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Review

Sodium Glucose Cotransporter Inhibition in Acute Heart Failure: An In-Depth Review

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ABSTRACT

Inhibitors of the sodium glucose cotransporters were initially developed for the treatment of type 2 diabetes but have since been shown to provide many benefits in heart failure, especially in heart failure with reduced ejection fraction (HFrEF). Already an established and foundational therapy for HFrEF, many uncertainties remain with respect to the use and initiation of SGLT2 inhibitors in hospitalized settings and in sicker individuals. Unfortunately, clear guidance or guidelines on this topic is lacking, but over the past few years, several trials have come out attempting to answer this question. This in-depth review aims at summarizing the current evidence not only as it pertains to the use of SGLT2 inhibitors in acute decompensated heart failure but also during acute myocardial infarction. From a brief examination of the history of SGLT2 inhibitor development to an appraisal on where along the spectrum of heart failure SGTL2 inhibition initiation should be considered, this review will also focus on potential advantages of starting SGLT2 inhibition in hospitals, the likely "sweet spot" in terms of timing of initiation, the diuretic augmentation effects of SGLT2 inhibition and how it compares with more traditional sequential blockade with thiazides, and, finally, an in-depth review of the safety surrounding the use of SGLT2 inhibitors in hospitalized patients.

RÉSUMÉ

Les inhibiteurs des cotransporteurs sodium-glucose (SGLT2) ont été initialement développés pour traiter le diabète de type 2, mais il a été démontré depuis qu'ils apportaient de nombreux bénéfices dans l'insuffisance cardiaque, en particulier dans l'insuffisance cardiaque avec fraction d'éjection réduite (ICFER). Les inhibiteurs du SGLT2 constituent déjà un traitement établi et fondamental de l'ICFER, mais de nombreuses incertitudes subsistent quant à l'utilisation et à l'instauration de ce traitement en milieu hospitalier et chez les personnes les plus malades. Malheureusement, il n'existe pas d'orientation ou de lignes directrices claires sur ce sujet, mais au cours des dernières années, plusieurs essais ont été réalisés pour tenter de répondre à cette question. Cette revue de littérature approfondie vise à résumer les évidences actuelles non seulement en ce qui concerne l'utilisation des inhibiteurs du SGLT2 dans l'insuffisance cardiaque aiguë décompensée, mais aussi au cours de l'infarctus aigu du myocarde. Depuis un bref examen de l'histoire du développement des inhibiteurs du SGLT2 jusqu'à une réflexion sur le moment adéquat dans la progression de l'insuffisance cardiaque pour commencer l'inhibition des SGLT2, cette revue se concentrera également sur les avantages potentiels de l'initiation de l'inhibition du SGLT2 en milieu hospitalier, le "moment idéal" en termes de temporalité de cette initiation, les effets d'augmentation diurétique de l'inhibition du SGLT2 et comment cette dernière se compare à un blocage séquentiel plus traditionnel avec les thiazides, et enfin, une revue approfondie de la sécurité entourant l'utilisation des inhibiteurs du SGLT2 chez les patients hospitalisés.

Heart failure (HF) represents a heterogeneous disease with various classification systems. Of these, great focus has been given to HF with reduced ejection fraction (HFrEF), defined as an ejection fraction less than 40%, given its increased mortality.[1,2] At present, foundational therapy for HFrEF consists of agents that antagonize pathologic remodelling of the left ventricle and help alleviate symptoms. This is known as guideline directed medical therapy (GDMT), and in HFrEF typically consists of quadruple therapy with a combination of an angiotensin converting enzyme inhibitor/

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angiotensin receptor blocker (ACEI/ARB) or angiotensin receptor neprilysin inhibitor (ARNI), a beta blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium glucose cotransporter-2 inhibitor (SGLT2i).[3] Despite GDMT having been shown to significantly reduce mortality and HF rehospitalization by up to 70% to 80%, including evidence for its rapid uptitration, a significant proportion of individuals with HFrEF are either not on all appropriate medications or are not optimally dosed (between 30% and 60%), thus conferring an excess mortality risk.[4-8] Hospitalization therefore presents an ideal time to initiate GDMT and potentially reduce a high morbidity/mortality curve.

The spectrum of HF extends to the acutely decompensated stage, commonly termed acute heart failure (AHF).[1,2,9] In the latter situation, the Forrester classification is a frequently employed clinical staging system that has been shown to carry prognostic information and is included in guidelines.[10,11] Traditionally, this would classify an individual based on symptoms and signs of congestion (hypervolemic, or "wet" vs euvolemic, or "dry") and signs of hypoperfusion (low cardiac output, or "cold" vs good cardiac output, or "warm"). Amalgamating the possible permutations of these binary classifications creates 4 groups (warm and dry, warm and wet, cold and dry, and cold and wet), which can be used to create a spectrum of disease for HF (Fig. 1). Prognosis is better the more rightward and upward an individual falls within the spectrum depicted on Figure 1, with a leftward shift increasing the risk of end-organ dysfunction (hypervolemic spectrum) and a downward shift increasing the risk of developing low cardiac output syndrome (LCOS). LCOS is a form a cardiogenic shock that can be either compensated or decompensated, with the latter portending a poorer prognosis and requiring immediate support. At which point an individual falls on this spectrum likely determines the safety of GDMT initiation, including an SGLT2i start.

