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REVIEW

Sodium–glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction

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Sodium–glucose co-transporter 2 (SGLT2) inhibitors have recently been recommended as a foundational therapy for patients with heart failure (HF) and reduced ejection fraction (HFrEF) because of their favourable effects on mortality, clinical events and quality of life. While clinical practice guidelines have recommended dapagliflozin or empagliflozin in all patients with HFrEF, or sotagliflozin in those with HFrEF and concomitant diabetes, the timing and practical integration of these drugs in clinical practice is less well defined. We propose that these drugs are candidates for early, upfront administration to patients with newly diagnosed HFrEF and for patients hospitalized with HF. Growing evidence has established early benefits, with clinically meaningful reductions in clinical events that reach statistical significance within days to weeks, following dapagliflozin, empagliflozin or, in diabetic patients, sotagliflozin initiation. Secondly, although major clinical trials have tested these drugs in patients already receiving background HF therapy, secondary analyses showed that their efficacy is independent of that. Third, SGLT2 inhibitors are generally safe and well tolerated, with clinical trial data reporting minimal effects on blood pressure, glycaemia-related adverse events, and no excess in acute kidney injury. Rather, they exert renal protective effects and reduce risk of hyperkalaemia, properties that favour initiation, tolerance and persistence of renin–angiotensin system inhibitors and mineralocorticoid receptor antagonists. This review supports the early initiation of dapagliflozin and empagliflozin (or sotagliflozin limited to patients with diabetes) to rapidly improve clinical outcome and quality of life of HFrEF patients.

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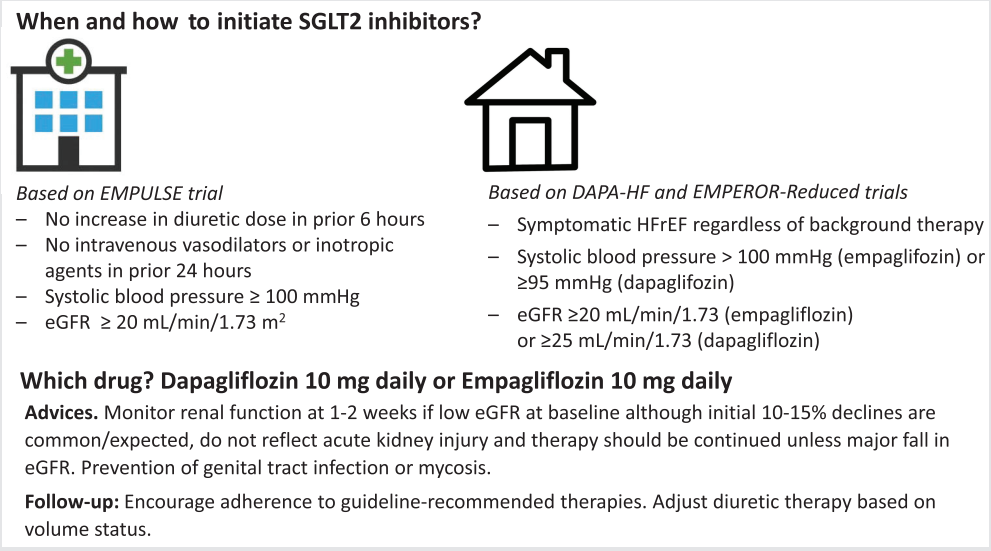
Graphical Abstract



When and how to initiate sodium–glucose co-transporter 2 (SGLT2) inhibitors. Data based on enrolment criteria of the DAPA-HF, EMPEROR-Reduced and EMPULSE trials. eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction.

Keywords Heart failure with reduced ejection fraction • Sodium–glucose co-transporter 2 inhibitors • Dapagliflozin • Empagliflozin • Sotagliflozin • Medical therapy

Introduction

Over the last few decades, major advances have occurred in the treatment of patients with heart failure (HF) with reduced ejection fraction (HFrEF) with the introduction of drugs to extend survival and reduce HF hospitalizations.[1] Neurohormonal modulation has been the mainstay of HFrEF treatment, with large randomized clinical trials demonstrating favourable outcomes with beta-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and, more recently, angiotensin receptor–neprilysin inhibitors (ARNI). Adherence to evidence-based medical treatment was associated with improved outcome.[2–4] However, results from the prospective CHAMP-HF (Change the Management of Patients with Heart Failure) registry showed significant gaps in the use and dose of guideline-directed medical therapy (GDMT), with only 1% of eligible patients prescribed triple therapy with ACEi/ARB/ARNI, beta-blocker, and MRA at recommended doses.[5] Many factors may lead to suboptimal prescription and/or underuse of these compounds, including older age, haemodynamic intolerance (e.g. hypotension, bradycardia), renal dysfunction, hyperkalaemia, costs, limited access, and/or clinician inertia.[6–9]

More recently, new therapeutic pathways beyond neurohormonal modulation, have been identified and subsequently shown to yield clinical benefits in major clinical outcome trials.[1,10–13] Particularly, sodium–glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce hospitalizations for HF, kidney disease progression, and cardiovascular (CV) mortality among outpatients with HFrEF and patients hospitalized for HF.[14–16] An estimation of the potential benefit of SGLT2 inhibitor prescription showed that in the United States, among 2 million eligible patients (69% of total HF patients), the addition of an SGLT2 inhibitor may prevent or postpone up to 34 125 deaths per year.[17] Thus, timing and sequencing of these drugs for HF treatment is critical. In this article, we review the body of evidence supporting the early administration of these agents to patients with HFrEF.

