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Sodium-glucose co-transporter 2 inhibitors in heart failure: an updated evidence-based practical guidance for clinicians

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The sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce risks of clinical events in patients with heart failure (HF), with early and sustained benefits regardless of ejection fraction, diabetic status, and care setting. As part and parcel of the modern foundational HF therapy, clinicians should be familiar with these drugs, in order to implement their use and limit the potential adverse effects. We present an up-to-date review of current evidence and a practical guide for the prescription of SGLT2 inhibitors in patients with HF, highlighting important elements for patient selection, treatment initiation, dosing, and problem solving.

Introduction

Over the last 5 years, sodium-glucose co-transporter 2 (SGLT2) inhibitors have been tested in dedicated heart failure (HF) trials with outstanding positive results (*Figure 1*). A recent metanalysis including 21.947 participants from five HF trials showed that SGLT2 inhibitors significantly reduced the risk of composite cardiovascular death or hospitalization for HF (hazard ratio [HR] 0.77; 95% confidence interval [CI], 0.72–0.82), cardiovascular death (HR 0.87; 95% CI, 0.79–0.95), first hospitalization for HF (HR 0.72; 95% CI, 0.67–0.78), and all-cause mortality (HR 0.92; 95% CI, 0.86–0.99), agnostic of left ventricular ejection fraction (LVEF) and diabetic status.[1] In light of the impressive results from recent trials, clinical practice guidelines recommend the use of SGLT2 inhibitors in HF patients across all the spectrum of ejection fraction and in a wide range of care settings.[2,3]

We provide an up-to-date review of current evidence and a practical guide for the prescription of SGLT2 inhibitors in patients with HF, highlighting important elements for patient selection, treatment initiation, dosing, and anticipated adverse effects.

SGLT2 inhibitors in patients with chronic heart failure

The SGLT2 inhibitors are, together with the renin-angiotensin-system inhibitors (RASi), angiotensin receptor-neprilysin inhibitors (ARNi), β-blockers, and mineralocorticoid receptor antagonists (MRA), the evidence-based backbone therapy in HF patients with reduced ejection fraction (HFrEF).[3] Indeed, a recent metanalysis including 95.444 participants from 75 trials showed that the association of ARNi, β-blockers, MRA, and SGLT2 inhibitors was the best combination for reducing all-cause death (HR 0.39; 95% CI, 0.31–0.49) and the composite outcome of cardiovascular death or first hospitalization for HF (HR 0.36; 95% CI, 0.29–0.46).[10] Currently, there are two major outcome trials assessing the effect of SGLT2 inhibitors in patients with chronic stable HFrEF with or without diabetes: DAPA-HF[8] (assessing dapagliflozin) and EMPEROR-Reduced[11] (assessing empagliflozin) trials (*Figure 1*). Overall, in these two studies, SGLT2 inhibition with