SGLT Inhibition: A Review

SGLT inhibition was originally borne from research on the compound phlorizin, initially isolated in 1835 by French chemists from the bark of apple trees. Although a nonselective inhibitor of SGLT1 and SGLT2, the effect of increased glycosuria on insulin sensitivity quickly became apparent as a therapeutic target for diabetes.[12]

By the time SGLT2is were ready for trials, the Food and Drug Agency (FDA) had already issued guidance (2008) that mandated that all new diabetic drugs required demonstration of cardiovascular (CV) safety, and the European Medicines Agency followed suit in 2012.[13,14] Subsequently, several pivotal CV safety trials came out showing not only safety but also major CV benefits with reduction in the composite of myocardial infarction (MI), stroke, and CV death.[15-17] Furthermore, a meta-analysis of the **Empa**gliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus-**R**emoving **E**xcess **G**lucose (EMPA-REG), **Can**agliflozin and Cardio**vas**cular and Renal Events in Type 2 Diabetes (CANVAS), and **D**apagliflozin **E**ffect on Cardiovascu**lar** **E**vents (DECLARE-TIMI 58) trials found a significant reduction in HF hospitalization (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.71-0.84; $P < 0.0001$) in patients with or without a history of cardiovascular disease.[18] This finding paved the way for further research in HF cohorts that showed similar benefits; however, those were in a chronic or outpatient setting.[19-21] Purported mechanisms include a direct diuretic effect and potential salutary effects on myocardial mechanisms and pleiotropic mechanisms at the cellular and tissue level.[22] In addition to these positive findings, SGLT2is have also been found to reduce the rate of progression of chronic kidney disease by 37% and reduce the risk of acute kidney injury by 23%, both in individuals with and without diabetes.[23] Moreover, they reduce the risk of severe hyperkalemia ($\geq$ 6 mmol/L) without increasing the risk of hypokalemia, even in those at higher risk of developing hyperkalemia, such as taking inhibitors of the renin-angiotensin-aldosterone system (ACEIs, ARBs, and MRAs).[24]

Despite their impressive benefits, SGLT2is are not without risks. The most feared complication is that of diabetic ketoacidosis (DKA), commonly with euglycemia. Randomized controlled trial (RCT) and observational data indicate a relative rarity to this complication, with a rate ranging between 0.6 to 2.2 events per 1000 person-years, but an approximate 2-fold to 3-fold higher risk than other antihyperglycemic agents.[25,26] There may be a molecule-specific effect, with the lowest risk seen with dapagliflozin (HR, 1.86; CI, 1.11-3.10), and highest with canagliflozin (HR, 3.58; CI, 2.13-6.03).[26,27] Common risk factors for the development of DKA with SGLT2is have been identified as acute illness (infection/sepsis, stroke, pulmonary embolism, MI), nutrition (fasting status; low carbohydrate and ketogenic diets), and being in the preoperative and postoperative setting, with a multifactorial mechanism thought to be from an imbalance in glucagon and insulin leading to enhanced lipolysis, ketogenesis, and ketone body reabsorption.[28,29] Finally, other complications seen with SGLT2is are increased risks of volume depletion (risk ratio [RR], 1.29; 95% CI, 1.13-1.48) and increased risks of mycotic genital infections (RR, 2.47-3.89) but not urinary tract infections (UTIs).[30-32]

Potential Advantages of Starting SGLT2is in Hospitals

Initiating an SGLT2i during hospitalization has 2 potential advantages. The first is the hope that earlier initiation or a predischarge prescription of a proven HFrEF medication would translate to greater reduction in HF outcomes after the hospitalization. The second potential benefit would be diuretic augmentation, which could translate to earlier achievement of euvolemia or simplification of diuretic regimens.

Evidence for improved HF outcomes with SGLT2i initiation in the hospitalized setting was found in a post hoc analysis of a single-center, prospective, observational HF cohort registry in Japan (SAKURA HF).[33] This study found that SGLT2i initiation during hospitalization was associated with a significant decrease in a composite of all-cause death or HF rehospitalization (HR, 0.62; 95% CI, 0.44-0.86; $P = 0.004$). Furthermore, SGLT2is had the lowest HRs of all GDMT medications for developing the composite outcome, an effect that persisted across all left ventricular ejection fraction (LVEF) group, and a subanalysis of early vs late initiation (using 3 days as the cut off) found that earlier initiation was associated with a lower risk of composite events (HR, 0.50; 95% CI, 0.26-0.96; $P = 0.037$). So then, what else does the body of literature suggest with regard to the initiation of SGLT2i in hospitalized individuals?