Sodium–glucose co-transporter 2 inhibitors: from the search for new glucose-lowering agents to success in heart failure trials

SGLT2 inhibitors were initially evaluated as glucose-lowering drugs, but CV outcome trials unexpectedly and consistently showed that they reduced major adverse CV events and hospitalization for HF in patients with type 2 diabetes mellitus (T2DM).[11,12,18–22] In 2019, DAPA-HF (Dapagliflozin And Prevention of Adverse outcome in Heart Failure) was the first trial demonstrating a significant benefit

of a SGLT2 inhibitor in patients with established HFrEF, regardless of diabetes history, with a 26% reduction in the risk of the composite endpoint of CV death or worsening HF (hospitalization or an urgent visit requiring intravenous therapy for HF). Each of the three components of the composite outcome occurred less frequently in the treatment group.[14] In 2020, the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial confirmed the results of DAPA-HF in a population with slightly different eligibility criteria, recruiting patients with more severe HF than in DAPA-HF.[15,23] Particularly, inclusion criteria required patients with left ventricular ejection fraction (LVEF) 31%–40% to have had at least one HF hospitalization in the last 12 months or progressively higher thresholds of natriuretic peptides for increasing LVEF values. The combined risk of CV death or hospitalization for HF was 25% lower among the patients who received empagliflozin than among those on placebo. Results were primarily driven by a 31% lower risk of hospitalization for HF, whereas reduction in CV mortality did not reach statistical significance. In both trials treatment effects were not different in patients with or without diabetes.[24,25] Both these trials were developed in chronic, stable patients, excluding those with current acute decompensated HF (or an hospitalization due to decompensated HF within 4 weeks prior to enrolment) and those with a recent CV event (i.e. myocardial infarction, coronary artery bypass graft surgery, or other major CV surgery, stroke or transient ischaemic attack 90 days prior to enrolment).

The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial randomized patients with HF and diabetes to sotagliflozin (a combined SGLT1/2 inhibitor) or placebo before or shortly after discharge following a HF hospitalization, regardless of LVEF. Patients with worsening HF with specific causes, such as pulmonary embolism, stroke or heart attack as well as patients with an acute coronary syndrome in the last 3 months were excluded.[16] The trial ended early because of loss of funding from the sponsor with a consequent reduction in power to test the original primary endpoint which was changed into total number of CV deaths, HF hospitalizations, and urgent visits for HF to accrue more events. Sotagliflozin reduced this new primary endpoint compared to placebo (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.52–0.85; $p < 0.001$) and in a time-to-event analysis of the original primary endpoint it was also associated with a 29% reduction in the first occurrence of either CV death or HF hospitalization.[16] Differently from dapagliflozin and empagliflozin, sotagliflozin is a non-selective SGLT inhibitor. Inhibition of both SGLT2 and 1 receptor may increase glycosuria, especially in diabetic patients. In addition, unlike SGLT2, SGLT1 is also expressed in other organs, including the gut, with less sodium absorption, and the heart. Sotagliflozin may protect cardiac tissue by interfering with glucose uptake and decreasing the production of reactive oxygen species. Thus, there is uncertainty whether benefits of sotagliflozin are comparable to those of SGLT2 inhibitors and whether this drug could be of incremental therapeutic value in patients with T2DM.[26,27]

More recently, the EMPULSE (a study to test the effect of empagliflozin in patients who are in hospital for acute HF) trial was concluded. This trial tested safety and efficacy of in-hospital initiation of empagliflozin, soon after initial stabilization, in patients with acute decompensated HF, regardless of their LVEF.[28] Patients with acute HF triggered by pulmonary embolism, cerebrovascular accident, or acute myocardial infarction were excluded. Initial stabilization was defined as systolic blood pressure (SBP) ≥100 mmHg, no symptoms of hypotension within 6 h, no increase in intravenous diuretic dose and no intravenous vasodilators, including nitrates, in the previous 6 h, no intravenous inotropic drug administration within 24 h. Overall, 530 patients (mean age 71 years; 67% males; 47% with diabetes; median LVEF 31%) were randomized to empagliflozin 10 mg daily or placebo.[29] Empagliflozin reduced the primary composite endpoint of death, number of HF events, time to first HF event and change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at 90 days of treatment, assessed by the stratified win ratio. The rates of clinical benefit were 53.9% in the empagliflozin group and 39.7% in the placebo group ($p = 0.0054$). Among secondary endpoints, there was also a significantly larger reduction in body weight in the empagliflozin group versus the placebo group (−1.5 kg; $p = 0.014$). Importantly, patients treated with empagliflozin had a lower rate of acute renal failure (7.7% vs. 12.1%).[29]

