with heart failure has the potential to significantly modify the clinical course and improve symptoms and outcomes for patients.

1. Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of drugs that include dapagliflozin, canagliflozin, empagliflozin, ertugliflozin and sotagliflozin. These drugs block the reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels[1]. As well as demonstrating robust efficacy in the reduction of glycated haemoglobin (HbA1c) without a significant risk of hypoglycaemia, they have also been associated with weight loss and lowering of blood pressure[2, 3].

In addition to the glucose-lowering effect of SGLT2 inhibitors, several clinical trials have also demonstrated a cardioprotective benefit, including a reduced incidence of cardiovascular (CV) events and hospitalisation for heart failure (HF) in individuals with and without diabetes, including those with and without chronic HF[4]. The results point towards an important role for SGLT2 inhibitors in the HF treatment pathway (defined here as the sequence of medications that is prescribed for HF management). Although the mechanisms responsible for the cardioprotective benefits remain unknown and are the subject of ongoing research, they may include diuresis/natriuresis, erythropoiesis, improved cardiac energy metabolism, reduction in inflammation, inhibition of the sympathetic nervous system, prevention of adverse cardiac remodelling, prevention of ischemia/reperfusion injury, inhibition of the sodium-hydrogen exchanger, increasing circulating pro-vascular progenitor cells, decreasing oxidative stress, and improving vascular function[5-7]

The clinical and economic burden of chronic HF is significant; five-year mortality is estimated to be 45–60%[8, 9], and there are estimated to be as many as 920,000 people living with HF in the UK[10]. It is estimated that HF accounts for 2% of NHS inpatient bed days, 5% of emergency medical admissions, and costs around 2% of the total NHS budget[11], with frequent, prolonged and repeat hospitalisations accounting for the majority of these costs[12]. Patients with diabetes have over twice the risk of developing HF than patients without diabetes[13] and have worse CV outcomes, more hospitalisations, and a worse prognosis than those without diabetes[14, 15].

Despite the current standard of care for HF with reduced ejection fraction (HFrEF), which includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRA), and angiotensin receptor neprilysin

inhibitors (ARNI), in combination with diuretic therapy such as loop diuretics, thiazides and potassium-sparing diuretics, mortality and morbidity remains high, and there remains a clear need for novel HF treatments. It is notable that prior to the SGLT2 inhibitor trials, the last drug shown to improve mortality in chronic HF was sacubitril-valsartan in 2014; advances in HF management have stalled for over seven years. With the emergence of new clinical evidence supporting the use of SGLT2 inhibitors in the management of HFrEF in people with and without diabetes, and as licensing and guidelines for SGLT2 inhibitors are updated, there is an immediate requirement to adapt HF treatment pathways and to encourage clinicians to start using this class of drugs as part of standard care for the treatment of HF.

Due to the lack of familiarity with the HF indication for SGLT2 inhibitors, guidance on their use in this new indication maybe be helpful to prescribers. Therefore, in this article we describe our proposed positioning of SGLT2 inhibitors within the HF treatment pathway, and provide clarity around appropriate prescribing and practical considerations for the use of SGLT2 inhibitors in people with HF with and without T2D, to encourage greater, and safe, use of SGLT2 inhibitors in this population. The guidance provided is based on the available evidence and the label indication, as well as consensus expert opinion. The authors attended a virtual roundtable meeting in which the available SGLT2 inhibitor data was examined and the risk-benefit profile of SGLT2 inhibitors reviewed, leading to the drafting of the manuscript outline. Follow up discussion and revisions of the manuscript were conducted via email correspondence.

2. Efficacy of SGLT2 inhibitors in people with HF

In recent years SGLT2 inhibitors have emerged as an important therapeutic modality for reducing CV risk in diabetes: across the SGLT2 inhibitor CV outcome trials EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)[16], CANVAS (Canagliflozin Cardiovascular Assessment Study)[17], DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58)[18], and VERTIS CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease)[19], treatment with an SGLT2 inhibitor reduced the risk of the

composite of CV death or hospitalisation for HF – should we mention sota evidence here (SCORED) given that it was listed earlier??. Whilst these previous clinical trials have shown that SGLT2 inhibitors reduce the risk of new-onset HF in people with T2D, data from DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)[20], which included patients with New York Heart Association (NYHA) class II-IV HFrEF (EF ≤ 40%) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) ≥600 pg/ml, 55% of whom did not have T2D, demonstrated that dapagliflozin improved outcomes among individuals with established HFrEF. At a median of 18.2 months, the primary outcome of CV death or worsening HF was significantly lower in the dapagliflozin group than in the placebo group (16.3% vs. 21.2%; hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.65 - 0.85; P<0.001). Importantly, this reduction in the primary outcome was similar in patients irrespective of the presence of T2D. Post-hoc analysis of the DAPA-HF trial data has suggested an early benefit with dapagliflozin, with a sustained statistically significant benefit of a reduction in the primary outcome observed 28 days after randomisation (HR 0.51; 95% CI 0.28 - 0.94)[21]. The secondary composite outcome (hospitalisation for HF or death from CV causes) was also significantly lower in the dapagliflozin group than in the placebo group (HR 0.75, 95% CI 0.65–0.85, P<0.001)[20]. In addition, analysis of data from DAPA-HF demonstrated a clinically important benefit on health-related quality of life as demonstrated by improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores with dapagliflozin [22]. Furthermore, the effects of dapagliflozin demonstrated consistent clinical benefits across all age groups, including in individuals ≥75 years, with no significant difference in tolerability or safety across age groups[23].