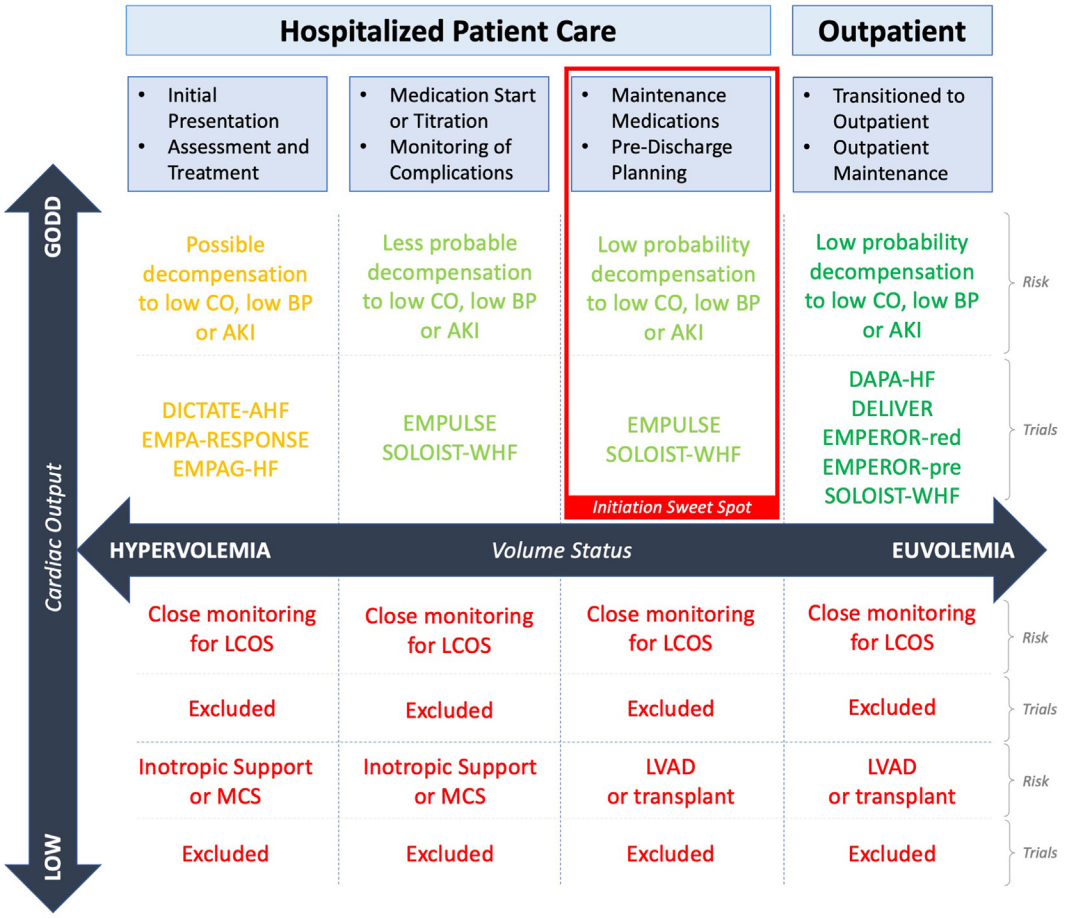

Figure 1. Heart failure spectrum of disease, timing of management, and recommendations for initiation of therapy informed by clinical trials. **Dark green** denotes a strong recommendation, **light green** a moderate recommendation, **orange** for cautionary use, and **red** a strong recommendation against use; refer to Table 2 for exact specifications. The "initiation sweet spot" denotes the likely ideal time for initiation of SGLT2i, at which risks/harms are likely at their lowest without significantly compromising benefits. AKI, acute kidney injury; BP, blood pressure; CO, cardiac output; LVAD, left ventricular assist device; LCOS, low cardiac output syndrome; MCS, mechanical circulatory support; SGLTi, sodium-glucose cotransporter-2 inhibitor.

Although there has been the development of a practical guideline for SGLT2i initiation in AHF, more trials have emerged since then.[34] The aim of this review is to synthesize the available data on SGLT inhibitors to guide clinicians managing patients hospitalized with AHF and provide guidance on the timing of SGLT2i initiation. A comprehensive literature review was performed and is up to date as per November 20, 2024, using the following search terms in PubMed and Google Scholar: "SGLT," "SGLT2," "sodium glucose cotransporter," "empagliflozin," "dapagliflozin," "sotagliflozin," "acute," "heart failure," and "randomized" (Supplemental Appendix S1: Search Terms). Study quality and risk of bias was assessed using the Cochrane Risk of Bias 2 tool, with most studies being at low risk of bias; the results are included in Supplemental Appendix S2: RCT Study Quality/Risk of Bias and Table S1.[35] Table 1 and Table S2 (Supplemental Appendix S3, Supplemental Table S2) summarize the most important and high-quality trials published in the past 5 years.

