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Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve blood glucose control by blocking renal glucose reabsorption with little subsequent risk of hypoglycemia. Consequently, there are decreases in plasma volume, body weight, and blood pressure. Additional putative benefits include improved cardiovascular energetics, decreased systemic inflammation, and less renal dysfunction. Multiple cardiovascular outcome trials in diabetic patients have demonstrated this drug class reduces the risk of adverse cardiovascular events. Reductions in heart failure (HF) hospitalization suggested that SGLT2 inhibitors might prove useful for the primary treatment of HF. Two large subsequent trials studying SGLT2 inhibitors in heart failure with reduced ejection fraction (HFrEF) demonstrated a reduction in cardiovascular mortality, HF hospitalizations, and renal-specific adverse events. This medication class is now recognized as a new pillar of therapy for patients with HFrEF. The cardiovascular and HF community await the results of ongoing trials of SGLT2 inhibition in patients with HF with preserved ejection fraction.

INTRODUCTION

Heart failure (HF) remains a major public health concern, with over 8 million people expected to have a diagnosis of HF in the United States by 2030 (1). HF costs in the United States remain high, with an estimated increase to $70 billion by 2030. Poor quality of life, mortality, and frequent hospitalizations remain common problems for patients with HF (2). Comorbidities, particularly hypertension, coronary artery disease, renal insufficiency, and type 2 diabetes mellitus (DM), are commonly found in patients with HF (3).

DIABETES MELLITUS AND CARDIOVASCULAR DISEASE

The intersection of DM and heart disease is complex. DM confers a high lifetime risk (67% in men and 57% in women) for developing cardiovascular disease (CVD) (4). Data from the Framingham Heart Study suggest that the presence of DM increases the risk of developing HF up to twofold in men and fivefold in women (5). The pathophysiology of type 2 DM is characterized by insulin resistance and consequent hyperglycemia. Insulin resistance is known to increase mitochondrial dysfunction, predispose patients to inflammation, and cause the activation of the renin-angiotensin-aldosterone system (6). These pathophysiologic processes that impact myocardial energetics and promote cardiac hypertrophy as well as fibrosis ultimately link DM to clinical HF.

The management of DM has historically relied upon lifestyle modifications and pharmacotherapies to help reduce the risk of complications. Medical management of DM has grown more complex over time, with now at least eight unique classes of US Food and Drug Administration (FDA)-approved DM medications that address disease complications (micro- and macrovascular), mortality, and quality of life (7). However, the reduction in cardiovascular risk among the DM drug classes is variable; in some cases such as with thiazolidinediones, CVD risk may even be increased (8). Thiazolidinediones act on peroxisome proliferator–activated receptor γ (PPAR-γ), which lowers blood glucose via gene expression and increasing insulin sensitivity in peripheral tissues. Studies have shown that thiazolidinediones may increase the risk of myocardial infarction and HF in patients with DM, reducing their potential utility (9, 10). Moreover, the thiazolidinediones experience highlighted the dissociation between the surrogate goal of glucose lowering and improving cardiovascular morbidity and mortality. Thus, there remained a large unmet need for DM therapeutics that could improve cardiovascular outcomes.

The sodium-glucose cotransporter (SGLT) is a channel protein that functions to import glucose into the intracellular space. SGLTs are expressed in organs within the human body, which include renal tubules, small intestines, and the brain (11). Phlorizin is a naturally occurring phenol and SGLT-competitive inhibitor that can be found in the root bark and leaves of the apple tree; it was discovered over 150 years ago and was known to increase glucose in the urine. However, the solubility and bioavailability of phlorizin are poor, and phlorizin can cause severe diarrhea (12). These issues limited phlorizin's utility as a therapeutic agent (13), but the potential for this mechanism of glucose lowering led to the development of SGLT2 inhibitors.