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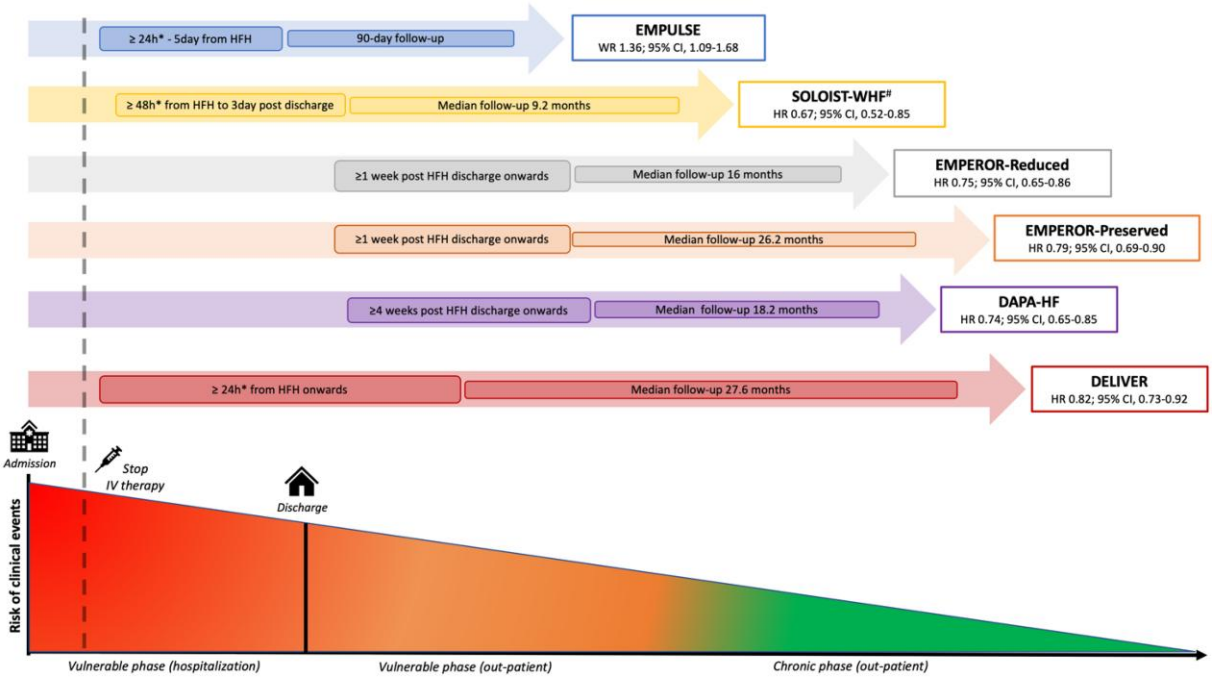

Figure 1 Timeline of SGLT2 inhibitor trials targeting patients with heart failure (HF). Large and narrow boxes show enrolment and follow-up period, respectively. The result for the primary outcome is reported below the trial name. Modified from Tromp *et al.*[4] Abbreviations: CHF, chronic heart failure; HR, hazard ratio; IV, intravenous; WR, win ratio. The primary endpoint was defined as (*A*) EMPULSE[4]—clinical benefit, defined as a hierarchical composite of death from any cause, number of HF events and time to first HF event, or a ≥5 point difference in change from baseline KCCQ score at 90 days, as assessed using a WR; (*B*) SOLOIST-WHF[5]—composite of deaths from cardiovascular causes, HF hospitalizations and urgent visits for HF (first and subsequent events); (*C*) EMPEROR-Reduced[6] and EMPEROR-Preserved[7]—composite of cardiovascular death or hospitalizations for HF; (*D*) DAPA-HF[8] and DELIVER[9]—composite of worsening HF (defined as either an unplanned hospitalization for HF or an urgent visit for HF) or cardiovascular death. *minimum time to randomization from the withdrawal of intravenous HF therapy in acute decompensated HF patients [EMPULSE—off inotropes for 24 h and no vasodilators or escalating diuretics for 6 h; SOLOIST-WHF—off IV inotropes or IV vasodilators (except for nitrates) for 48 h and having transitioned from IV to oral diuretic therapy; DELIVER—off intravenous HF therapy (including diuretics) for at least 24 h]. #enrolled only type 2 diabetic patients.

empagliflozin or dapagliflozin—when added to guideline-recommended therapy for HF—reduced all-cause and cardiovascular death, hospitalizations for HF, and serious adverse renal outcomes in patients with a broad spectrum of severity of HFrEF.[12] The benefit of empagliflozin and dapagliflozin on the primary endpoint of both trials—the combined risk of cardiovascular death or hospitalization for HF—was primarily driven by an approximately 30% relative reduction in the risk of hospitalization for HF. A benefit on hospitalizations for HF was observed whether the analysis was confined to first events or to all events (first and recurrent).[12] The modest size of the cardiovascular death benefit might explain why it is observed inconsistently in individual trials. Specifically, the relative reduction in cardiovascular death was 18% in DAPA-HF and 8% in EMPEROR-Reduced.[8,11]