SGLT2is in AHF

The **So**tagli**flo**zin in Patients With Diabetes and **W**orsening **H**eart **F**ailure (SOLOIST-WHF) trial is the largest study of SGLTis in AHF.[36] In this trial, 1222 patients with diabetes were randomized to sotagliflozin (a combined SGLT1/2 inhibitor [from here only to be referred as SGLT2i for simplicity]) after clinical stability was achieved. This was defined as a transition to oral from intravenous diuresis and being off oxygen. Fifty-one percent of patients received the first dose a median of 2 days after discharge. The study was marred by loss of funding because of COVID-19, resulting in a reduction in power to test the original primary endpoint, and a change of the original primary endpoint to a composite of total number of deaths from CV causes, as well as hospitalizations and urgent care visits for HF. Despite this, SOLOIST-WHF found statistically significant improvements with the addition of sotagliflozin in the primary outcome (HR, 0.67; 95% CI, 0.52-0.85; $P = 0.0009$) and multiple relevant secondary outcomes including total CV death and hospitalization (60 vs 86 events per 100 patient-years; $P = 0.003$), first CV death and hospitalization (33% vs 48%; $P = 0.003$), but not CV death over a median follow-up of 9 months. From a safety perspective, there was a slight nonsignificant increase in hypotension, hypoglycemia, and diarrhea in the sotagliflozin group, likely reflecting the

Table 1. Larger randomized controlled trials of SGLT inhibition in acute heart failure

Trial	N	Key inclusion and exclusion criteria	Outcomes
SOLOIST-WHF	1222	• Signs and symptoms heart failure treated with IV diuretic therapy, not previously on an SGLT inhibitor • Has T2DM • Off oxygen > 24 h • SBP >100 mm Hg • Transitioned to oral diuretics • eGFR >30 mL/min/1.73 m^2 • No inotropes > 2 d • No IV vasodilators > 2 d • No end stage heart failure • No recent ACS, CVA, or DKA (3 m) • No severe valvulopathy/HOCM • No T1DM	Primary—Composite of: • Deaths from CV causes • Hospitalizations for HF • Urgent care visits for HF HR, 0.67 (95% CI, 0.52-0.85), $P <$ 0.001 Secondary (hierarchical analysis): Only significant for • Hospitalizations and urgent visits for HF, HR, 0.64 (0.49-0.83), $P < 0.0001$ Not significant for • Deaths from CV causes • Deaths from any causes • Change in KCCQ • Change in GFR
EMPULSE	530	• Hospitalization for heart failure with a minimum of 40 mg IV furosemide dose (or equivalent IV dose of torsemide/bumetanide) • eGFR >20 • SBP >100 • No recent ACS or CVA (3 m) • No hypotension > 6 h • No increase IV diuretics > 6 h • No IV vasodilators > 6 h • No inotropes > 24 h • No history of DKA, • No T1DM	Primary—Hierarchical composite of • Death from any cause, • Number of HF events and time to first HF event, • ≥ 5-point difference from baseline in the KCCQ-TSS Stratified win ratio 1.36 (95% CI, 1.09-1.68), $P = 0.0054$ • Wins for death: 7.2% vs 4.0% • Wins for HF events: 10.6% vs 7.7% • Wins for KCCQ-TSS: 35.9% vs 27.5% • Ties: 6.4% Secondary: Greater diuretic response, greater decrease in NT-proBNP

ACS, acute coronary syndrome; CI, confidence interval, CV, cardiovascular; CVA, cerebrovascular accident; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; HR, hazard ratio; IV, intravenous; KCCC-TSS, Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

presence of SGLT1 receptors within the intestine. Otherwise, adverse events were similar between both groups (Supplemental Appendix S3: Supplemental Table S3).

The **Emp**agliflozin in Patients Hospitalized for Acute Heart Failure (EMPULSE) trial randomized 530 patients to empagliflozin 10 mg once daily a median of 3 days after hospital admission and found a meaningful improvement in the win ratio of a hierarchical composite of death, number of HF events, time to first HF event, and greater than 5-point change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) from baseline to 90 days.[37] The win ratio was mostly driven by a greater than 5-point change in the KCCQ-TSS.[38] The win ratio did not change meaningfully when accounting for ties (win ratio of 1.36 vs win odds of 1.33).[39] This clinical benefit was seen in both de novo HF and decompensated chronic HF. Despite being mostly driven by a change in KCCQ-TSS, patients on empagliflozin also won with regard to time to death (7.2% vs 4.0% wins) and HF events (10.6% vs 7.7% wins) but results were largely similar for time to first HF event (0.2% vs 0.6% wins). Furthermore, total deaths were fewer with empagliflozin (4.2% vs 8.3%) as were the total number of HF events (36 vs 52), the latter coming from 28 patients on empagliflozin and 39 patients on placebo. This important clinical data are unfortunately not well captured by the win ratio, and a secondary composite outcome of the incidence of cardiovascular death or HF events was no different between groups (HR, 0.69; 95% CI, 0.45-1.08). A previous paper thoroughly explains and summarizes the interpretation of the win ratio employed in EMPULSE.[40] With respect to safety, there were no signals of harm from SGLT2i therapy (Supplemental Appendix S3: Supplemental Table S3). A post hoc analysis of EMPULSE also found that those randomized later after hospital admission (defined as 3 to 5 days) experienced greater clinical benefit with empagliflozin than those randomized earlier (1 to 2 days).[41]