There are six known subtypes of SGLTs in the human body. SGLT1 and SGLT2 are the most abundant. SGLT2 is predominantly present in the S1 segment of the proximal renal tubule, and it is not found in the heart. SGLT2 is responsible for 90% of the glucose reabsorption within the kidney (13). SGLT imports glucose into the intracellular space along with sodium ions (Na^+), using the Na^+ concentration gradient between the inside and outside of cells (e.g., leading to a net Na^+ flux into the cell). Consequently, blocking this cotransporter of glucose and Na^+ leads to the lowering of serum glucose, with subsequent increases in both Na^+ and glucose loss in the urine. A host of other downstream effects have also been documented (see below). SGLT1 is also

found in the proximal renal tubule but to a lesser extent, and it is found in healthy myocardium and in small intestinal enterocytes (14, 15).

MECHANISM OF BENEFIT

The primary mechanism of action of SGLT2 inhibitors is to increase glucosuria with a concomitant mild diuretic effect. This mechanism of action is dependent on blood glucose levels and is independent of the actions of insulin; as blood glucose levels rise and the filtered glucose increases, the amount of glucose that is reabsorbed decreases. As a result, the overall risk for hypoglycemia is low. Importantly, class efficacy is reduced in individuals with renal impairment.

However, the putative mechanisms that explain how SGLT2 inhibition leads to a positive impact on cardiovascular outcomes in patients with HF (and chronic kidney disease) remain unclear. Chronic kidney disease is considered present when there is kidney damage or a glomerular filtration rate of less than 60 mL/min/1.73 m^2 for greater than 3 months, regardless of the cause of damage. Some of these mechanisms may be indirect systemic benefits, and direct myocardial benefits have been proposed. There are multiple theories to explain cardiovascular benefits, including diuresis, natriuresis, blood pressure reduction (16), reduction in inflammation, weight loss (17, 18), improved glycemic control, sympathetic nervous system inhibition, reducing uric acid levels, decreasing epicardial fat mass, and improving vascular function (19).

As a mild diuretic, SGLT2 inhibition is associated with plasma volume contraction and reduction in cardiac preload (20). Plasma volume reduction is accompanied by an increase in hematocrit, which has been observed in patients treated with SGLT2 inhibitors. When compared with bumetanide, use of dapagliflozin was associated with greater interstitial volume reduction (as compared to intravascular blood volume) (21). However the benefit of these agents in HF is not completely explained by a diuretic effect, given the lack of event reduction with other diuretics in HF. The increase in hematocrit may be a result of erythropoiesis rather than plasma volume contraction (22).

In addition to glycosuria, SGLT2 inhibitors cause a uricosuric effect, which may be beneficial, as increased plasma uric acid is associated with oxidant stress and increased cardiovascular complications (23). Other markers of inflammation (TNF-α and IL-6) are decreased in patients receiving SGLT2 inhibitors (24). SGLT2 inhibition leads to increased levels of ketone bodies, which can have anti-inflammatory properties and may provide an alternative source of myocardial fuel (25).

More direct myocardial effects have been noted as well. SGLT2 inhibitors may act within the heart to inhibit the activity of sodium-hydrogen exchanger-1 (NHE-1) (26). Since in both HF and DM there is increased expression of NHE-1, which is linked to calcium overload (27), SGLT2 inhibitors may also prevent or even reverse adverse cardiac remodeling. In animal HF models, empagliflozin reduces left ventricular mass and chamber size and increases systolic function (28). Improved myocardial energetics were suggested, since greater myocardial ATP content was found in the animals who received empagliflozin.

Figure 1 provides a summary of potential mechanisms leading to clinical benefit for this class of drugs.