In chronic stable HF patients with mildly reduced (HFmrEF) or preserved (HFpEF) ejection fraction, two large outcome trials evaluated the effect of SGLT2 inhibitors in patients with or without diabetes: DELIVER[9] (assessing dapagliflozin) and EMPEROR-Preserved[7] (assessing empagliflozin) trials (*Figure 1*). In both these studies, SGLT2 inhibition similarly and strongly reduced the combined risk of cardiovascular death or hospitalization for HF (primary endpoint) in a broad range of patients. Similar to HFrEF trials on SGLT2 inhibitors, risk reductions in the primary composite endpoint were driven by substantial treatment effects on hospitalizations for HF (average 26% relative risk reduction), with modest effects on cardiovascular death. The main finding of the DELIVER trial that distinguished it from the EMPEROR-Preserved trial (and also other neurohormonal blockade trials) was the benefit among patients with an LVEF of 60% or more and among those with an LVEF that had improved to more than 40% (namely HF with improved LVEF—HFimpEF). Indeed, DELIVER demonstrated no hint of therapeutic heterogeneity in the higher range of EF and in patients with HFimpEF, where dapagliflozin was as effective as it was at the lower end of the EF spectrum.[9]

Providing SGLT2 inhibition in HF patients not only reduces hard outcomes but also improves the quality of life. Indeed, a large metanalysis of five trials (DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF) showed that more participants in the SGLT2 inhibitor groups than in placebo groups had clinically meaningful improvements and fewer participants had clinically meaningful deterioration in each of the three KCCQ summary scores by 8 months, without evidence of heterogeneity by trial.[1]

SGLT2 inhibitors in patients with acute heart failure

Patients with acutely decompensated and acute heart failure (AHF) constitute a particularly vulnerable cohort since

they show a high post-discharge readmission and mortality rates,[13] together with limited evidence regarding outcome-modifying treatments.[3]

To date, SGLT2 inhibitors have been tested in AHF in two dedicated outcome trials: the SOLOIST-WHF and the EMPULSE trials (*Figure 1*). In the SOLOIST-WHF trial,[5] 1222 diabetic patients with an acute or recent episode of HF (49% of patients initiated therapy in-hospital and 51% within a median of 2 days after discharge) were randomized to the SGLT1/SGLT2 inhibitor sotagliflozin or placebo. After a median follow-up of 9 months, patients randomized to sotagliflozin showed a lower risk of total CV deaths, HF hospitalizations, or urgent HF visits than the placebo group (HR 0.67; 95% CI, 0.52–0.85).

Differently from SOLOIST-WHF trial, the EMPULSE trial[14] included AHF patients ($n = 530$) with and without diabetes, randomized in-hospital (median 3 days after admission) to either empagliflozin or placebo, and continuing treatment during the 90 days post-discharge (i.e. 'vulnerable phase'). EMPULSE used a hierarchical clinical composite endpoint of all-cause death, number of HF events (HF hospitalizations, urgent visits for HF, and unplanned outpatient visits), time to first HF event, and health-related quality of life (≥5-point difference in change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days) using the win ratio (WR), a method that considers the order and clinical importance of the events, with death as the most important event.[4] The results showed that more patients treated with empagliflozin had a clinical benefit compared with placebo (stratified WR 1.36; 95% CI, 1.09–1.68), both in the acute *de novo* and decompensated chronic HF group and regardless of EF and diabetic status. The SOLOIST-WHF and the EMPULSE trials showed that SGLT2 inhibitors are also safe in the AHF setting without excess risk compared with a placebo.[5,14] Recently, a small clinical trial (EMPAG-HF)[15] demonstrated that the early addition of empagliflozin (25 mg daily) to standard diuretic therapy increases urine output (25% increase over 5 days vs. placebo) without affecting renal function in patients hospitalized for AHF. A phase 3 trial evaluating dapagliflozin in HFrEF patients hospitalized for decompensated HF (DAPA ACT HF-TIMI 68; NCT04363697) is now ongoing and slated to report in 2023.[16]

SGLT2 inhibitors in patients with heart failure and chronic kidneys disease

Chronic kidney disease (CKD) is one of the most common comorbidities in HF and is a powerful predictor of morbidity and mortality.[17] SGLT2 inhibitors reduce the risk of serious adverse renal outcomes in type 2 diabetes,[18] but the renal effects of these drugs in patients with HF remain uncertain. Empagliflozin and dapagliflozin have been reported—after an initial decrement (early dip) in the estimated glomerular filtration rate (eGFR) due to secondary changes in intraglomerular pressures (i.e. restoration of tubular-glomerular feedback)[19]—to slow the rate of decline in renal function (*Table 1*).[7–9,11] However, changes in the eGFR slope may not predict the effects of these drugs on major renal outcomes. A significant reduction of serious adverse renal events (i.e. profound and sustained decreases in eGFR or renal-replacement therapy) was demonstrated only in the EMPEROR-Reduced trial (empagliflozin vs. placebo: HR 0.50, 95% CI, 0.32–0.77),[11] while in all other HF outcomes trials testing this hypothesis the effect on renal outcomes was modest (*Table 1*).