The OASIS-HF trial was a 2-centre, nonrandomized, open-label, prospective observational cohort study performed in Japan and aimed at evaluating the effectiveness of SGLT2is (10 mg of empagliflozin or dapagliflozin, a median of 1.8 days after admission) in older adults hospitalized with AHF.[42] Three hundred and sixty patients were included in a per-protocol analysis (198 in the conventional group and 163 in the SGLT2i group) with a median follow-up of 24.9 months. The trial included individuals aged 75 years and over, with and without diabetes, and across the spectrum of ejection fraction (EF) and excluded patients who required cardiac surgery or revascularization, had end-stage kidney disease, cirrhosis, advanced cancer, or advanced dementia. Patients who died during the index admission were excluded

from the final analysis (42 individuals), as were those who developed adverse events (8 of whom had UTIs and 2 who had hypotension: both events only occurring in the SGLT2i arm). It is also unclear if the participants were on SGLT2i before their index admission (not reported), which is relevant, given an approximate 12-hour half-life for both dapagliflozin and empagliflozin. Notwithstanding these shortcomings, the trial found a significant decrease in the primary composite outcome of cardiovascular death or rehospitalization caused by worsening HF (HR, 0.61; 95% CI, 0.41-0.91: $P = 0.016$), mostly driven by the latter. Of note, many individuals were on tolvaptan therapy (although significantly fewer in the SGLT2i group [49% vs 61%]), and traditional GDMT was extended to include most individuals irrespective of EF (ie, approximately 55% of individuals with EF $\geq$ 40% in both groups were on ACEI/ARB/angiotensin receptor-neprilysin inhibitor [ARNIs], beta blockers, and MRAs). Other than the hypotension and UTIs in the SGLT2i arm mentioned here, the trial did not report adverse events.

A recent meta-analysis, including trials of SGLT2i use in AHF, excluding OASIS-HF, and incorporating 9 randomized controlled trials and 4 observational studies, showed a significant benefit in all-cause mortality (RR, 0.82; 95% CI, 0.70-0.96; $P = 0.01$), readmission rates (RR, 0.85; 95% CI, 0.74-0.98;$P = 0.02$), and HF exacerbation events post-discharge (RR, 0.69; 95% CI, 0.50-0.95; $P = 0.02$).[43] For the latter, this reduction increased from 31% to 43% when only using studies with in-hospital initiation of SGLT2i (RR, 0.57; 95% CI, 0.39-0.81; $P = 0.002$), suggesting initiation SGLT2i before discharge appears to have a larger overall benefit. There were no differences in adverse events.

Despite this evidence, several questions remain: what is the optimal timing for initiation of SGLT2i therapy in AHF: Is earlier better? What is the overall diuretic effect of SGLT2i in AHF? Is the use of SGLT2i in AHF from acute MI beneficial and safe? Is there any evidence for the use of SGTL2i specifically for AHF in stress cardiomyopathy? Unfortunately, the only data for the latter come from a case report in which canagliflozin was thought to provoke stress cardiomyopathy from potentiating euglycemic DKA, leading to discontinuation of the drug.[44] We will attempt to answer the remaining important questions in the following sections.

SGLT2i in AHF: The First 24 Hours

The first 24 hours of care in individuals presenting with AHF is unfortunately lacking robust data for care, as only small RCTs with surrogate outcomes thus far have investigated SGLT2i use in this timeframe. The Efficacy and Safety of Dapagliflozin in Acute Heart Failure (DICTATE-**AHF**) randomized 240 patients with or without type 2 diabetes to dapagliflozin 10 mg daily or usual care within 24 hours of presentation to the emergency department until day 5 or hospital discharge.[45] This was in the context of an aggressive intravenous loop diuretic regimen aiming for 3 to 5 liters of urine output per day in combination with a sodium and fluid restricted diet (2 g/d and 2L/d, respectively). A primary outcome of diuretic efficiency failed to show statistical significance (odds ratio [OR], 0.65; 95% CI, 0.41-1.02) but did show a significantly lower median cumulative dose of loop diuretic (560 mg, interquartile range [IQR]: 260-1150 mg vs 800 mg, IQR: 380-1715 mg; $P = 0.006$) with less dose uptitration in the dapagliflozin group. Secondary outcomes also showed increased natriuresis and diuresis at 24 hours in the dapagliflozin group.

The Effects of **Empa**glifozin on Clinical Outcomes in Patients With **A**cute Decompensated **H**eart **F**ailure (EMPA-RESPONSE-AHF) randomized 80 patients within 24 hours to empagliflozin 10 mg daily or placebo and noted no difference in a primary outcome composite of a visual analogue dyspnea score, diuretic response, N-terminal pro-B-type natriuretic peptide (NT-pro BNP), and length of stay.[46] There was a signal toward an improved burden of HF/death at 60 days, but these results were part of a secondary outcome analysis and must be considered in the context of the small study size, both of which are prone to statistical errors (ie, type 2 errors) and thus are significant limiters to the conclusions being able to be drawn from this trial.

Empagliflozin in Acute Decompensated **H**eart **F**ailure (EMPAG-HF) randomized 60 patients with acute decompensated HF within 12 hours of hospitalization to empagliflozin 25 mg orally daily or placebo and noted a 25% increase in cumulative urine output over a 5-day period.[47] This improvement was without a concomitant increase in markers of kidney injury and a signal toward lower uric acid levels in the empagliflozin group (the study did not comment on specific gout events, however).