CARDIOVASCULAR OUTCOME TRIALS

In 2015, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial became the first SGLT2 inhibitor study focused on cardiovascular outcomes (29). In this trial, 7,020 patients with DM at high cardiovascular risk were randomized to either empagliflozin or placebo. Patients were followed for a median follow-up time of 3.1 years, and those in the empagliflozin group experienced

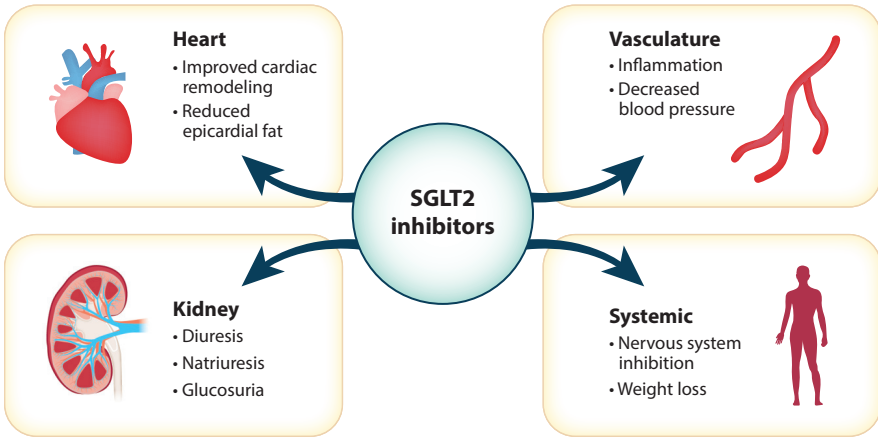

Figure 1

Potential mechanisms of benefit for sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 inhibition acts across multiple systems, including the heart, kidney, and vasculature, and has systemic effects.

a reduction in cardiovascular death, HF hospitalization, and mortality. While the authors concluded that the use of empagliflozin could reduce the primary composite cardiovascular outcome and mortality, there was an unexpected finding of a reduction in HF hospitalization (2.7% versus 4.1%, 35% relative risk reduction). This finding helped lay the groundwork for future trials focusing on patients with HF.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) trials studied the impact of the SGLT2 inhibitor canagliflozin on cardiovascular, renal, and safety outcomes in patients with DM and elevated cardiovascular risk (30). A total of 10,142 patients were randomized to canagliflozin or placebo; the rate of the primary outcome (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) was lower with canagliflozin [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.75–0.97; $p < 0.001$]. Similar to EMPA-REG, canagliflozin also reduced the risk of HF hospitalization (HR 0.67, 95% CI 0.52–0.87, $p < 0.001$).

In 2019, the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial investigated whether dapagliflozin could improve cardiovascular and renal outcomes in 17,160 patients with DM at elevated cardiovascular risk (31). Of the original cohort, 10% of patients had a known history of HF. After a median follow-up of 4.2 years, there was not a reduction in the primary efficacy end point of cardiovascular death, myocardial infarction, or ischemic stroke (HR 0.93, 95% CI 0.84–1.03, $p = 0.17$), but there was a lower rate of the second primary outcome (composite of cardiovascular death and HF hospitalization). This finding was driven by a reduction in HF hospitalization (HR 0.73, 95% CI 0.61–0.88), and there was no difference in cardiovascular death (HR 0.98, 95% CI 0.82–1.17). Renal events [decrease in estimated glomerular filtration rate (eGFR), end stage renal disease, and renal death] were also lower for patients who received dapagliflozin (HR 0.76, 95% CI 0.67–0.87).

The consistent finding of a reduction in HF hospitalizations across the published cardiovascular outcome trials (see **Table 1**) provided a strong rationale to pursue randomized trials in patients with established HF. Moreover, because of the renal benefits and low adverse event profiles noted in the diabetes cardiovascular outcome trials, it followed that SGLT2 inhibitors could be studied in HF patients with and without DM and with and without chronic kidney disease.