Pre-specified analysis of SGLT2 inhibitor trials demonstrated similar reductions in the primary outcome of cardiovascular death or hospitalization for HF across the spectrum of ejection fraction regardless of baseline eGFR and albuminuria.[20–23] DAPA-HF enrolled patients with eGFR ≥30 mL/min/1.73 m2,[8] while the eGFR threshold was ≥25 mL/min/1.73 m^2 in DELIVER[9] and ≥20 mL/min/1.73 m^2 in both EMPEROR-Reduced[11] and EMPEROR-Preserved[7] (in all trials eGFR was calculated by CKD-EPI formula). Based on the safety data from these studies, as well as on trials specifically targeting the CKD population (i.e. DAPA-CKD and EMPA-Kidney),[24,25] current labelling encourages treatment when eGFR is ≥25 mL/min/1.73 m^2 for dapagliflozin and ≥20 mL/min/1.73 m^2 for empagliflozin (*Figure 2*).

Timing for initiation of SGLT2 inhibitors

Clinical practice guidelines recommend (class IA) an early initiation of dapagliflozin and empagliflozin together with the classical foundational therapy (betablockers, RASi/ARNI, and MRA) in HFrEF patients in order to reduce mortality and HF hospitalizations.[2,3] For patients with HFmrEF and HFpEF, recent AHA guidelines recommend treatment with SGLT2 inhibitors in class IIA (the higher among the other outcome-modifying treatments),[2] basing their recommendation only on EMPEROR-Preserved data (but published data from DELIVER trial are anticipated to strengthen current treatment recommendations in this population). Both empagliflozin and dapagliflozin can be taken at the dose of 10 mg once daily, irrespective of food.

Recent evidence suggests that SGLT2 inhibition should be implemented as soon as possible. Indeed, in patients with HFrEF, a sustained statistically significant reduction in clinical events (primary endpoint) was observed by 28 days after randomization (HR 0.51; 95% CI, 0.28–0.94) in DAPA-HF,[26] and after only 12 days (HR 0.76; 95% CI, 0.67–0.87) in EMPEROR-Reduced.[6] Similarly, in HFmrEF/HFpEF patients, dapagliflozin reduced the risk for the primary endpoint within 2 weeks of treatment initiation (HR 0.45; 95% CI, 0.20–0.99),[27] while empagliflozin takes 18 days from randomization to induce a sustained reduction of clinical events (HR 0.41; 95% CI, 0.17–0.99).[28] Early SGLT2 inhibition is even more crucial in patients at higher risk, such as those with a recent episode of AHF. Indeed, in a post-hoc analysis of the DAPA-HF trial patients in closer proximity to a prior HF hospitalization experienced greater relative and absolute risk reductions of the composite of death and HF hospitalization when treated with dapagliflozin.[26]

Patients hospitalized for AHF without symptomatic hypotension or need for diuretic escalation, inotropic drugs or IV vasodilators within the previous 6 h may be eligible for SGLT2 inhibitors (*Figure 2*). In this setting, an early introduction (within the first 5 days) of these drugs has been demonstrated safe and effective in improving clinical outcomes.[29]

Taken together these results reinforce early sustained clinical benefits with SGLT2 inhibitors in patients with HF, underscoring the need for timely initiation of therapy. Moreover, SGLT2 inhibitors can be easily implemented in the complex HF therapy (single dose, low impact on blood

Table 1 Effect of SGLT2 inhibitors on the change of renal function and kidney outcomes