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial extended the results with SGLT2 inhibitors to patients with HF and mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) with a significant reduction in the primary composite outcome of CV death or hospitalization for HF (HR 0.79; 95% CI 0.69–0.90; $p < 0.001$) with empagliflozin versus placebo in patients with New York Heart Association (NYHA) class II–IV HF and LVEF >40%.[30,31] The combined endpoint of CV death, HF hospitalization or an emergent/urgent HF was significantly reduced (HR 0.77; 95% CI 0.67–0.87; $p < 0.0001$) and this reached statistical significance as early as at 18 days after randomization.[32] Thus, although this review is aimed at being focused only on patients with HFrEF, the early efficacy of empagliflozin versus placebo in EMPEROR-Preserved and of sotagliflozin in SOLOIST-WHF further supports the rationale of a strategy of early integration of SGLT2 inhibitors in HF treatment regardless of LVEF.

Sodium–glucose co-transporter 2 inhibitors as first-line therapy in heart failure with reduced ejection fraction

Early beneficial effects

Clinical trials show that substantial clinical benefits of SGLT2 inhibitors occur early, within days to weeks after initiation. In a secondary analysis of DAPA-HF, aiming to investigate timing to onset of clinical benefit with dapagliflozin, HRs for the primary efficacy outcome were calculated by time following randomization.[33] The reduction in the risk of CV death or worsening HF was evident early, as demonstrated by the early separation of the Kaplan–Meier curves. Statistical significance for the primary outcome was reached at 28 days after randomization (HR 0.51, 95%

Table 1 **Effects of sodium–glucose co-transporter 2 inhibitors on primary outcome and quality of life in patients with heart failure, including time to clinical benefit and a comparison between patients with or without chronic kidney disease**

Trial	Intervention (sample size)	Main eligibility criteria	Follow-up (years)	Primary outcome	Overall treatment effect HR (95% CI)	Time to significant benefit (days)	QoL outcome	CKD subgroups (eGFR, ml/min/1.73 m^2)	Treatment effect in CKD HR (95% CI)	*p*-value for CKD interaction
DAPA-HF[14,36,40,44,55,65]	Dapagliflozin 10 mg o.d. vs. placebo (n = 4744)	LVEF ≤40%; NYHA II–IV; eGFR ≥30 ml/min/1.73 m^2	1.5	Worsening HF or CV death	0.74 (0.65–0.85)	28	Fewer deterioration in KCCQ-TSS with dapagliflozin (OR 0.84 [0.78–0.90]) and more small, moderate, and large improvements (OR 1.15 [1.08–1.23]; OR 1.15 [1.08–1.22]; OR 1.14 [1.07–1.22], respectively) at 8 months	<60 (n = 1926) ≥60 (n = 2816)	0.72 (0.59–0.86) 0.76 (0.63–0.92)	NS
EMPEROR-Reduced[15,25,34,35,41,53,56]	Empagliflozin 10 mg o.d. vs. placebo (n = 3730)	LVEF ≤40%; NYHA II–IV; eGFR ≥20 ml/min/1.73 m^2	1.3	HF hospitalization or CV death	0.75 (0.65–0.86)	12[a]	More patients on empagliflozin had ≥5-point (OR 1.20 [1.05–1.37]), 10-point (OR 1.26 [1.10–1.44]), and 15-point (OR 1.29 [1.12–1.48]) improvement and fewer had ≥5-point (OR 0.75 [0.64–0.87]) deterioration in KCCQ-CSS at 3 months	<60[b] (n = 1978) ≥60 (n = 1746)	0.83 (0.69–1.00) 0.67 (0.55–0.83)	NS
SOLOIST-WHF[16]	Sotagliflozin 200 mg o.d. (up-titrated up to 400 mg) vs. placebo (n = 1222)	Type 2 diabetes; recent worsening HF; eGFR ≥30 ml/min/1.73 m^2 (administered before discharge in 48.8% of patients and early after discharge in 51.2%)	0.75	Total number of CV deaths and hospitalizations and urgent HF visits	0.67 (0.52–0.85) (consistency of the treatment effect according to timing of first dose)	28	–	<60 (n = 854) ≥60 (n = 368)	0.59 (0.44–0.79) 0.90 (0.58–1.37)	NS

CI, confidence interval, CKD, chronic kidney disease; CV, cardiovascular; DAPA-HF, Dapagliflozin And Prevention of Adverse outcome in Heart Failure; eGFR, estimated glomerular filtration rate; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; HF, heart failure; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaires clinical summary score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaires total summary score; LVEF, left ventricular ejection fraction; NYHA, New York Hear Association; OR, odds ratio; QoL, quality of life; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure.