In a multinational health-economic analysis of DAPA-HF, treatment with dapagliflozin was estimated to increase life-years and quality-adjusted life-years (QALY) and reduce lifetime hospitalisations for HF. The incremental cost-effectiveness ratios were £5822, €5379 and €9406/QALY in the UK, Germany, and Spain, respectively. In probabilistic sensitivity analyses, more than 90% of simulations were cost-effective at a willingness-to-pay threshold of £20 000/QALY in UK and €20 000/QALY in Germany and Spain[24].

Following the clinical and cost effectiveness results from the DAPA-HF trial, the US Food and Drug Administration (FDA), the Japanese Ministry of Health, Labour and Welfare, the European

Commission, and the UK National Institute for Health and Care Excellence (NICE) have approved dapagliflozin for the treatment of adults with HFrEF both with and without diabetes[25-28]. Dapagliflozin is the first SGLT2 inhibitor recommended by NICE as an option for the treatment of symptomatic chronic HFrEF in adults, as an add-on to optimised standard care. NICE recommends that dapagliflozin is started on the advice of a HF specialist, and that monitoring should be by the most appropriate healthcare professional.

The potential benefits of empagliflozin in patients with HFrEF were examined in the EMPEROR-Reduced trial[29], which included patients with NYHA class II-IV HF with EF ≤ 40% and elevated NT-proBNP with threshold dependent on heart rhythm and EF. As in DAPA-HF, the incidence of CV death or hospitalisation for HF was significantly lower with the SGTL2 inhibitor compared with placebo (19.4% vs. 24.7%; HR 0.75; 95% CI, 0.65 to 0.86; P<0.001). Again, the benefit was seen regardless of diabetes status. In addition, the annual rate of decline in estimated glomerular filtration rate (GFR) was slower in those treated with empagliflozin compared to placebo; 0.55 versus 2.28 mL/min per 1.73 m^2 respectively. Mortality was not significantly reduced in those treated with the SGLT2 inhibitor in this study, unlike the findings in DAPA-HF. However, the patient population and their management differed from those in DAPA-HF. There were more patients in EMPEROR-Reduced with more severe HF; lower mean EF (27% vs. 31%), higher median levels of NT-proBNP (1900 vs. 1450 pg/mL) and lower mean GFR (62 vs. 66 mL/min/m^2). A meta-analysis of the DAPA-HF and EMPEROR-Reduced trials demonstrated significant effects on mortality with a 13% reduction in all-cause death (pooled HR 0.87; 95% CI 0.77-0.98; P=0.018) and a 14% reduction in CV death (HR 0.86; 95% CI 0.76-0.98; P=0.027)[30]. Table 1 shows the overall treatment effects for DAPA-HF, EMPEROR-Reduced and the meta-analysis for all-cause mortality, CV mortality, first hospitalisation for HF or CV mortality, first hospitalisation for HF, first kidney composite outcome, and all (first and recurrent) hospitalisations for HF or CV mortality. The findings from both trials provide compelling evidence that SGLT2 inhibitors should be added to guideline recommended treatments for patients with chronic HFrEF, with and without diabetes.

The mechanism of action of SGLT2 inhibitors has also been shown to translate into beneficial effects in terms of renal function in people with and without T2D[16, 18, 31, 32]. The effects include

a delay in decline of eGFR and reduction in albuminuria progression. With this in mind, there is growing focus on the use of SGLT2 inhibitors from the perspective of renal outcome benefits, independent of glucose lowering effects. Furthermore, the HF outcome benefits of SGLT2 inhibitors appear to be consistent across all thresholds of eGFR[20, 29]. Consequently, as people with combined CKD and HF have an increase in HF morbidity and mortality[33], in absolute terms SGLT2 inhibitor therapy in people with cardio-renal syndrome may have greater absolute HF outcome benefits, related to the greater absolute disease burden in such patients. Should we add more detail on DAPA-CKD specifically, having mentioned the renal benefits for Empa in EMPEROR??

3. The positioning of SGLT2 inhibitors within the HF treatment pathway

The goals of HF treatment are to improve symptoms and quality of life and reduce hospitalisations and death. Effective management of HFrEF in the clinic setting has been outlined by the NICE guideline for chronic HF[34] which recommends offering an ACE inhibitor (or an ARB if ACE inhibitors are contraindicated or not tolerated) and a beta-blocker, as first line treatment. Addition of a MRA is recommended if symptoms continue. In patients who remain symptomatic despite optimal treatment, the ARNI sacubitril–valsartan is recommended to replace ACE inhibitors (or ARBs)[35], based on the results of the PARADIGM HF trial[36].