	Mean baseline eGFR (mL/min/1.73 m^2)	Mean absolute eGFR dip in the SGLT2 inhibitor group (mL/min/1.73 m^2)	Mean slope of eGFR change (mL/min/1.73 m^2 per year)	Between-groups difference in eGFR slope (95% CI)	Renal adverse outcomes
DAPA-HF	66	−4.2	Dapagliflozin, −1.09 vs. placebo, −2.85	1.73 (1.10; 2.37) mL/min/1.73 m^2 per year; $P<0.001$	HR 0.71 (95% CI, 0.44-1.16)[a]
EMPEROR-Reduced	62	−3.8	Empagliflozin, −0.55 vs. placebo, −2.28	1.73 (1.10; 2.37) mL/min/1.73 m^2 per year; $P<0.001$	HR 0.50 (95% CI, 0.32-0.77)[b]
EMPEROR-Preserved	61	–	Empagliflozin, −1.25 vs. placebo, −2.62	1.36 (1.06; 1.66) mL/min/1.73 m^2 per year; $P<0.001$	HR 0.95 (95% CI, 0.73-1.24)[b]
DELIVER	61	− 3.7	Dapagliflozin, 1.0 vs. placebo, −1.5	1.4 (1.0; 1.8) mL/min/1.73 m^2 per year; $P<0.001$	HR 1.08, (95% CI, 0.79-1.49)[a]
SOLOIST-WHF	50 (median)	–	Sotagliflozin, −0.34 vs. placebo, −0.18	−0.16 (−1.30; 0.98) mL/min/1.73 m^2 per year; $P=$ NS	–
EMPULSE	52 (median)	–	–	–	Not possible to fit a model due to low event rate[c]

The dash stands for not reported or not investigated data.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; NS, non-significant; HR, hazard ratio.

[a]Composite of sustained reduction of ≥50% in the eGFR for ≥28 days or sustained eGFR < 15 mL/min/1.73m^2 for ≥28 days or long-term dialysis treatment or renal transplantation or death from renal causes.

[b]Composite of ≥40% sustained decline eGFR or end-stage renal disease (defined as: 1) chronic dialysis; 2) renal transplantation; or 3) a sustained eGFR <15 mL/min/1.73 m^2 [for patients with baseline eGFR ≥30] or sustained eGFR < 10 mL/min/1.73m^2 [for patients with baseline eGFR <30 mL/min/1.73 m^2]).

[c]Occurrence of chronic dialysis or renal transplant or sustained reduction of ≥40% eGFR or sustained eGFR <15 mL/min/1.73 m^2 [for patients with baseline eGFR ≥30] or sustained eGFR < 10 mL/min/1.73 m^2 [for patients with baseline eGFR <30 mL/min/1.73 m^2]).