[a]Statistical significance was first reached at 12 days but was sustained from day 34.

[b]Or albumin-to-creatinine ratio > 300 mg/g.

CI 0.28–0.94; $p = 0.03$) (*Table 1*) with similar results for each component of the outcome.[33] In EMPEROR-Reduced, empagliflozin reduced the combined risk of death or worsening HF, compared with placebo, as early as 12 days after randomization (HR 0.76; 95% CI 0.67–0.87; $p < 0.0001$) and the effect was maintained during follow-up (*Table 1*).[34] Patients treated with empagliflozin were also less likely to require intensification of diuretic treatment, and more frequently experienced an improvement in NYHA class compared with placebo-treated patients, with statistical significance reached as early as 4 weeks after randomization and confirmed during long-term follow-up.[34] Similarly, in SOLOIST-WHF, the initiation of sotagliflozin before or shortly after discharge from an HF hospitalization, significantly reduced the primary endpoint of total CV death, HF hospitalization or urgent HF as soon as 4 weeks after randomization.[16]

In a secondary analysis of EMPEROR-Reduced, empagliflozin significantly improved patient-reported outcomes, namely KCCQ clinical summary score (CSS), TSS and overall summary score (OSS), compared to placebo. Using clinically relevant thresholds of a 5-, 10-, or 15-point increase and a 5-point decline, patients on empagliflozin were more likely to have improvement and less likely to experience deterioration. Such benefits were relevant since the first post-randomization assessment (at 3 months) and remained significant at 8 and 12 months (*Table 1*).[35] In DAPA-HF, patients treated with dapagliflozin had a significant improvement in mean KCCQ-TSS, CSS, and OSS at 4 months, and the effect was amplified over time.[36]

Early initiation of sodium–glucose co-transporter 2 inhibitors in patients hospitalized for acute heart failure

Hospitalization for acute HF has been advocated as an ideal setting for the initiation or optimization of GDMT in efforts to reduce the high rates of death and hospital readmissions.[1,37,38] DAPA-HF and EMPEROR-Reduced trials mainly enrolled stable, ambulatory HF patients. However, SOLOIST-WHF enrolled patients with type 2 diabetes hospitalized for worsening HF and, according to the study design, the first dose of sotagliflozin or placebo was administered before discharge, after discontinuation of intravenous diuretics and haemodynamic stabilization (defined as SBP ≥100 mmHg, no requirement for intravenous inotropic therapy or intravenous vasodilators), in 48.8% of patients ($n = 596$) and early after discharge in 51.2% ($n = 626$) (median, 2 days [interquartile range 1–3]). This study demonstrated the beneficial effects of sotagliflozin when started before discharge or early after a hospitalization for acute HF, independently of when treatment was started (HR 0.71, 95% CI 0.51–0.99 and HR 0.64, 95% CI 0.45–0.90 for initiation before and after discharge, respectively).[16] These results may be extended to the other SGLT2 inhibitors that showed as beneficial in HFrEF, dapagliflozin and empagliflozin. These drugs were not discontinued during hospitalizations for HF in DAPA-HF or EMPEROR-Reduced and their efficacy was independent of concomitant therapy.[39–41]

Further trials with early initiation of empagliflozin in patients hospitalized for acute HF have been recently concluded. The multicentre, placebo-controlled EMPA-RESPONSE-AHF pilot study randomized 80 patients with acute HF, presenting signs and symptoms of fluid overload, within 24 h after hospital admission, to empagliflozin 10 mg/day or placebo for 30 days. Empagliflozin was safe and well tolerated. It had non-significant effects, likely because of the size of the study group, on symptoms, diuretic response, natriuretic peptide levels, and length of hospital stay and reduced significantly the combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days, compared with placebo ($p = 0.014$).[42] These results were extended and confirmed in EMPULSE.[28,29] In this trial, 530 patients hospitalized for acute HF were randomized to empagliflozin or placebo on top of standard therapy within 1 to 5 days after hospitalization, regardless of LVEF and diabetes status. The primary endpoint was clinical benefit at 90 days, consisting of a composite of all-cause death, HF events, and ≥5 point change from baseline in KCCQ-TSS, assessed using a 'win-ratio' approach.[28] Compared with those on placebo, patients treated with empagliflozin were more likely to achieve a clinical benefit, 39.7% on placebo versus 53.9% of those on empagliflozin (stratified win ratio: 1.36, 95% CI 1.09–1.68; $p = 0.0054$). The results were consistent across different subgroups, including estimated glomerular filtration rate (eGFR) and LVEF, and serious adverse events were more frequent in patients on placebo.[29] The effects on the clinical outcome of CV death or worsening HF of in-hospital initiation of dapagliflozin in a target sample of 2400 patients with HFrEF who have been stabilized during hospitalization for acute HF are currently evaluated in the randomized, double-blind, placebo-controlled DAPA ACT HF-TIMI 68 trial (Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure-Thrombolysis in Myocardial Infarction 68; ClinicalTrials.gov NCT04363697).