Table 1 Comparison of cardiovascular outcome trials

Trial	Inclusion criteria	Intervention drug	Comparison	Outcome(s)
EMPA-REG ($N = 7{,}020$)	Age ≥18 years, T2DM, BMI ≤45, eGFR at least 30 mL/min/1.73 m^2, established CVD, or any of the following three criteria: no intake of glucose-lowering agents for 12 weeks before randomization, HbA1c 7 to 9 who had glucose-lowering agent 12 weeks before randomization, and HbA1c of at least 7 and no more than 10	Empagliflozin 10 or 25 mg	Standard care with placebo	Reduced 3P-MACE mortality among those taking empagliflozin (10.5% versus 12.1%, HR 0.86, 95% CI 0.74–0.99, $p < 0.001$ for noninferiority and $p = 0.04$ for superiority) Significant reduction in all-cause mortality (5.7% versus 8.3%, HR 0.68, 95% CI 0.57–0.82, $p \leq 0.001$) Significant reduction in cardiovascular mortality (3.7% versus 5.9%, HR 0.62, 95% CI 0.49–0.77, $p \leq 0.001$) Significant reduction in hospitalization for heart failure (2.7% versus 4.1%, HR 0.65, 95% CI 0.50–0.85, $p \leq 0.002$) Significant reduction in hospitalization for heart failure and death from cardiovascular causes, excluding stroke (5.7% versus 8.5%, HR 0.66, 95% CI 0.55–0.79, $p \leq 0.001$)
DECLARE-TIMI 58 ($N = 17{,}160$)	Age ≥40 years, Hb1Ac 6.5–12, creatinine clearance ≥60 mL/min); majority of patients had no previous atherosclerotic CVD	Dapagliflozin 10 mg	Placebo	No significant difference in the 3P-MACE in the dapagliflozin group (8.8% versus 9.4%, HR 0.93, 95% CI 0.84–1.03, $p = 0.17$) Significant reduction in cardiovascular death and hospitalization for heart failure (4.9% versus 5.8%, HR 0.98, 95% CI 0.83–0.95, $p = 0.005$)
CANVAS program ($N = 10{,}142$)	Age ≥30 years with HbA1c ≥7–10.5 and history of symptomatic atherosclerotic CVD; age ≥50 years with two or more risk factors with CVD (SBP >140 mg Hg, eGFR >30 mL/min/1.73 m^2)	Canagliflozin 100 or 300 mg daily	Placebo	Reduced 3P-MACE mortality in the intervention group (26.9 versus 31.5 participants with an event per 1,000 patient years, HR 0.86, 95% CI 0.75–0.97, $p < 0.001$ for noninferiority and $p = 0.02$ for superiority)

Table adapted from Rehman et al. (49). Abbreviations: 3P-MACE, 3-point major adverse cardiac event; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

HEART FAILURE TRIALS

There are now multiple randomized controlled trials studying SGLT2 inhibition in patients with established HF, with and without a history of DM. The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial was a randomized controlled trial that assigned 4,744 patients with symptomatic heart failure and reduced ejection fraction (HFrEF) to dapagliflozin versus placebo (32). The primary outcome was a composite of worsening HF or cardiovascular death. Patients were followed for a median of 18 months, and there was a significant reduction in the primary end point (HR 0.74, 95% CI 0.65–0.85, $p < 0.001$). Multiple secondary outcomes were improved with dapagliflozin, including hospitalization for HF, total mortality, and quality of life. The impact was seen in patients with and without DM, and the effect of the therapeutic intervention was additive to background HFrEF therapies. Importantly, the reduction in the primary outcome was rapidly apparent, with a benefit seen within 28 days after randomization (HR 0.51, 95% CI 0.28–0.94, $p = 0.03$), which has direct implications for clinical practice. In addition to the main results of the trial, investigators have explored the impact of dapagliflozin in HF patients with chronic kidney disease, a common comorbidity in HF. Dapagliflozin was associated with a

lower rate of decline in eGFR, and this benefit was independent of baseline renal function (33). These results from DAPA-HF suggest that dapagliflozin may be the first drug for HFrEF that addresses the cardiorenal syndrome, a complex spectrum of disorders involving both the heart and kidneys, in which acute or chronic abnormalities in either system lead to deterioration of the other. DAPA-HF demonstrated the benefit of dapagliflozin in improving both cardiovascular and renal outcomes in patients with HFrEF.