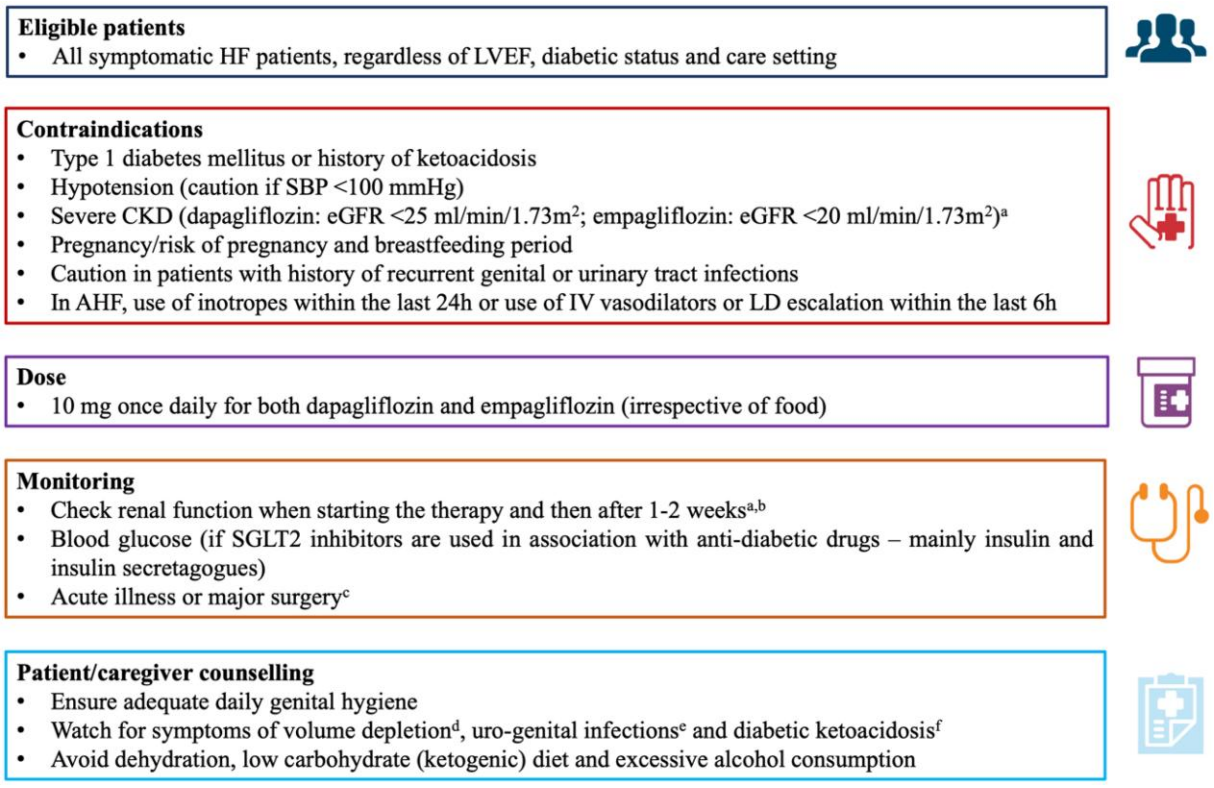

Figure 2 Practical guide to initiation of SGLT2 inhibitors in patients with heart failure. Abbreviations: AHF, acute heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IV, intravenous; LD, loop diuretics; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure. [a]eGFR calculated by CKD-EPI formula. [b]Initial decline in eGFR of 3–4 mL/min/1.73 m^2 or 10–15% from baseline (mainly in patients with initial low eGFR) is common/expected, does not reflex acute kidney injury and therapy should be continued unless major fall in eGFR. [c]FDA recommend to withhold SGLT2 inhibitors in case of prolonged fasting or 3 days before major surgery. The treatment can be restarted only once the patient's oral intake is restored and any other risk factors for ketoacidosis are resolved. [d]Symptoms of volume depletion are weakness, orthostatic hypotension, weight decrease >1 kg over 24 h or >2 kg in 1 week. [e]Symptoms of uro-genital infections are pain or burning on urination, redness, swelling, itching in the genital area, nasty-smelling vaginal or penile secretion, and fever. [f]Symptoms of diabetic ketoacidosis are excessive thirst, sweet-smelling breath, a change in urine or sweat odour, nausea, vomiting, abdominal pain, confusion, weakness, and fever. Note that it could also manifest with relatively normal glucose levels (euglycemic diabetic ketoacidosis).

pressure, no impact on heart rate) fitting almost all treatment strategies.[30] Finally, clinical inertia should be avoided considering the broad eligibility to these drugs,[31,32] and the consequent expected strong clinical benefit in the treated population.

Management of concomitant treatments

Heart failure treatment and its comorbidities are met with significant polypharmacy, which is associated in turn with an increased risk of drug-drug interactions and lower patient compliance.

Subgroup analyses of the DAPA-HF and EMPEROR-Reduce trials demonstrated the efficacy of dapagliflozin and empagliflozin regardless of concomitant MRA or ARNi use,[33-36] supporting the combined use of SGLT2 inhibitors with these drugs. Interestingly, SGLT2 inhibitors showed to reduce the incidence of clinically meaningful hyperkalaemia in HF patients, possibly enabling the concomitant use or up-titration of renin-angiotensin-aldosterone system inhibitors to target doses.[37]

For stable patients with HF, loop diuretics dose should be adapted on longitudinal evaluation of clinical signs and symptoms of congestion. None of the SGLT2 inhibitor trials had a routine protocolized adjustment of loop diuretics when initiating study therapy. In general, the prevalence of subjects who experienced volume depletion across the trials was low (i.e. ≈7% in DAPA-HF and ≈11% in EMPEROR-Reduced) and on average not significantly different compared with placebo.[8,11] Notably, in the DAPA-HF trial volume depletion was slightly more common with dapagliflozin than with placebo (8.0% vs. 4.9%) in the higher-dose diuretic group (≥40 mg of furosemide equivalent per day).[38] Accordingly, it is important to regularly assess the patient's volume status and correct hypovolemia-modulating loop diuretic doses as deemed appropriate. Patients and caregivers should be educated to recognize the warning symptoms of volume depletion (excessive reduction in body weight, low blood pressure, dizziness, etc.) (*Figure 2*).