Tolerability and safety

SGLT2 inhibitors are safe and well tolerated, supporting their priority in HFrEF treatment. Hypotension, renal dysfunction and electrolyte disturbances are frequent causes of underuse of evidence-based treatment and withholding of neurohormonal therapy,[6–9,43] whereas major clinical trials showed only modest or absent blood pressure lowering and no excess in acute kidney injury or other serious adverse events with SGLT2 inhibitors compared to placebo. In DAPA-HF, dapagliflozin only slightly reduced SBP and was well tolerated in the subgroup of patients with the lowest SBP where mean SBP reduction with dapagliflozin was 1 mmHg.[44] There was no difference between dapagliflozin and placebo in the occurrence of adverse events in patients with SBP <110 mmHg. The benefit of dapagliflozin was consistent across the range of SBP at baseline, or even larger in those with the lowest SBP, who had higher rates of the primary outcome compared to the other subgroups.[44] Similar data were shown for empagliflozin in EMPEROR-Reduced.[45] Corrected for placebo, a slight early increase in SBP was observed in patients with a SBP <110 mmHg at baseline, no change in those with a SBP of 110–130 mmHg, and a slight reduction in those with a SBP >130 mmHg. SBP at baseline did not influence the effect of empagliflozin on HF events or renal endpoints. Treatment with empagliflozin had no effect on

the rate of hypotension or symptomatic hypotension in any SBP subgroup. Its beneficial effects on kidney function and outcomes were independent of SBP at baseline.[45]

Chronic kidney disease (CKD) often coexists with HF due to shared risk factors and pathophysiology, and also as a consequence of HF itself.[46] SGLT2 inhibitors may cause an initial decline in eGFR.[15,24] Concomitant treatment with loop diuretics and thiazides may predispose, especially in patients with acute HF, to excessive diuresis, dehydration, symptomatic hypotension and pre-renal failure.[47] However, even if evidence is still limited, no excess in acute renal failure was reported in EMPA-RESPONSE-AHF and in the larger EMPULSE trial.[29,42] In EMPA-RESPONSE-AHF, diuretic response, measured as weight change per 40 mg furosemide, was similar, whereas urinary output until day 4 was significantly larger, with empagliflozin versus placebo.[42] Diuresis was mostly related with glycosuria and osmotic diuresis, with no increase in natriuresis, both in diabetic and non-diabetic patients.[48] Overall, these data suggest that the diuretic effect of SGLT2 inhibitors is not their main mechanism of action and should not have a major impact on kidney function also in patients with acute HF. In a small study, including 100 diabetic patients hospitalized for decompensated HF, dapagliflozin significantly improved urine output, total fluid loss, and fluid balance, with no significant change in serum potassium or kidney function.[49] Thus, adding a SGLT2 inhibitor may lead to a slight increase in diuresis and may allow a decrease in loop diuretic doses.

The initial drop in eGFR, described in major randomized trials in patients with HFrEF, is due to the beneficial effect of SGLT2 inhibitors on intraglomerular pressure and is reversible and followed by a significant decrease in long-term progression of kidney disease.[18,50] Renal outcomes were included as secondary endpoints in the two major HFrEF trials. In EMPEROR-Reduced, empagliflozin was associated with a slower annual rate of decline in eGFR compared to placebo (−0.55 vs. −2.28 ml/min1.73 m^2 of body-surface area per year, $p < 0.001$), and empagliflozin-treated patients had a lower risk of serious renal outcomes.[15] The incidence of the pre-specified renal composite outcome was not statistically significant between the treatment groups in DAPA-HF.[14,24] However, these inconsistent findings may be merely explained by different study designs, instead of difference in efficacy. In EMPEROR-Reduced, patients were excluded when eGFR was <20 ml/min/1.73 m^2, instead of <30 ml/min/1.73 m^2, as in DAPA-HF, resulting in worse baseline renal function. Second, the endpoint of worsening renal function was defined as a sustained decline in eGFR of ≥40%, instead of ≥50%, as in DAPA-HF.[14,15,23,24] Dapagliflozin improved outcomes in patients with CKD in the DAPA-CKD trial.[51] Empagliflozin and dapagliflozin exerted similar benefits on the slope of eGFR decline and their efficacy was similar across subgroups of patients with or without CKD (*Table 1*).[52,53] In patients with diabetes and CKD, with or without albuminuria, sotagliflozin improved CV outcome in the SCORED trial.[54]