Currently pending is the Randomized, Double-Blind, Placebo-Controlled, Multicenter Pilot Study on the Effects of **Empa**gloflozin on Clinical Outcomes in Patients With **A**cute Decompensated **H**eart **F**ailure (EMPA-AHF), a trial in Japan that will look at the use of empagliflozin vs placebo within 12 hours of admission in those admitted with AHF with a urine output of $<$ 300 cc within 2 hours after an adequate dose of furosemide.[48] It will compare death within 90 days, HF rehospitalization within 90 days, worsening HF during hospitalization, and urine output within 48 hours after treatment initiation using the win ratio.

In summary, small studies have suggested that patients with AHF may have SGLT2i (empagliflozin or dapagliflozin) added to their diuretic regimen in the first 24 hours for an increase in cumulative urine output. Unfortunately, there are no meta-analyses of these trials, and none of these studies used robust endpoints such as death or HF rehospitalization; therefore, use in this population should be exercised with caution. Although there were no differences in adverse events, this is likely because of a combination of careful patient selection and low patient numbers. As a side note, there may be an additional role for the use of SGLT2i patients with elevated serum uric acid levels and recurrent gouty attacks, as these agents have been shown to reduce serum uric acid levels and may confer a lower risk of gout compared with other diuretics: a finding also seen in EMPULSE and **Emp**agliflozin Outcome Trial in Patients With Chronic Heart Failure and a **Reduced** Ejection Fraction (EMPEROR-Reduced).[20,37] A recent subanalysis of EMPEROR-Reduced showed that therapy with SGLT2i reduced serum uric acid within 4 weeks, and levels remained lower than placebo.[49] Furthermore, despite a well-described increased risk of triggering a gout flare with rapid uric acid lowering, this analysis also found a 38% reduction in acute gout, gouty arthritis, or initiation of other urate-lowering therapy in the empagliflozin arm.[49,50]

SGLT2i: Diuretic Augmentation and Diuretic Resistance

Because of their mechanism of action in blocking proximal glucose and associated sodium reabsorption, it is unsurprising that the addition of SGLT2i to loop diuretics increases diuresis. Another purported and likely more potent/important mechanism of SGLT2i-mediated diuresis is via the inhibition of the sodium-hydrogen exchanger isoform 3 (NHE3) in the proximal convoluted tubule.[51] In a prespecified subanalysis of the EMPULSE trial, the use of empagliflozin was associated with a greater amount of weight loss at days 15 (−1.97 kg; 95% CI, −2.86 to −1.08; $P < 0.0001$), 30 (−1.74 kg; 95% CI, −2.73 to −0.74; $P = 0.0007$), and 90 (−1.53 kg; 95% CI, −2.75 to −0.31; $P = 0.0137$), although the magnitude of difference did appear to contract over time.[52] The earlier, more immediate differences in weight loss likely reflect increased diuresis, and as the doses of loop diuretics were similar between both groups, this suggests an increase in diuresis in the SGLT2i group. Furthermore, the **Emp**agliflozin Outcome Trial in Patients With Chronic Heart Failure and **Preserved** Ejection Fraction (EMPEROR-Preserved) and EMPEROR-Reduced trials showed that the use of empagliflozin resulted in less outpatient uptitration of loop diuretics and greater weight loss, both of which can serve as a surrogate marker of increased diuresis.[20,21] Finally, in a prespecified subanalysis of the **D**apagliflozin **E**valuation to Improve the **Liv**es of Patients With Preserved **E**jection F**r**action Heart Failure (DELIVER) trial, there was less need for the initiation of a maintenance loop diuretic, although it did not reduce discontinuation of those already on one.[53]

Smaller trials have also shown increased urine output and weight loss, lower doses of maintenance loop diuretics, and the need for less uptitration of loop diuretic regimens with the use of SGLT2is.[46,47,54] Interestingly, a recent meta-analysis by Hou and colleagues[43] also showed a total lower cumulative furosemide dose; however, no differences in diuretic response (loss in weight in kg per 40 mg furosemide equivalents) were shown and was favoured against SGLT2is for increased diuresis (less cumulative urine output). A review by Packer and Butler[51] on the similarities between SGLT2i and acetazolamide provides insights into the potential reasons why this may be so, making the argument that neither these medications on their own produce a meaningful or sustained diuresis, given the marked upregulation of counterregulatory mechanisms promoting more distal sodium reabsorption. There are no comparisons between acetazolamide and SGLT2is with respect to their diuretic augmentation potential, and the aforementioned paper provides a good review and critique on use of these medications for diuretic purposes that will not be revisited here.[51]

A not uncommon circumstance in HF is the concept of diuretic resistance. Although lacking a formal quantitative definition, a qualitative description of this condition is that of an inadequate amount of decongestion/diuresis despite an adequate diuretic regimen, and it is associated with increased mortality.[55-58] Given its clinical importance, there has also been an attempt at creating an algorithm to predict those who are at risk of developing diuretic resistance using machine- learning methods.[59] A common strategy for diuretic resistance is adding a thiazide-like diuretic such as metolazone. Could the addition of SGLT2i improve the treatment of patients with diuretic resistance?