Introducing the drug classes in a stepwise approach, whereby each drug is titrated to full dose before adding the next, has the potential to significantly delay initiation of indicated therapies, leading to treatment inertia. As the guideline recommended drug classes are complementary, acting on distinct pathophysiological pathways, contemporary HFrEF treatment should consist of combination therapy, unless contraindicated, consisting of the simultaneous prescription of ACE inhibitor/ARB/ARNI alongside a beta blocker and MRA. Support for such a strategy has recently been provided by a cross-trial analysis that included patient-level data from three randomized, controlled trials (EMPHASIS-HF, PARADIGM-HF and DAPA-HF) to estimate the treatment effects of comprehensive therapy (ARNI, beta blocker, MRA, and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and beta blocker) in people with chronic HFrEF. From indirect comparisons of these pivotal trials, the comprehensive quadruple therapy strategy was predicted to reduce the primary end point of

CV death or hospitalisation for HF as well as each of these end points individually and all-cause mortality[37].

In light of recent robust and favourable clinical trial data with SGLT2 inhibitors and also considering updated licensing, as well as our expert consensus opinion, we recommend these drugs are used as a new pillar of HF therapy, in patients with symptomatic HFrEF, with or without T2D (Figure 1). We suggest that adjunctive SGLT2 inhibitor treatment should be initiated in people with GFR > 30 mL/min per 1.73 m^2. As there is limited experience with SGLT2 inhibitors for the treatment of HF in patients with GFR < 30 mL/min per 1.73 m^2 prescription of SGLT2 inhibitors in these patients should be with caution – what does 'caution' mean?. The initiation of SGLT2 inhibitors in such circumstances should be supported by the local heart failure multidisciplinary team. It is important to note that currently only dapagliflozin has a licence for the treatment and management of HF, and therefore at this time we recommend that symptomatic chronic HFrEF patients with estimated GFR > 30 ml/min/1.73^2 be initiated with this particular SGLT2 inhibitor, as an add-on to optimised standard care, in line with the label indication.

For HF patients with comorbidities, the four pillars of adjunctive therapy may not be appropriate and following a stepwise approach whereby specific therapies, according to patient characteristics and comorbidities, are offered early in the treatment pathway may have a greater impact on patient outcomes (Figure 2). For people with T2D and HF our consensus recommendation is to initially offer an ACE inhibitor or ARNI as first line treatment to prevent worsening heart failure events, improve health-related quality of life and reduce mortality. Due to the overwhelming evidence supporting the use of SGLT2 inhibitors early in the treatment pathway we recommend, as a general rule, addition of an SGLT2 inhibitor followed by addition of a beta blocker and then an MRA. In agreement with the 2019 ESC guidelines[38], we recommend an SLGT2 inhibitor is considered as first-line therapy glucose lowering therapy for treatment-naive T2D patients. In patients treated with an SGLT2 inhibitor for both HF and T2D, additional glucose-lowering treatment may be necessary if GFR falls persistently below 45 mL/min per 1.73 m^2, due to reduced glucose-lowering at this level of renal function.

For HF patients without T2D with a history of myocardial infarction or arrhythmia/rapid ventricular rates in atrial fibrillation we recommend a beta-blocker-first strategy followed by an ACE inhibitor/ARB, then an SGLT2 inhibitor, and then an MRA, as trial data for this population has demonstrated beta-blocker therapy to be more effective than ACE inhibitors as initiation therapy[39, 40]. For people without T2D, whose HF is non-ischaemic, we recommend initiation with an ACE inhibitor or beta blocker, followed by an SGLT2 inhibitor and then an MRA. For HF patients with a history of hypotension treatment (does this mean hypertension?) we suggest the order of therapy to be ACE inhibitor or ARNI first followed by a beta blocker, then an SGLT2 inhibitor and then an MRA.

We expect that early use of an SGLT2 inhibitor may have practical advantages with respect to HF management in addition to the recognised outcome benefits of reducing hospitalisation for HF, morbidity and mortality[20, 29] In particular, these advantages are likely to include an early improvement in symptoms, nephroprotective effects in terms of delayed estimated GFR decline as well as the absence of any detrimental impact on sodium or potassium concentrations. The low risk of electrolyte perturbations is particularly appealing as there is a wealth of data supporting an association between both hypo- and hyperkalaemia with adverse outcomes in people with HF[41-44]. Furthermore, the absence of a deleterious effect on serum potassium per se with an SGLT2 inhibitor may enable optimal ACE inhibitor / ARB / ARNI dose titration.