ACEi or ARNI and MRA, among the pillars of HFrEF therapy, often cause hyperkalaemia, especially in patients with CKD, leading to under-prescription of evidence-based treatment and worse outcome.[7,8] SGLT2 inhibitors were not associated with significant changes in potassium levels in major trials, also reducing the need for close laboratory monitoring. A sub-analysis of DAPA-HF showed lower rates of hyperkalaemia with dapagliflozin in the subgroup of individuals treated with MRAs.[55] Although this observation has not been confirmed in EMPEROR-Reduced, results showed fewer discontinuation of MRAs among patients prescribed with empagliflozin.[56] Reduced rates of hyperkalaemia with SGLT2 inhibitors have also been demonstrated in adjacent clinical trials of patients with CKD.[57] Adverse events observed in major clinical trials are summarized in *Table 2*. Genital infections are among the most common complications in patients with diabetes treated with SGLT2 inhibitors as a consequence of glycosuria.[18] Of note, sotagliflozin was associated with more frequent adverse events, including diarrhoea, hypotension and hypoglycaemia, generally not observed in the other SGLT2 inhibitor trials.[16] This adverse event rate can likely be attributed to additional inhibition effects exerted by sotagliflozin on the gastrointestinal and renal SGLT1.

Another feared complication is represented by the extremely rare occurrence of euglycaemic ketoacidosis. Shift to fatty substrate utilization in response to SGLT2 inhibition produces ketones.[58] Another consequence of SGLT2 inhibitor use is the accumulation of ATP in the kidney, due to the lack of function of the ATPase sodium/potassium, which, if active, would generate a sufficient sodium gradient for SGLT2 to work. Thus, ATP-generating processes like renal ammoniagenesis are inhibited, leading to urinary loss of bicarbonate, which, combined with ketosis, could reduce the threshold to induce ketoacidosis, mainly in the presence of triggers like infections or fasting. This event is mostly observed in diabetic patients receiving insulin. Physicians should be aware that ketoacidosis in individuals taking SGLT2 inhibitors may occur in the presence of relatively normal blood glucose concentrations. Thus, the major concern of early SGLT2 inhibitor use is that in-hospital patients may be in a fasting state, increasing the risk of euglycaemic ketoacidosis.[59] The risk of ketoacidosis is higher only in diabetic patients taking SGLT2 inhibitors, although only few events occurred in participants of major trials and no events have been reported among non-diabetic participants.[14,15,50,57] Consistent with a good tolerability also in the acute setting are the results in patients with acute HF as well as DARE-19.[29,42,60] The DARE-19 trial randomized 1250 coronavirus disease 2019 (COVID-19) non-critically ill hospitalized patients with at least one cardio-metabolic risk factor to dapagliflozin or placebo. The trial proved the safety of dapagliflozin in the in-hospital setting, with any serious adverse events reported in 10.6% of patients receiving dapagliflozin vs. 13.3% in the placebo group. Acute kidney injury (3.4% vs. 5.5%) and diabetic ketoacidosis (0.3% vs. 0%) occurred with a similar extent in both groups.[60] Indeed, once critically ill, fasting, patients are excluded, the early administration of SGLT2 inhibitors seems to be safe and well tolerated.

Additive benefits with other guideline-directed treatments

Neurohormonal modulators provide beneficial effects that are additive and independent.[1] Secondary analyses of DAPA-HF and

Table 2 Adverse events in major cardiovascular and heart failure trials with sodium–glucose co-transporter 2 inhibitors

	EMPA-REG OUTCOME[22,62,63] (empagliflozin 25 mg vs. 10 mg vs. placebo)	DECLARE-TIMI 58[21] (dapagliflozin vs. placebo)	CANVAS Program[20] (canagliflozin vs. placebo)	DAPA-HF[14] (dapagliflozin vs. placebo)	EMPEROR-Reduced[15] (empagliflozin vs. placebo)	SOLOIST-WHF[16] (sotagliflozin vs. placebo)	EMPEROR-Preserved[30] (empagliflozin vs. placebo)
AEs of interest (%)							
Volume depletion	5.3 vs. 4.9 vs. 4.9	2.5 vs. 2.4	26.0 vs. 18.5*	7.5 vs. 6.8	10.6 vs. 9.9	9.4 vs. 8.8	
Hypotension	–	–	–		9.4 vs. 8.7	6.0 vs. 4.6	10.4 vs. 8.6
Renal AE	5.3 vs. 5.2 vs. 6.6*	1.5 vs. 2.0*	19.7 vs. 17.4	6.5 vs. 7.2	–	4.1 vs. 4.4	12.1 vs. 12.8
Fracture	3.7 vs. 3.9 vs. 3.9	5.3 vs. 5.1	15.4 vs. 11.9*	2.1 vs. 2.1	2.4 vs. 2.3	2.0 vs. 1.5	4.5 vs. 4.2
Amputation	–	1.4 vs. 1.3	6.3 vs. 3.4*	0.5 vs. 0.5	0.7 vs. 0.5	0.7 vs. 0.2	0.5 vs. 0.8
Severe hypoglycaemia	27.6 vs. 28.0 vs. 27.9	0.7 vs. 1.0*	50.0 vs. 46.4	0.2 vs. 0.2	1.4 vs. 1.5	1.5 vs. 0.3	2.4 vs. 2.6
Diabetic ketoacidosis	<0.1 vs. 0.1 vs. <0.1	0.3 vs. 0.1*	0.6 vs. 0.3	0.1 vs. 0.0	0.0 vs. 0.0	0.3 vs. 0.7	0.1 vs. 0.2
Fournier's gangrene	–	–	–	0.0 vs. <0.1	–	–	–
Urinary tract infections	17.8 vs. 18.2 vs. 18.1	1.5 vs. 1.6	40.0 vs. 37.0	0.5 vs. 0.7	4.9 vs. 4.5	8.6 vs. 7.2	9.9 vs. 8.1
Genital infections	6.3 vs. 6.5 vs. 1.8*	0.9 vs. 0.1*	34.9 vs. 10.8* (males) 68.8 vs. 17.5 (mycotic infections in females)	–	1.7 vs. 0.6	0.8 vs. 0.2	2.2 vs. 0.7
Diarrhoea	–	–	–	0.2 vs. 0.2	–	6.9 vs. 4.1	–
Pneumonia	–	–	–	3.2 vs. 3.5	–	4.5 vs. 5.1	–
Hyperkalaemia	–	–	–	0.1 vs. 0.2	–	4.3 vs. 5.1	–
Pancreatitis	–	–	–	0.0 vs. 0.0	–	0 vs. 0.5	–
Venous thrombotic events	0.9 vs. 0.4 vs. 0.9	–	1.7 vs. 1.7	0.0 vs. 0.0	–	0 vs. 1.1	–
AEs leading to treatment discontinuation (%)	17.0 vs. 17.7 vs. 19.4*	8.1 vs. 6.9*	35.5 vs. 32.8	4.7 vs. 4.9	–	–	–