SGLT2 inhibitors show a modest effect on blood pressure lowering across the published HF trials, with an average reduction of −1.32 (−2.19; −0.45) mmHg and −1.06 (−3.20; 1.08) mmHg in systolic and diastolic blood pressure, respectively.[39] Accordingly, SGLT2 inhibitors seem rather neutral from a blood pressure standpoint and their initiation should not raise any issue about other HF treatments impacting on blood pressure. Discontinuing these

drugs in patients with hypotension should probably be perceived as questionable, given that patients with low blood pressure are intrinsically more at risk of events and experience a strong benefit from SGLT2 inhibitors.[40]

Given the expected mild reduction in glycated haemoglobin (0.5–1.2%) and the low incidence of hypoglycaemia in patients with type 2 diabetes, the dose adjustment of glucose-lowering medications is usually not required. A notable exception is the concomitant therapy with insulin and insulin secretagogues—such as sulfonylureas—where the incidence of hypoglycaemic events slightly increases (although remaining rare). In these cases, a down-titration of insulin dose could be required after consulting a diabetologist.[41]

Adverse effects and problem solving

Although SGLT2i are generally well tolerated, several adverse effects may limit patient compliance and the overall effectiveness of the medication (*Figure 2*).

The most common major safety concern of SGLT2 inhibition is the increased risk of genital mycotic infections. The incidence of genital infections is between 5% and 15% and is four to five times more frequent in women—as mycotic vulvovaginitis—than in men—who usually develop a mycotic balanitis.[42] A history of genital infection, obesity, and premenopausal state are all risk factors for the development of mycotic infections during SGLT2 inhibitors treatment.[43] The incidence of this complication is the highest in the first few months of treatment followed by an attenuation in frequency. The infections are mostly symptomatic and typically respond to topical or single-dose oral antifungal therapy, usually without the need for interruption of SGLT2 inhibitors.[44] An adequate genital hygiene may reduce the incidence of this complication.

SGLT2 inhibitors should be withheld in diabetic patients during periods of anticipated or unexpected poor oral intake, including the preparation for elective surgeries, due to the increased risk of diabetic ketoacidosis. Although uncommon, it is a potentially life-threatening condition that could manifest at relatively lower glucose levels (euglycemic diabetic ketoacidosis) and with vague symptoms (i.e. polyuria, abdominal pain, nausea/vomiting, and confusion).[42] The U.S. Food and Drug Administration released multiple warnings on this issue, recommending to discontinue SGLT2 inhibitors 3 days (4 days for ertugliflozin) before scheduled surgery and restarting the treatment only once the patient's oral intake is restored and any other risk factors for ketoacidosis are resolved.[45] Patients and their caregivers should be also counselled to avoid very low carbohydrates, ketogenic diets, and excessive alcohol consumption.

Osmotic diuresis with SGLT2 inhibitors may lead to orthostatic hypotension (frequency of 1.2–1.5%), especially among the elderly and in the first weeks of treatment. Prevention of hypovolemia ensuring an adequate hydration and modulating diuretic treatment might reduce the occurrence of this event.[46]

Conclusions

Sodium-glucose co-transporter 2 inhibitors reduce the risk of clinical events in a broad range of patients with HF, irrespective of ejection fraction, diabetic status, or care setting. Their clinical benefit has been demonstrated early and sustained, without any major safety concern. Therefore, unless contraindicated, SGLT2 inhibitors should be rapidly initiated as part of the foundational therapy in all patients with HF. Clinicians should be confident in handling these drugs, in order to implement their use and limit the potential adverse effects.

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Data availability

DAS: Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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