5. Appropriate prescribing of an SGLT2 inhibitor in HF patients

Selecting appropriate people with HF for SGLT2 inhibitor treatment is critical for minimising the risks and maximising potential benefits associated with this treatment class. Based on the DAPA-HF and EMPEROR-Reduced data as well as recent clinical guidance and the label indication, we have developed a checklist that serves as a mitigation tool to reduce the risk of side effects while giving confidence to practitioners to safely prescribe these drugs (Figure 3). The checklist follows a traffic light system which recommends that clinicians should consider prescribing an SGLT2 inhibitor for people in the green section, in accord with patients included in the DAPA-HF and EMPEROR-Reduced trials, and in alignment with the licence, i.e., symptomatic stable chronic HF patients with an

EF ≤ 40% (HFrEF) and eGFR >30 ml/min/1.73m^2. SGLT2 inhibitors should be considered for patients with or without T2D.

As there is limited experience with SGLT2 inhibitors for the treatment of HF in patients with eGFR < 30 mL/min per 1.73 m^2 prescription of SGLT2 inhibitors in those with eGFR 20-30 ml/min/1.73m^2 should be with caution (amber section of the checklist). In addition, as SGLT2 inhibitors may induce osmotic diuresis and natriuresis in the context of hyperglycaemia and T2D, translating into modest reductions in blood pressure[45], we advise that SGLT2 inhibitors should be prescribed with caution in patients with T2D and HF for whom a further fall in blood pressure could pose a risk. It is, however, noteworthy that within the SGLT2 inhibitor clinical trials in both people with and without T2D, irrespective of HF as a comorbidity, there was no excess in volume depletion or hypotension reported within the SGLT2 inhibitor arm of the trials as compared with placebo. As such, whilst consideration should be given to the issue of blood pressure reduction in people with T2D and HF, it should not represent a barrier to the use of SGLT2 inhibitors. Should we mention loop diuretics here?

We do not recommend SGLT2 inhibitor use, at this time (red section of the checklist) if eGFR is less than 20 mL/min per 1.73 m^2; an analysis from EMPEROR-Reduced trial studying the effect of empagliflozin on CV and kidney outcomes across the spectrum of kidney function demonstrated that the effect of empagliflozin was consistent across a broad range of baseline kidney function, including patients with eGFR as low as 20 ml/min/1.73m^2. People with HF and an EF > 50% (heart failure with preserved ejection fraction [HFpEF]), acute decompensated HF, or HF with concomitant type 1 diabetes should also not be currently considered for treatment with an SGLT2 inhibitor as there is limited experience in these population groups and therefore the clinical efficacy and safety of these drugs in these groups remains uncertain at this time, although trials in these populations are currently in progress (NB: people with type 1 diabetes without HF can be prescribed 5mg dapagliflozin in according to the label, with the indication focused on glucose lowering effects[46]). In addition, due to serious consequences associated with diabetic ketoacidosis (DKA), patients that previously experienced DKA should not be prescribed an SGLT2 inhibitor.

6. Practical considerations

As with any drug therapy, especially in high-risk populations, there have been reports of adverse events in the SGLT2 inhibitor CV outcome trials (Table 2) and in post-marketing pharmacovigilance reporting. However, most of the adverse events associated with SGLT2 inhibitors in the HF population are consistent with the glycosuria mechanism of action of this drug class and include minor complications such as genital mycotic infections and volume depletion. A number of less common, and potentially serious safety issues in the population with T2D were raised in early data, including hypoglycaemia, ketoacidosis, fractures, amputations, and Fournier's gangrene (necrotizing fasciitis of the perineum). However, it is very important to note that the risks of each of these are extremely low, as demonstrated by the meta-analysis of the DAPA-HF and EMPEROR-REDUCED trials which found no excess in adverse events compared to the respective placebo groups[30]. Consequently, prescribers should not allow these rare adverse events to overshadow the significant benefits associated with this drug class which can be given once daily and does not require dose modifications. Furthermore, their use is not accompanied by adverse events that have been associated with the use of other guideline recommended HF treatments, for example hypotension, bradycardia, hyperkalaemia, and azotaemia [47].

Current evidence from trials of SGLT2 inhibitors in patients with HF suggests these drugs are generally well tolerated, with very low numbers of adverse events recorded (Table 2). However, when using an SGLT2 inhibitor in routine clinical practise it is important to be aware of the possible issues and have strategies in place to mitigate any risks.

SGLT2 inhibitors increase diuresis which may potentially lead to volume depletion and hypotension[45]. In the clinical trials, however, the incidence of these events has been minimal (Table 2). In general, volume status of HFrEF patients should always be assessed and corrected as appropriate, regardless of SGLT2 inhibitor use, supported by heart failure teams.

There was no significant increase in hypoglycaemia observed with any of the SGLT2 inhibitors in the clinical trials (Table 2). Although SGLT2 inhibitors are unlikely to cause hypoglycaemia independently, when combined with other therapies especially insulin, sulphonylureas or glinides in patients with concomitant diabetes, hypoglycaemia may occur. Therefore, when

initiating SGLT2 inhibitors in HF patients who also have diabetes reducing the dose of these background anti-diabetes therapies should be considered.