The only RCT to look at this was Sodium Glucose Cotransporter-2 Inhibitor **Dapa**gliflozin vs Thiazide Diuretic in Patients With Heart Failure and Diuretic **Resist**ance (DAPA-RESIST), a randomized, multicentre, open-label trial that randomized 61 individuals with diuretic resistance to receive either dapagliflozin 10 mg daily or metolazone 5 to 10 mg daily.[58] Diuretic resistance was defined as a decrease in weight < 1 kg or negative fluid balance < 1 L over the previous 24 hours with ongoing symptoms despite a cumulative dose of ≥ 160 mg intravenous furosemide over that preceding 24 hours. There was no significant difference in the primary outcome of weight change at 96 hours; however, there was a trend for higher weight loss in the metolazone group. There was also a lower mean cumulative (704 mg vs 977 mg; $P = 0.02$) and corresponding mean daily doses (185 mg vs 255 mg) of furosemide with the use of metolazone compared with dapagliflozin, respectively. More importantly, however, was the lack of mortality difference at 90 days and a similar safety profile between both drugs. There was a signal toward more hypotension and volume depletion with metolazone, likely reflecting its more potent diuretic augmenting effect. Finally, there were no clinically meaningful or significant differences in electrolyte derangements, although it is difficult to draw conclusions for this given the very small sample size of this trial.

DICTATE-AHF was not specifically targeted at patients with diuretic resistance, but the study methods specified the addition of thiazide like diuretics when daily intravenous loop diuretic dose reached 960 mg/day of intravenous furosemide, which would be considered well above the definition of diuretic resistance, and much higher than the 160 mg/day of intravenous furosemide used in DAPA-RESIST.[45,60] This makes any interpretation difficult and likely not applicable to clinical practice.

In summary, SGLT2is may augment diuresis and typically result in a lower cumulative dose of diuretic to achieve a similar amount of diuresis. Still, SGLT2is do not appear to be superior to the addition of metolazone when decongesting patients with diuretic resistance, although they may carry a favourable safety profile with regards to hypotension and electrolyte derangements. There are no direct comparisons between SGLT2i and acetazolamide for decongestion.

SGLT2i in AHF: Is it Safe?

A key component of the larger RCTs included in this review are their inclusion and exclusion criteria. SOLOIST-WHF required individuals to have type 2 diabetes (patients with type 1 diabetes were excluded), be off oxygen for > 24 hours, have a systolic blood pressure > 100 mm Hg, an estimated glomerular filtration rate (eGFR) of > 30 mL/min/1.73 m^2, be off inotropes and vasopressors for at least 2 days, not be considered to have end-stage heart failure (ie, no LCOS), be without severe valvulopathy or hypertrophic obstructive cardiomyopathy, not have had an acute coronary syndrome (ACS), stroke, or DKA within the last 3 months, and be transitioned to oral diuretics.[36] EMPULSE, on the other hand, required individuals to have a systolic blood pressure > 100 mm Hg and be without hypotension for at

least 6 hours, an eGFR of > 20 mL/min/1.73 m^2, not requiring increases in intravenous diuretic doses or intravenous vasodilators for at least 6 hours, be off inotropes for at least 24 hours, not have had a recent ACS or stroke in the last 3 months, and be without type 1 diabetes or have any history of DKA.[37] A summary of exclusion criteria can be found in Table 1.

Expanding on the literature provided earlier in the text, SLGT2is have been shown to be safe if used in carefully selected individuals with AHF. The rates of adverse events in the RCTs reviewed herein were quite low and, more importantly, there were no significant differences in the rate of hypotension (5.4% vs 5.6%; $P = 0.85$), acute kidney injury (5.5% vs 6.6%; $P = 0.212$), DKA (0.22% vs 0.36%; $P = 0.481$), hypoglycemia (3.2% vs 2.5%; $P = 0.288$), or UTI (3.9% vs 5.1%; $P = 0.187$) between SGLT2i and placebo, respectively (Supplemental Appendix S3: Supplemental Table S3).[36,37,45-47,60,61] The safety of SGLT2i use in AHF is also further supported by a meta-analysis showing no increase in adverse events compared with placebo.[43]

As such, there is no robust evidence to support SGLT2i use in cardiogenic shock/LCOS, and so SGLT2i therapy should be avoided in this very sick population, with therapy focused on inotropic support and optimizing hemodynamics, using traditional means until dedicated research emerges in this field.