AE, adverse event; CANVAS Program (CANVAS, Canagliflozin Cardiovascular Assessment Study and CANVAS-R, CANVAS-Renal); DAPA-HF, Dapagliflozin And Prevention of Adverse outcome in Heart Failure; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure.
*$p < 0.05$ (p-value not available for EMPEROR-Reduced, SOLOIST-WHF and EMPEROR-Preserved trials).

Table 3 Early 'upfront' use of sodium–glucose co-transporter 2 inhibitors

Medical treatment	Days 1–7	Day 7–14	Day 14–28	Day 21–42
ARNI/ACEi[a]	Initiate (low dose)	Initiate or continue and titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated
Beta-blocker	Initiate (low dose)	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated
MRA	Initiate (low dose)	Initiate and continue or titrate, as tolerated	Continue or titrate, as tolerated	Continue or titrate, as tolerated
Dapagliflozin or empagliflozin[b]	Initiate	Continue	Continue	Continue

ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.
The simultaneous or rapid sequence strategy for quadruple medical therapy in patients with heart failure with reduced ejection fraction should be personalized depending on patient characteristics. Medications may be rapidly sequenced starting each a few days apart or alternatively started simultaneously in naïve patients while foundation therapies should be implemented in all the others. Due to lack of experience, when quadruple therapy is simultaneously or rapidly introduced, close monitoring of electrolytes, kidney function and blood pressure is required. Based on tolerability, target dose may or may not be achieved or in certain circumstances decreases in dosing may be required, to ensure each medication is well tolerated. Evidence-based treatment must be initiated except in case of contraindications or intolerance. In selected patients, based on clinical status and comorbid conditions, less rapid sequencing may be considered.
[a]ARNI may be considered as first-line therapy instead of an ACEi. The use of ARNI as a replacement for ACEi in suitable patients who remain symptomatic on ACEi is recommended.
[b]Sotagliflozin may also be considered in patients with type 2 diabetes mellitus.
Modified with permission from references.[68,69]

EMPEROR-Reduced showed that both efficacy and safety were not affected by concomitant administration of HF therapy.[40,41] The majority of patients enrolled in DAPA-HF (96%) were treated with at least two of an ACEi/ARB or ARNI, a beta-blocker and/or an MRA, with 3091 (65%) patients on all three of these classes of drugs. Docherty et al.[40] found consistent results across all subgroups examined. In DAPA-HF a small proportion of patients (7%) was on ARNI. The proportion of patients receiving ARNI in EMPEROR-Reduced was higher (19.5%), whereas a similar proportion was on triple therapy (61.1%).[61] Empagliflozin was effective in reducing the primary composite endpoint regardless of background therapy or its target doses (HR for ACEi or ARBs <50% of the target dose 0.85 [0.69–1.06] and for doses ≥50% HR 0.67 [0.52–0.88]; *p* interaction = 0.18; HR for beta-blockers <50% of the target dose 0.66 [0.54–0.80]) and for doses ≥50% HR 0.81 [0.66–1.00]; *p* interaction = 0.15). No treatment interaction was observed when comparing patients on triple therapy versus those that were not.[41] In addition, empagliflozin reduced both the risk of CV death or HF hospitalization and slowed the rate of decline in eGFR irrespective of treatment with sacubitril/valsartan.[61]