A common side effect of SGLT2 inhibitors is genital mycotic infections (are these reported in non-diabetics??), which typically manifest early during treatment exposure. Increased severity of genital mycotic infections is more likely in immunocompromised patients as well as individuals with poorly controlled diabetes, morbid obesity or poor hygienic habits[48]. The importance of good personal hygiene should be discussed with the patient to prevent infection. Should infection occur it can be effectively managed with over-the-counter antifungal creams or a single-dose oral antifungal drug.

Based on post-marketing surveillance, concerns were initially raised that SGLT2 inhibitors may increase the risk of Fournier's gangrene for patients with diabetes. Although clinicians need to be aware of this serious life-threatening adverse event, the incidence of Fournier's gangrene is extremely low: there were no cases in the treatment group of DAPA-HF, and it is also notable that of the six cases observed in the DECLARE trial, five were in the placebo group versus a single case in the SGLT2 inhibitor arm. If Fournier's gangrene is suspected (a combination of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise), patients are advised to stop SGLT2 inhibitor treatment and immediately seek medical assessment.

Canagliflozin and ertugliflozin have been associated with an increased lower extremity fractures – were the bony fractures lower limb?? and/or amputations (Table 2)[17, 19]. The risk was not observed with dapagliflozin nor with empagliflozin. However, regardless of the SGLT2 inhibitor used, annual foot review and regular self-examination should be encouraged particularly for HF patients with diabetes who are at higher risk than those without diabetes. People should be advised to speak to a healthcare professional immediately if acute foot issues such as infection or ulceration emerge during treatment, and SGLT2 inhibitors should be temporarily stopped until resolution of the medical problem. SGLT2 inhibitors may not be an appropriate choice of therapy for people with previous amputation or active foot ulceration. Previous amputation and active ulceration are very different??

Most of the clinical trials have observed a slight increase of DKA cases in the SGLT2 inhibitor group compared to placebo but only in people with diabetes?? (Table 2), and anecdotally cases of DKA appear to be more frequent in routine clinical practice. DKA is an acute metabolic complication of diabetes characterized by hyperglycaemia, hyperketonaemia, and metabolic acidosis. It is considered a medical emergency due to the dehydration and electrolyte imbalances that can lead to coma or even death. DKA occurs more frequently with type 1 diabetes, although 10% to 30% of cases occur in patients with T2D[49]. Patients who may be at higher risk of DKA include those with a low insulin-producing capacity in the pancreas, e.g., history of pancreatitis, latent autoimmune diabetes in adults (LADA). In addition, patients with a very low carbohydrate intake or those who have had a sudden reduction in insulin dose, an increased insulin requirement (due to illness or surgery), or conditions that can restrict food intake or lead to severe dehydration also place individuals at increased risk of DKA. SGLT2 inhibitors should be used with caution in these groups. The symptoms of DKA include excessive thirst, frequent urination, dehydration, nausea, vomiting, abdominal pain, shortness of breath, unusual sleepiness or tiredness, confusion, stomach pain and altered sensorium. Patients may also report malaise, dizziness, and syncope, with or without fever. People receiving treatment with an SGLT2 inhibitor should be advised to discontinue the treatment and call their primary care practitioner, or go to the nearest accident and emergency (A&E) hospital, if they develop these symptoms. Clinicians should discontinue the SGLT2 inhibitor if the patient has not already done so and test for ketone levels, preferably in blood rather than urine. It is important to note that ketone testing should be undertaken even if blood glucose is not particularly high, due to the possibility of euglycemic DKA (DKA without marked hyperglycaemia). If DKA is confirmed, appropriate measures should be taken including the replacement of fluid and electrolytes and the administration of insulin. The SGLT2 inhibitor should never be restarted in individuals who have had DKA confirmed.

Future HF indications for SGLT2 inhibitors

The discussion above and the consensus recommendations we have made are currently directed towards patients with stable HFrEF. For patients with acute HF data, although clinical

guidelines currently recommend intravenous diuretic therapy via either a bolus or infusion strategy as initial pharmacological treatment[50], data are emerging regarding the potential role of SGLT2 inhibitors; the EMPULSE trial (NCT04157751) is a superiority study that is currently in progress and which aims to determine whether in-hospital administration of empagliflozin results in improvements in HF-related clinical events and patient-reported outcomes in patients hospitalised for acute HF (de novo or decompensated chronic HF). You could mention the sota trial here that initiated during the hospital stay? Or omit sota from the review entirly since it is unlikely to be marketed??