SGLT2I: Initiation During Admission of Acute MI

Acute MI frequently results in AHF.[62] Acute MI/ACS was an exclusion criterion in all the trials reviewed in this paper so far. To study this patient population, the **Dapa**gliflozin Effects in Patients Without Diabetes With **M**yocardial **I**nfarction (DAPA-MI) and Effect of **Empa**gliflozin on Hospitalization for Heart Failure and Mortality in Patients With Acute **M**yocardial **I**nfarction (EMPACT-MI) trials were undertaken.[61,62] DAPA-MI randomized 4017 stable individuals without previous diabetes or chronic HF within 10 days after acute MI to dapagliflozin vs placebo and found better cardiometabolic outcomes (less diagnoses of new type 2 diabetes, more weight loss; HR, 0.53 [95% CI, 0.36-0.77] and −1.65kg [95% CI, −2.12 to −1.18], respectively) compared with placebo, with no difference in cardiovascular outcomes over a 2-year follow-up (major adverse cardiovascular events [MACE] 3.4% vs 3.6%, CV death/HF hospitalization/MI 4.1% vs 4.3%, and all-cause mortality 2.0% vs 1.7%, all $P > 0.05$).[63] The authors employed a win ratio with a hierarchical composite of death, HF hospitalization, nonfatal MI, atrial fibrillation/flutter event, new type 2 diabetes, New York Heart Association class, and weight decrease of ≥ 5% as a primary outcome. There was no difference in adverse events between the dapagliflozin and placebo group (hypotension, DKA, etc).

The EMPACT-MI trial randomized 6522 stable patients with ACS at risk for AHF to empagliflozin vs placebo in acute MI within 14 days of admission. The trial found no difference in the composite of first hospitalization of HF or death from any cause during a median follow-up of 17.9 months.[64] There was a significant trend for lower first hospitalization for HF (HR, 0.77; 95% CI, 0.60-0.98). Serious adverse events were rare and similar between both groups.

Table 2. Summary of patient characteristics for initiation SGLT inhibitor in AHF

Eligible
- Stable patients with AHF (cause by reduced or preserved ejection fraction)
  - Stable dose of diuretics (preferably transitioned to oral diuretics)
  - Preferably off any intravenous support (vasopressors, vasodilators, inotropes) for at least 24 hours

Caution
- Hypovolemia
- History of amputation or in the presence of severe peripheral artery disease
- History of severe urinary tract infections
- Fasting
- Intolerance to negative inotropy such as beta blockers
- Acute kidney injury
- Unexplained anion gap
- ACS/MI*

Not advised
- History of diabetic ketoacidosis
- Type 1 diabetes
- eGFR < 20-25 mL/min/1.73 m^2
- Cardiogenic shock/LCOS
- IV inotropic/vasopressor support
- Severe hypotension (< 100 mm Hg systolic)
- Stroke 90 days before initiation.

Monitoring during hospitalization, and 1 to 2 weeks after discharge.
- Blood pressure
- Creatinine
- Volume status
- Nutrition status

Patient guidance
- Holding SGLT inhibitor if limited oral intake because of acute illness or upcoming surgery
- Fastidious genital hygiene

ACS, acute coronary syndrome; AHF, acute heart failure; AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; IV, intravenous; LCOS, low cardiac output syndrome; MI, myocardial infarction; SGLT, sodium-glucose cotransporter-2.

*Data from DAPA-MI and EMPACT-MI suggest a relative safety of SGLT2I initiation in AMI, so this was downgraded to "Caution" as opposed to "Exclusion," as long as proper inclusion criteria are followed.[61,62]

Prespecified subanalyses of that trial also showed that total hospitalizations for HF were significantly lower in the empagliflozin group (RR, 0.67; 95% CI, 0.51-0.89; $P = 0.006$), and consistent across all subgroups analyzed (including age less or greater than 65 years; ST-elevation myocardial infarction (STEMI) vs non−ST-elevated ACS (NSTEACS), with or without type 2 diabetes, among others).[65] A higher proportion of patients (57%) within EMPACT-MI had symptoms of congestion at study onset, likely representing a higher HF risk population than DAPA-MI.[61,62] As with DAPA-MI, there was no difference in adverse events.

Finally, a meta-analysis of 5 RCTs of SGLT2i use in acute MI—the results of which were mostly driven by DAPA-MI and EMPACT-MI—showed that their use significantly reduced the risk of hospitalizations for HF (RR, 0.76; 95% CI, 0.61-0.88; $P = 0.001$) but had no benefit with respect to cardiovascular mortality and all-cause hospitalizations.[66] Overall, the data suggest a limited benefit for SGLT2i use in acute MI in those who are also at risk for AHF but did reveal that this therapy appears safe to use within this population (with inclusion and exclusion criteria requiring clinical stability).

Conclusions

In summary, large higher-quality RCT data support the use of SGLT2i in AHF once stability has been reached. The exact timing of this initiation or when stability is established is not well defined and is likely based on individual, clinical, and biochemical factors. Risk of decompensating from HF should be weighed against potential benefit of the agent. In general, very acute illness or states with risks for starvation or low cardiac output increases adverse events from use of SGLT2i and therefore likely are not ideal for initiation. Combined with no clear benefit or only marginal benefits of very early initiation, the likely "sweet spot" may be later in the admission or around the time of discharge (Fig. 1 and Table 2). It is unclear if the use or the initial use of an SGLT2i is sufficient or whether a combination of SGLT1 and SGLT2 inhibition would provide more benefit; however, long-term SGLT2i has been well studied and is currently recommended for long-term heart failure therapy. Finally, careful patient selection and consideration of timing of SGLT2i initiation during hospitalization should be able to provide long-term HF benefits with an acceptable risk profile.

Ethics Statement

The research in this paper adhered to ICMJE and EQUATOR network guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a review article that does not use individual patient information.

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Disclosures

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Supplementary Material

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