The findings in DAPA-HF were reaffirmed with another SGLT2 inhibitor, empagliflozin. In October 2020, the results of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial were published (34). Investigators randomized 3,730 patients with symptomatic HFrEF to either empagliflozin or placebo and evaluated them for the primary outcome of cardiovascular death or hospitalization for worsening HF. Patients were followed for a median of 16 months, and those who received empagliflozin had a reduction in the primary end point (HR 0.75, 95% CI 0.65–0.86, $p < 0.001$). Similar to the DAPA-HF trial results, the benefit was seen regardless of baseline diabetes status (35). In addition, empagliflozin was associated with less need for intensive care hospitalization or vasopressor/inotropic support. Importantly, the cardiorenal benefits of this class of drug were again apparent. The coprimary end point of the annual rate of decline in eGFR was slower in the empagliflozin arm. Patients with eGFRs as low as 20 mL/min/1.73 m^2 were eligible, and the reduction in the rate of kidney function decline was consistent across the spectrum of baseline renal function (36).

Based on results from the DAPA-HF and EMPEROR-Reduced trials, the 2021 "Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment" (37) recommends the use of SGLT2 inhibitors as part of first-line therapy for patients with HFrEF, regardless of their diabetes status.

Sotagliflozin is a dual inhibitor of SGLT1 (found primarily in the small intestine) and SGLT2 (38). Sotagliflozin's effectiveness in inhibiting SGLT2 is similar to that of dapagliflozin and canagliflozin but is more than tenfold more potent in inhibiting SGLT1. Sotagliflozin delays glucose absorption in the small bowel, which reduces postprandial glucose concentrations in patients with DM (39). In contrast to SGLT2, SGLT1 is reported to be expressed in autopsied human hearts, so the inhibition of SGLT1 may have direct myocardial benefits.

Sotagliflozin was studied in the randomized controlled trial Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST WHF), which enrolled patients with DM who were hospitalized or recently discharged for worsening HF (40). Patients were randomized to either sotagliflozin (during hospitalization or within 3 days of discharge) or placebo and were followed for a median of 9 months. While this trial was stopped prematurely due to loss of funding related to the COVID-19 pandemic, the primary end point of reduction in total cardiovascular death, HF hospitalization, or urgent visit for HF was achieved (HR 0.67, 95% CI 0.52–0.85, $p = 0.0009$). A subset of patients in SOLOIST WHF had heart failure with preserved ejection fraction (HFpEF). The early termination of the study limited the sample size of this cohort, but there were signs of improvement in outcomes in patients with HFpEF. The authors stated there was no evidence of heterogeneity of treatment effect according to ejection fraction, but early termination of the trial and the small sample size of the HFpEF subgroup ($N = 257$) made it difficult to draw any firm conclusions. The authors concluded that the use of sotagliflozin initiated before or shortly after discharge reduced cardiovascular deaths and HF hospitalizations.

In aggregate, the totality of randomized controlled data of SGLT inhibition supports the use of these drugs in both ambulatory and hospitalized HF patients (41) (**Table 2**).