Treatment is more challenging in people with HFpEF, with currently no approved therapy demonstrating a clear mortality benefit, Limiting treatment largely to diuretics for the alleviation of the symptoms of fluid overload, addressing reversible causes and risk factor management. Recent results from SOLOIST-WHF[51] and SCORED[52] have demonstrated for the first time, in a prospective trial, improved outcomes for patients with HFpEF with sotagliflozin (a dual SGLT2/1 inhibitor). Benefits were also observed for people with acute decompensated HF and for those with chronic kidney disease across the full range of proteinuria. Although the results should be interpreted with caution as results were from truncated versions of the trials following a (trials were closing down before Covid-19) loss of funding (with endpoints changed to accommodate fewer accrued events), the results highlight the potential for this class of drugs in HFpEF. Data from the EMPEROR-Preserved trial with empagliflozin (NCT03057951)[53] and the DELIVER trial with dapagliflozin (NCT03619213)[54] will provide further evidence to direct the use of these drugs for this challenging patient population. Demonstration of a benefit of SGLT2 inhibitors on HF events in these studies would dramatically broaden the clinical impact of SGLT2 inhibitors.

7. Summary

SGLT2 inhibitors are generally well-tolerated with a low risk of serious adverse effects and these should not overshadow the significant cardioprotective benefits. Considering the benefits observed with SGLT2 inhibitors in patients with HF, both with and without T2D, SGLT2 inhibitors should no longer be considered only as glucose-lowering therapy and cardiologists and HF specialists should familiarise themselves with their use and begin to prescribe an appropriate SGLT2 inhibitor as a new

pillar of therapy for HFrEF, alongside an ACE inhibitor/ ARB/ ARNI, a beta blocker and MRA. There are a number of practical considerations to bear in mind to support the optimal use of these drugs in routine clinical practice regarding appropriate prescribing and counselling of patients regarding potential side effects and sick day guidance, particularly in those with concomitant T2D. However, adding an SGLT2 inhibitor to standard of care in HF represents an opportunity to significantly modify the clinical course and improve symptoms and outcomes for patients.

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Availability of data and material

Not applicable.

Code availability

Not applicable.