SGLT2 inhibitors were also effective in reducing hospitalization for HF in patients with diabetes and at high CV risk and most of them were not receiving HF therapy.[20–22,62,63] Lastly, in EMPULSE, both patients with *de novo* or decompensated chronic HF were enrolled. Results showed no treatment interaction across different subgroups. Thus, also those patients with *de novo* HF, who are not treated with HF drugs, may benefit from SGLT2 inhibitors.[29] Based on all these considerations, we can likely assume that the benefit of SGLT2 inhibitors is additive to (and independent of) the benefits of established HF treatments. When cumulative benefits were considered, it was estimated that 'quadruple therapy' may reduce all-cause mortality by 73% over 2 years.[17] Thus, the choice of first-line treatment is almost a practical issue and may be driven by the easier way to reach quadruple therapy in all patients with HFrEF who can tolerate it in the shortest time as possible (*Table 3*).

Concluding remarks

Clinical inertia should not defer initiation of evidence-based treatment. Starting effective therapy can rapidly decrease morbidity, mortality, and economic burden of HF.[64,65] Given the benefits shown in large major trials, SGLT2 inhibitors should be considered as foundational therapy in patients with HFrEF, together with ARNI/ACEi/ARB, MRA and beta-blockers. In both DAPA-HF and EMPEROR-Reduced trials, SGLT2 inhibitors were initiated in patients on maximally tolerated evidence-based therapy. As a consequence, the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment recommends adding an SGLT2 inhibitor (dapagliflozin or empagliflozin) as part of HFrEF therapy in patients who are already receiving beta-blockers, an ARNI/ACEi/ARB and MRA.[66] However, SGLT2 inhibitors have no significant interaction with other HF treatments and there is no rationale in waiting for patients to achieve maximally tolerated evidence-based treatment. In the Canadian Cardiovascular Society/Canadian Heart Failure Society HF guidelines update, early initiation of SGLT2 inhibitor treatment in eligible patients is considered 'reasonable'.[67] The simultaneous or rapid sequence initiation of low doses of all four classes of quadruple HF therapy, followed by a gradual up-titration, has been proposed and recommended by several HF experts.[68,69] In the recently published 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF, dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACEi/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status; sotagliflozin is recommended in patients with HFrEF and type 2 diabetes mellitus.[1] Treatment optimization during an hospitalization for acute HF is also encouraged in 2021 ESC guidelines. The recommendation is to initiate, restart or up-titrate oral optimal medical therapy with beneficial effects on outcome before discharge and/or in the early post-discharge phase.[1] No sequence for the initiation of drug therapy is recommended but a position statement by the Heart Failure Association

of the ESC emphasized the importance of a personalized approach based on the main clinical characteristics of the patient.[70]

In the present review we summarized data supporting an early initiation of dapagliflozin, empagliflozin or, limited to diabetic patients, sotagliflozin, in patients with HFrEF. These drugs embody most of the ideal characteristics for a HFrEF medication, including single dose, once daily administration, no need for titration, early beneficial effects on clinical events and patient-reported quality of life, and favourable safety and tolerability profile.[71] The tendency to focus on possible side effects may lead to under-prescription of evidence-based medical therapy. However, in the case of SGLT2 inhibitors, serious adverse events are not different from placebo, so that strong and early efficacy is associated with safety and tolerability. Importantly, this includes minimal to no effect on SBP, reduced risk of hyperkalaemia, and favourable effects on renal outcomes, all of which complicate and limit management with neurohormonal antagonists and modulators. Guideline recommendations support the use of SGLT2 inhibitors (e.g. dapagliflozin, empagliflozin and sotagliflozin if concomitant T2DM) in addition to other GDMTs.[1] In the rare case of really naive patients, until recently, there was only evidence for the start of ACEi and beta-blockers together. With the presentation of EMPULSE trial results, we have also evidence for the safe and effective initiation of the SGLT2 inhibitor, empagliflozin, in patients with both *de-novo* acute HF or decompensated chronic HF, once stabilization is achieved (*Graphical Abstract*). Thus, data summarized in this review support the early 'upfront' use of dapagliflozin or empagliflozin, rather than sequencing behind the other drugs acting on neurohormonal mechanisms (*Table 3*). The option for a simultaneous or rapid sequence strategy for quadruple medical therapy in patients with HFrEF should be personalized depending on patient characteristics and it is reasonable to propose different sequences with, however, SGLT2 inhibitors as possible first-line therapy in most cases.[70] Based on tolerability, target dose may or may not be able to be achieved or in certain circumstances decreases in dosing may be required, to ensure each medication is well tolerated. Due to lack of experience, when quadruple therapy is simultaneously or rapidly introduced, physicians should be more cautious and a close monitoring of electrolytes, kidney function and blood pressure may be appropriate.

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