Mechanistic insights into SGLT2 inhibitor benefit in HF continue to be pursued. The specific impact of SGLT2 inhibitors on hemodynamics in patients with HF was examined in the

Table 2 Comparison of recently published HF trials studying SGLT2 inhibitors

Trial	Inclusion criteria	Median follow up (months)	Age (years)	Women (%)	eGFR (mL/min/1.73/m^2)	Diabetes (%)	LVEF (%)	Comparison	Primary outcome (95% CI)	Cardiovascular death or HHF (95% CI)	HHF (95% CI)	Cardiovascular death (95% CI)	All-cause mortality (95% CI)
DAPA-HF ($N = 4,744$)	LVEF ≤40% and NT-proBNP ≥600 pg/mL (without AF) or ≥900 pg/mL (with AF) LVEF ≤40% and HHF in past 12 months and NT-proBNP ≥400 pg/mL (without AF) or ≥900 pg/mL (with AF) eGFR ≥30 mL/min/1.73 m^2	18	66.5	23.0	65.5	41.8	30.9	Dapagliflozin versus placebo	0.74 (0.65–0.85), $p < 0.001$	0.75 (0.65–0.85)	0.70 (0.59–0.83)	0.82 (0.69–0.98)	0.83 (0.71–0.97)
EMPEROR-Reduced ($N = 3,730$)	LVEF ≤40% and NT-proBNP ≥600 pg/mL (without AF) or ≥900 pg/mL (with AF) LVEF ≤40% and HHF in past 12 months and NT-proBNP ≥400 pg/mL (without AF) or ≥900 pg/mL (with AF) eGFR ≥30 mL/min/1.73 m^2	16	66.5	24.4	62.2	49.8	27.2	Empagliflozin versus placebo	0.75 (0.65–0.86), $p < 0.001$	0.75 (0.65–0.86)	0.69 (0.59–0.81)	0.92 (0.75–1.12)	0.92 (0.77–1.10)

(*Continued*)

Table 2 (*Continued*)

Trial	Inclusion criteria	Median follow up (months)	Age (years)	Women (%)	eGFR (mL/min/1.73/m^2)	Diabetes (%)	LVEF (%)	Comparison	Primary outcome (95% CI)	Cardiovascular death or HHF (95% CI)	HHF (95% CI)	Cardiovascular death (95% CI)	All-cause mortality (95% CI)
SOLOIST WHF ($N = 1,222$)	Admission with HF Treatment with diuretics Stabilized, off oxygen, transitioned to oral diuretics BNP ≥150 pg/mL (≥450 pg/mL if AF) or NT-proBNP ≥600 pg/mL (≥1,800 pg/mL if AF) T2DM	9	69.0	34.0	50.0	100 (median A1C% 7.2)	35.0	Sotagliflozin versus placebo	0.67 (0.52–0.85), $p = 0.0009$	0.64 (0.49–0.83), $p < 0.001$	NA	0.84 (0.58–1.22) 0.36	0.82 (0.59–1.14)

Abbreviations: A1C, glycosylated hemoglobin A1c; AF, atrial fibrillation; BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hypertensive heart failure; LVEF, left ventricular ejection fraction; NA, not applicable; NT-proBNP, N-terminal-pro hormone BNP; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

Empagliflozin Evaluation by Measuring the Impact on Hemodynamics in Patients with Heart Failure (EMBRACE-HF) trial (42). Sixty-five patients with HF and a previously implanted pulmonary artery (PA) pressure sensor (CardioMEMS) were randomized to either empagliflozin or placebo. Patients who were randomized to receive empagliflozin had reductions in PA pressures without a difference in mean loop diuretic dose between treatment groups. The authors concluded that a benefit of SGLT2 inhibitors is the rapid reduction in PA pressures independent of loop diuretic therapy.

Cardiac remodeling has also been explored, particularly in light of animal data. In a substudy from the Empagliflozin in Heart Failure Patients with Reduced Ejection Fraction (EMPIRE HF) study (43), an exploratory post hoc analysis focused on echocardiographic findings in the trial. In this substudy, 190 patients were randomized to empagliflozin versus placebo; those in the empagliflozin arm had reductions in left ventricular end-systolic volume index, left ventricular end-diastolic volume index, and left atrial volume index. There was no observed change in left ventricular ejection fraction. In this small, randomized, short-term study, it appeared that empagliflozin was associated with modest cardiac remodeling, characterized by reductions in left ventricular and left atrial volumes but no change in left ventricular ejection fraction.

The question as to whether SGLT2 inhibitors will have a positive impact in patients with HFpEF remains to be answered. Two large randomized controlled trials are currently being conducted to investigate both dapagliflozin and empagliflozin [Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure (EMPEROR-Preserved)] in patients with HFpEF (**https://clinicaltrials.gov/ct2/show/NCT03057951**, **https://clinicaltrials.gov/ct2/show/NCT03619213**). The company involved with the EMPEROR-Preserved trial has announced its primary end point has been met and the results will be presented at the European Society of Cardiology Congress 2021 (44).

Given the signs of potential benefit seen in SOLOIST WHF as well as in the SCORED trial (45), there remains optimism that this class of medication may improve outcomes in this challenging group of patients with limited therapeutic options.

TOXICITIES

SGLT2 inhibitors are well tolerated, but select complications are worth noting. These drugs shift energetic sources from carbohydrates to lipid oxidation, increasing the risk for ketoacidosis (46) despite euglycemia. Euglycemic ketoacidosis is uncommon but more likely to occur in patients with insulin-deficient diabetes with a precipitating trigger (e.g., infection, medication dose change). The incidence of euglycemic ketoacidosis in EMPA-REG was less than 0.1%; rates were similarly low in EMPEROR-Reduced and DAPA-HF (29, 32, 34). In contrast, genitourinary yeast infections are not uncommon. Hyperglycemia, glucosuria, and decreased humoral and cellular immunity appear to predispose patients to this adverse event (47). The incidence of these infections in diabetic patients treated with SGLT2 inhibitors has ranged from 0% to 14% depending on drug and dose (47). Of note, there were no genitourinary infections reported in DAPA-HF; however, there were slightly more frequent uncomplicated urinary tract infections seen in EMPEROR-Reduced (32, 34). Patient education about genital hygiene is recommended, particularly those with DM. Early concerns about limb amputation were noted with canagliflozin, but subsequent tracking in both clinical trials and prospective registry data did not confirm this risk, and the FDA removed this warning for canagliflozin in 2020. Hypovolemia may occur due to glycosuria and natriuresis, and diuretics should be modified to attenuate this complication. Hypoglycemia per se

is usually due to the use of concomitant glucose-lowering therapies (e.g., insulin), and decreases in dosing with such drugs should be considered.

FUTURE DIRECTIONS

The use of SGLT2 inhibitors in patients with HFrEF clearly improves HF outcomes and provides additional benefits on top of the established HFrEF drug classes, renin-angiotensin aldosterone system antagonists, beta-blockers, and mineralocorticoid antagonists; it would appear that quadruple therapy is the new norm for HF therapeutics. A critical issue going forward will be to address the long-standing challenge of optimizing the use of HF drugs, including sacubitril/valsartan, for which marked clinical benefit was demonstrated in the Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) in 2015. The data to date for the use of SGLT2 inhibitors in patients with established HFrEF are strong, but multiple barriers to implementation exist, including cost/access to medications, clinical inertia, knowledge deficits, and concerns for polypharmacy (48). The results of studies in HFpEF and in patients with more advanced HF have yet to be published. Although early initiation of this drug class has been advocated, the order of introduction and dose titration of HF medications, for example, sequencing, remain practical considerations in clinical practice, particularly in light of the many indicated drug classes for HFrEF. We hope mechanistic studies will continue to shed light on how this drug class fundamentally changes the outcomes of patients afflicted with HF, a morbid and mortal disorder.

CONCLUSIONS

SGLT2 inhibitors were originally developed to manage DM but have since evolved to become part of evidence-based therapies for the management of HFrEF. The specific mechanisms remain unclear, and there are likely many. Increasing the use of these agents in patients with HFrEF will be an ongoing challenge. Their potential benefit in HFpEF will be elucidated in the near future.

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