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Figures

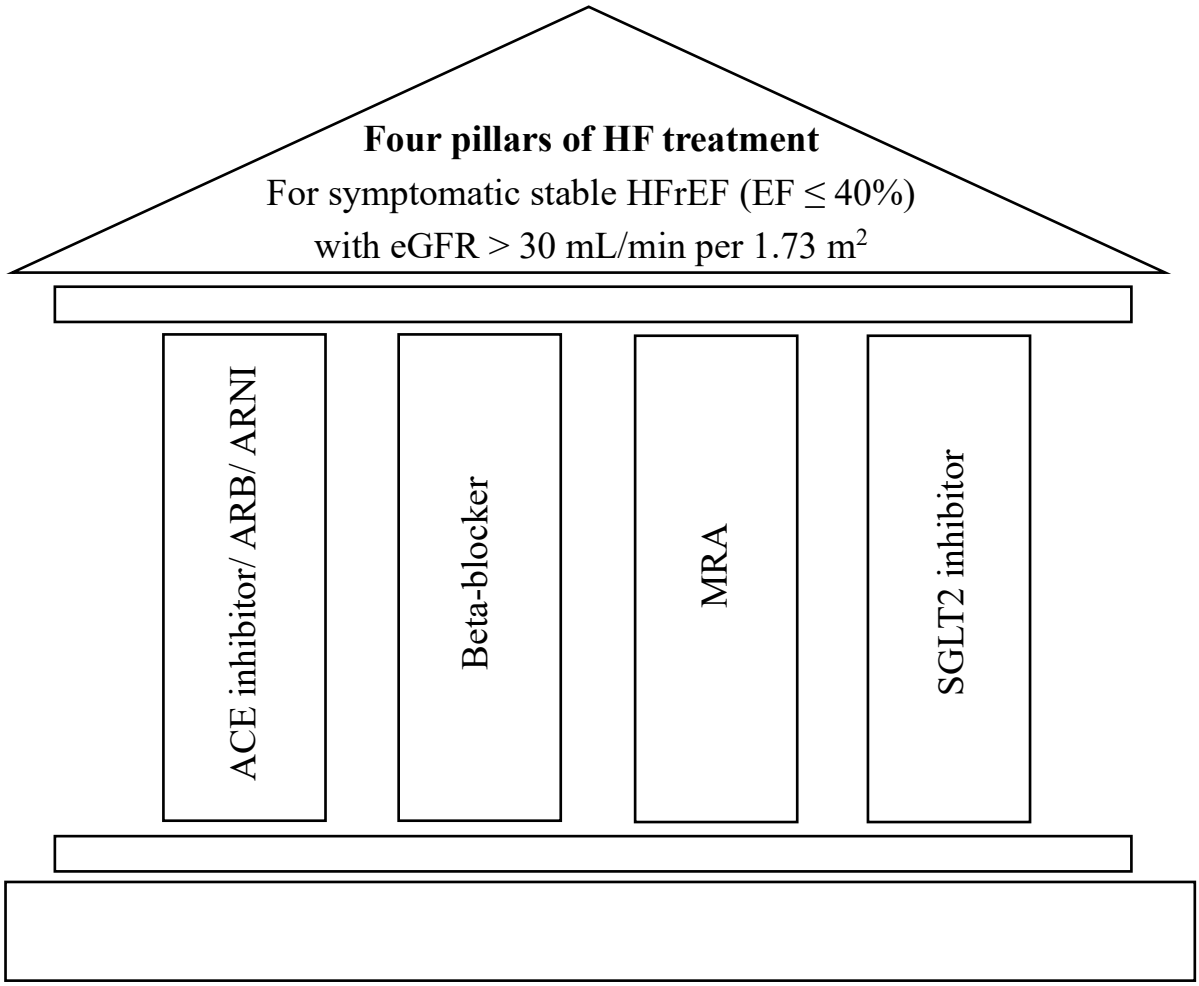


Figure 1. The four pillars of HF treatment

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; eGFR: estimated glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose cotransporter 2

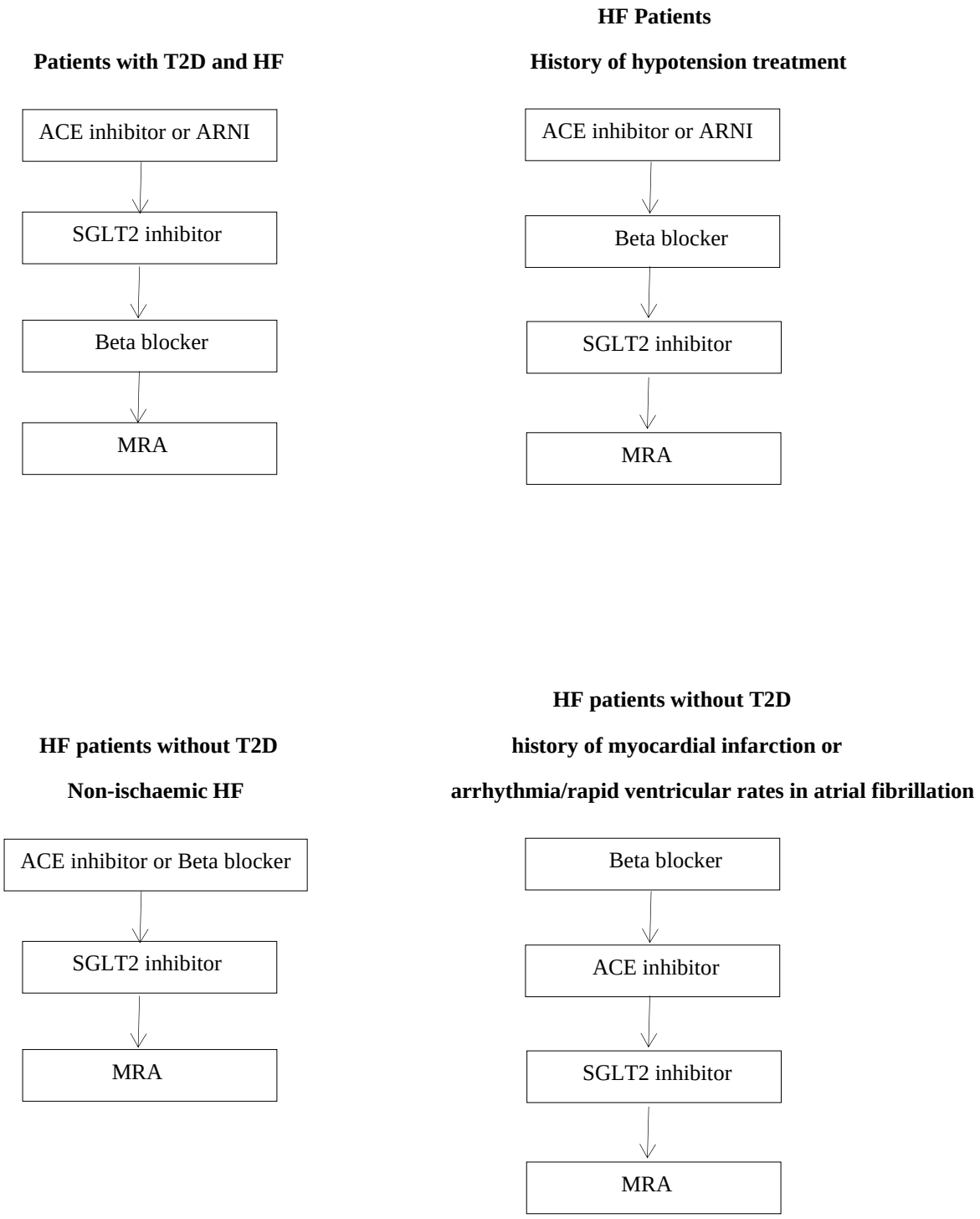


Figure 2. Proposed positioning of SGLT2 inhibitors in the treatment pathway for HF patients with comorbidities

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; HF: heart failure; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose cotransporter 2; T2D: type 2 diabetes

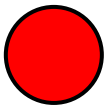
	Consider prescribing an SGLT2i for symptomatic stable HF patients (with or without T2D) with *ALL* of the following
	EF ≤ 40% eGFR >30 ml/min/1.73m^2
	Possibly consider prescribing with caution an SGLT2i for symptomatic stable HF patients (with or without T2D) with *ANY* of the following
	eGFR 20-30 ml/min/1.73m^2 T2D where further blood pressure reduction may be undesirable
	Do not consider prescribing an SGLT2i for symptomatic stable HF patients (with or without T2D) with *ANY* of the following
	eGFR<20 ml/min/1.73m^2 EF ≥ 50%* Acute decompensated HF* Type 1 diabetes* Previous DKA Previous amputation Active foot ulceration

Figure 3. Checklist for appropriate prescribing of SGLT2i in HF

DKA: diabetic ketoacidosis; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure; sBP: systolic blood pressure; T2D: type 2 diabetes

* The clinical efficacy and safety of these drugs in these groups remains uncertain at this time, although trials in these populations are in progress or planned.

Tables

Table 1. Summary of SGLT2 inhibitor treatment effects in the HF published studies

	DAPA-HF[20]	EMPEROR-Reduced[29]	Meta-analysis[30]
All[a] cause mortality	0.83 (0.71–0.97)	0.92 (0.77–1.10)	0.87 (0.77–0.98)
CV mortality	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.86 (0.76–0.98)
First HHF or CV mortality	0.74 (0.65–0.85)	0.75 (0.65–0.86)	0.74 (0.68–0.82)
First HHF	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.69 (0.62–0.78)
First kidney outcome composite[b]	0.71 (0.44–1.16)	0.52 (0.29–0.92)	0.62 (0.43–0.90)
All[a] HHF or CV mortality	0.75 (0.65–0.88)	0.76 (0.65–0.89)	0.75 (0.68–0.84)

CV: cardiovascular; HHF: hospitalisation for heart failure

Note: All values reported are hazard ratio (95% confidence interval), except for all HHF or CV mortality which is reported as relative risk (95% confidence interval)

[a]All = first and recurrent

[b]Kidney composite was defined as time to first occurrence of any of the components of 50% or higher sustained decline in estimated glomerular filtration rate, end-stage renal disease, or renal death.

Table 2. Differences reported between SGLT2 inhibitor and placebo for adverse event rates, across the clinical trials

	EMPA-REG OUTCOME[16]	**CANVAS PROGRAM[17]**	**VERTIS CV[19]**	**DECLARE-TIMI 58[18]**	**DAPA-HF[20]**	**EMPEROR REDUCED[29]**
SGLT2 inhibitor	empagliflozin	canagliflozin	ertugliflozin	dapagliflozin	dapagliflozin	empagliflozin
Number of patients	7,020	10,142	8,238	17,160	4,744	3,730
Median follow up (years)	3.1	5.7	3.5	4.5	1.5	1.3
DKA	No difference	Increased with SGLT inhibitor (0.6 vs 0.3 per 1000 pt-yr)	Increased with SGLT inhibitor (0.3 vs 0.1 %)	Increased with SGLT inhibitor (0.3 vs 0.1 %)	Increased with SGLT inhibitor (0.1 vs 0 %)	No cases
Urinary tract infections	No difference	No difference	Increased with SGLT inhibitor (12.1 vs 10.2 %)	No difference	No difference	No difference
Genital mycotic infections	Increased with SGLT inhibitor (6.4 vs 1.8 %)	Increased with SGLT inhibitor (68.8 vs 17.5 per 1000 pt-yr)	Increased with SGLT inhibitor (5.8 vs 1.8 %)	Increased with SGLT inhibitor (0.9 vs 0.1 %)	No difference	Increased with SGLT inhibitor (1.3 vs 0.4 %)
Fournier Gangrene	No cases	No cases	No cases	Increased with placebo (5 vs 1 case)	Increased with placebo (1 vs 0 case)	Increased with SGLT2 inhibitor (1 vs 0 case)
Fractures	No difference	Increased with SGLT inhibitor (15.4 vs 11.9 per 1000 pt-yr)	No difference	No difference	No difference	No difference
Amputations	No difference	Increased with SGLT inhibitor (6.3 vs 3.4 per 1000 pt-yr)	Increased with SGLT inhibitor (2.1 vs 1.6 %)	No difference	No difference	No difference
Hypoglycaemia	No difference	No difference	No difference	No difference	No difference	No difference
Volume depletion	No difference	Increased with SGLT inhibitor (26 vs 18.5 per 1000 pt-yr)	No difference	No difference	Increased with SGLT inhibitor (7.2 vs 6.5 %)	Increased with SGLT inhibitor (10.6 vs 9.9 %)

CrCl: Creatinine clearance; eGFR: estimated glomerular filtration rate; pt-yr: patient years; SGLT2:Sodium-Glucose Transporter 2

* Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. Creatinine clearance rate (CCr or CrCl) is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR.