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The role of SGLT-2 inhibitors in managing type 2 diabetes

ABSTRACT

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are an exceptionally versatile class of medication, and their glycemic and nonglycemic benefits could help millions of patients with type 2 diabetes. Of note, they have been shown to improve cardiac and renal outcomes, much-needed benefits in patients with type 2 diabetes, who are at a higher risk for developing cardiac and renal dysfunction than those who do not have diabetes. The indications for SGLT-2 inhibitors may continue to expand as ongoing clinical trials provide more insight into these drugs.

KEY POINTS

SGLT-2 inhibitors improve glycemic control, reduce hospitalizations for heart failure, and slow the progression of renal disease.

Consider an SGLT-2 inhibitor as first- or second-line therapy (after metformin) in patients with type 2 diabetes with cardiovascular disease or renal disease, or both, regardless of glycemic control.

Consider an SGLT-2 inhibitor in overweight or obese patients with type 2 diabetes.

Be aware of the possibility of genital infections and diabetic ketoacidosis with SGLT-2 inhibitor use.

OPTIONS FOR TREATING type 2 diabetes mellitus have expanded with the introduction of the sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like protein-1 (GLP-1) receptor agonists. These drugs improve glycemic control and possess cardiovascular and metabolic benefits.

This article will discuss and interpret recent studies regarding the benefits of SGLT-2 inhibitors and their role in the treatment of type 2 diabetes. By doing so, we aim to provide guidance for clinicians, particularly primary care physicians and general internists, in their decision-making in managing type 2 diabetes.

■ SODIUM-GLUCOSE COTRANSPORTER-2

The kidneys play a role in regulating blood glucose levels by filtering out glucose in the glomerulus and then reabsorbing it in the proximal tubule. They can filter and reabsorb approximately 180 g of glucose per day, and less than 1% is excreted into the urine.[1,2] The transporters responsible for reabsorbing glucose from the tubular lumen into the blood stream are the sodium-glucose cotransporters 1 and 2 (SGLT-1 and SGLT-2, respectively). SGLT-1 is located in the distal segment of the proximal tubule and reabsorbs approximately 10% of the glucose that is filtered by the glomerulus, while SGLT-2 is located in the proximal portion of the proximal tubule and reabsorbs about 90%.[3]

In type 2 diabetes, expression of SGLT-2 is increased, which increases the ability of the kidneys to reabsorb glucose.[3] This in turn causes glucose to not spill into the urine un-

TABLE 1

Absolute change in hemoglobin A$_{1c}$ with SGLT-2 inhibitor monotherapy compared with placebo

Empagliflozin[a]		Canagliflozin[b]		Dapagliflozin[c]		Ertugloflozin[d]	
Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose
−0.74%	−0.85%	−0.90%	−1.20%	−0.54%	−0.60%	−0.50%	−0.50%

[a] Empagliflozin low dose = 10 mg, high dose = 25 mg.[6]
[b] Canagliflozin low dose = 100 mg, high dose = 300 mg.[5]
[c] Dapagliflozin low dose = 5 mg, high dose = 10 mg.[7]
[d] Ertugloflozin low dose = 5 mg, high dose = 15 mg.[8]

til the plasma glucose level reaches about 220 mg/dL, instead of the usual threshold of about 180 mg/dL. Conversely, drugs that inhibit SGLT-2 promote glycosuria in exchange for lower plasma glucose. An advantage of these drugs is that their mechanism of action is independent of insulin secretion, beta-cell function, and insulin resistance.[4]

■ EFFECT ON GLYCEMIC CONTROL

Currently, there are 4 approved SGLT-2 inhibitors on the market: empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin. No head-to-head trials have compared glycemic control with the individual drugs within the class, but in placebo-controlled trials, SGLT-2 inhibitors lowered hemoglobin A$_{1c}$ by 0.6 to 1.2 percentage points when used as monotherapy (**Table 1**),[5–8] by 0.5 to 0.9 percentage points when added to metformin therapy,[4,9–11] and by 0.4 to 0.6 percentage points when added to insulin and other oral antihyperglycemic agents.[12–14]

Because SGLT-2 inhibitors lower glucose independently of insulin, hypoglycemia is rare when they are used as monotherapy or in conjunction with noninsulin secretagogue oral agents.[4–7,9,10] The incidence of hypoglycemia increases with the use of insulin or insulin secretagogues such as sulfonylureas, but severe hypoglycemic episodes remain uncommon.[12–14]

Nevertheless, when SGLT-2 inhibitors are used in combination with insulin or insulin secretagogues, one should consider reducing the dose of insulin or insulin secretagogue to prevent hypoglycemia:

- For patients using basal insulin, some suggest decreasing the basal insulin dose by 20% if the fasting plasma glucose level is less than 106 mg/dL and decreasing it by 10% if the fasting plasma glucose level is between 106 and 145 mg/dL
- For patients using bolus insulin, consider reducing the dose by 20% if the blood glucose level is less than 106 mg/dL before meals, and by 10% if it is between 106 and 145 mg/dL
- For patients using both insulin and an insulin secretagogue, consider reducing the dose of insulin secretagogue or discontinuing it altogether, particularly if blood glucose levels are less than 106 mg/dL before starting the SGLT-2 inhibitor.[15]

■ EFFECT ON CARDIOVASCULAR OUTCOMES

Approximately one-third of patients with type 2 diabetes have cardiovascular disease: about 20% have coronary artery disease and 15% have heart failure.[16] Patients with type 2 diabetes who also have heart failure have worse quality of life and a poorer prognosis.[17,18] Cardiovascular disease is responsible for half of the deaths in this patient population,[16] and those with type 2 diabetes who develop heart failure have a 9 to 12 times greater mortality risk than those who do not.[19,20] Therefore, the ability of SGLT-2 inhibitors to reduce cardiovascular deaths and hospitalizations for heart failure is crucial in managing this population.

Four large randomized clinical trials (**Table 2**)[21–24] have provided insight into the effects

Drugs that inhibit SGLT-2 promote glycosuria in exchange for lower plasma glucose

TABLE 2

Cardiovascular outcomes in 4 major trials of SGLT-2 inhibitors

	EMPA-REG OUTCOME[21]	CANVAS[22]	DECLARE-TIMI 58[23]	VERTIS-CV[24]
Population	Type 2 diabetes + cardiovascular disease	Type 2 diabetes + cardiovascular disease or multiple risk factors for it	Type 2 diabetes + cardiovascular disease or multiple risk factors for it	Type 2 diabetes + cardiovascular disease
Number of patients	7,020	10,142	17,160	8,246
History of cardiovascular disease	99%	65.6%	40.6%	100%
History of heart failure	10.1%	14.4%	10.2%	23.7%
Outcomes with SGLT-2 inhibitor				
MACE (relative risk reduction)	14%	14%	Not significant	Not significant
MACE (number needed to treat)	63	217	Not available	Not available
Cardiovascular death (relative risk reduction)	38%	Not significant	Not significant	Not significant
Hospitalization for heart failure (relative risk reduction)	35%	33%	27%	30%
Hospitalization for heart failure (number needed to treat)	71	312	125	91

CANVAS = Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MACE = major atherosclerotic cardiovascular events; VERTIS CV = Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes

of SGLT-2 inhibitors on cardiovascular outcomes in patients with type 2 diabetes.

EMPA-REG OUTCOME (the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)[21] found that empagliflozin reduced the incidence of major atherosclerotic cardiovascular events (composite of cardiovascular death, hospitalization for heart failure, and ischemic stroke) by 14%, cardiovascular death by 38%, and hospitalization for heart failure by 35%. There was no significant difference in efficacy between empagliflozin 10 mg and 25 mg.

CANVAS (the Canagliflozin Cardiovascular Assessment Study)[22] found that canagliflozin reduced major atherosclerotic cardio-vascular events by 14% and hospitalizations for heart failure by 33% but did not reduce cardiovascular deaths significantly.

DECLARE-TIMI 58 (the Dapagliflozin Effect on Cardiovascular Events trial)[23] found that dapagliflozin did not reduce the rate of major atherosclerotic cardiovascular events, but it did reduce cardiovascular deaths by 17% and hospitalizations for heart failure by 27%.

VERTIS CV (the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial)[24] found that ertugliflozin did not significantly reduce major atherosclerotic cardiovascular events or cardiovascular deaths, but it reduced hospitalizations for heart failure by 30%.

In summary, SGLT-2 inhibitors have been shown to have moderate benefits in terms of preventing major adverse cardiovascular events and a robust benefit in preventing hospitalizations for heart failure.

A further look at heart failure

Individually, these trials lacked the statistical power to evaluate differences in efficacy between subgroups such as those with established atherosclerotic cardiovascular disease (ASCVD) vs those with cardiovascular risk factors but without established ASCVD.

A meta-analysis[25] of EMPA-REG OUTCOME,[21] CANVAS,[22] and DECLARE-TIMI 58[23] found that in patients with established ASCVD, major atherosclerotic cardiovascular events were reduced by 14% (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.80–0.93, $P = .0002$) but no treatment effect was found in the multiple cardiovascular risk factors group. The composite outcome of cardiovascular death or hospitalization for heart failure showed a 23% relative risk reduction, regardless of whether the patients had ASCVD or heart failure. When patients with and without a history of heart failure were compared, the difference in the rate of the composite outcome of cardiovascular death or hospitalizations for heart failure was not statistically significant.[25]

Overall, SGLT-2 inhibitors' effect on major adverse cardiac events appears to be confined to patients with established ASCVD, but their effect on reducing hospitalizations for heart failure appears to be independent of established ASCVD, risk factors, or history of heart failure.

Heart failure type and the benefit of SGLT-2 inhibitors

In view of the clear benefit of SGLT-2 inhibitors in preventing heart failure hospitalizations, a subanalysis of the DECLARE-TIMI 58 trial was undertaken to further assess this benefit in regard to heart failure phenotype (heart failure with reduced ejection fraction vs heart failure with preserved ejection fraction).[26]

Treatment differs for the 2 groups. For those with heart failure with reduced ejection fraction, agents such as angiotensin-converting enzyme inhibitors and beta-blockers reduce the risk of death. However, no treatments to date have been shown to lower the mortality rate in heart failure with preserved ejection fraction, and the guidelines are limited to recommending treatment of any underlying comorbidities such as hypertension, atrial fibrillation, coronary artery disease, and diabetes.[27] The answer to whether SGLT-2 inhibitors benefit both types of heart failure will have an enormous impact on the future management of heart failure.

DECLARE-TIMI 58,[26] in a subgroup analysis, found that dapagliflozin significantly reduced hospitalizations for heart failure and cardiovascular deaths in those with heart failure with reduced ejection fraction more than in those with preserved ejection fraction or unclassified heart failure (HR 0.62 vs 0.88, $P = .046$). On the other hand, it appeared to reduce hospitalizations for heart failure in all patients regardless of their heart failure phenotype.

DAPA-HF (Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction)[28] evaluated the efficacy of dapagliflozin in patients with heart failure with reduced ejection fraction regardless of diabetes diagnosis The incidence of the primary outcome (composite of worsening heart failure—unplanned hospitalization for heart failure or an urgent visit resulting in intravenous therapy for heart failure—or death from cardiovascular causes) was 26% lower in the dapagliflozin group than in the placebo group (HR 0.74, $P < .001$) with a number needed to treat of 20. Hospitalizations for heart failure alone were reduced by 30%. These benefits were comparable in patients with or without diabetes in the study based on a subgroup analysis.[28]

In May 2020, the US Food and Drug Administration (FDA) expanded the indications for dapagliflozin to include heart failure with reduced ejection fraction.[29]

EMPEROR-Reduced (the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction)[30] investigated the efficacy of empagliflozin in patients with heart failure with reduced ejection fraction with or without diabetes. The incidence of the primary outcome (composite of adjudicated cardiovascular death or hospitalization for heart failure) was

Approved SGLT-2 inhibitors: empagliflozin, canagliflozin, dapagliflozin, ertugliflozin

25% lower in the empagliflozin group (HR 0.75, *P* < .001) with a number needed to treat of 19. Hospitalizations for heart failure were reduced by 30%. These results were similar to those of the DAPA-HF trial.

CVD REAL 2 (the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study)[31] reinforced the cardiovascular benefits of SGLT-2 inhibitors. This was a large multinational observational study including cohorts from regions that were not well represented in the clinical trials mentioned above such as Asia Pacific and the Middle East. Also, the study population more closely resembled that of clinical practice in which the majority (approximately 74%) did not have established cardiovascular disease.

Nonetheless, SGLT-2 inhibitors, compared with other glucose-lowering drugs, significantly reduced the risk of death from any cause (49% relative risk reduction), hospitalization for heart failure (36% reduction), composite of all-cause death and hospitalization for heart failure (40% reduction), myocardial infarction (19% reduction), and stroke (32% reduction) in patients with type 2 diabetes.[31] Despite differences in study population and design, the results were similar to those in previous clinical trials and were also consistent across countries.

The CVD REAL 2 study suggests that the cardiovascular benefits of SGLT-2 inhibitors may apply to a broader population of patients.[31]

■ POSSIBLE MECHANISMS OF CARDIOVASCULAR BENEFIT

How SGLT-2 inhibitors exert their cardioprotective benefits is not fully understood, but several mechanisms have been hypothesized.

Osmotic diuresis. By increasing glycosuria and natriuresis, SGLT-2 inhibitors increase urine output and therefore decrease plasma volume and ventricular preload.[32]

Inhibition of the sodium-hydrogen exchanger. Cytosolic sodium concentration and sodium-hydrogen exchanger activity are both increased in the myocytes in people with diabetes and heart failure,[33] and sodium-hydrogen exchanger inhibition has been shown to

reduce hypertrophy in heart failure.[34]

Inhibition of fibrosis. Cardiac fibrosis is widely regarded as an essential factor in the development of heart failure. In a study using human cardiac fibroblasts, empagliflozin suppressed gene expression of key profibrotic markers such as type I collagen and connective tissue growth factor.[35] This inhibition may lead to protection from cardiac fibrosis independent of glycemic status.

Bottom line. SGLT-2 inhibitors should be considered for all patients with type 2 diabetes who do not have contraindications to them, given their efficacy in preventing hospitalizations for heart failure in all patients regardless of ASCVD or heart failure history. They should be considered even more strongly in patients with established ASCVD. Guidelines for integrating SGLT-2 inhibitors into diabetes management are discussed further below.

■ EFFECT ON RENAL OUTCOMES

Another benefit of the SGLT-2 inhibitor class of medications is renal protection. Diabetes is the leading cause of kidney failure in the United States,[36] and dialysis carries a poorer prognosis than some cancers.[37] Furthermore, early diabetic kidney disease shortens life by 16 years compared with those without diabetes or kidney disease.[38] Thus, preventing or slowing the progression of diabetic kidney disease is a key aspect of diabetes management.

CREDENCE (the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial)[39] was a large, randomized, placebo-controlled, multicenter trial that assessed the effect of canagliflozin on renal outcomes in patients with type 2 diabetes and chronic kidney disease. All the participants had to have an estimated glomerular filtration rate (eGFR) of 30 to 90 mL/min/1.73 m^2 and a urine albumin-to-creatinine ratio of 300 to 5,000 mg/g. The primary outcome was a composite of end-stage renal disease, doubling of serum creatinine, or death from renal or cardiovascular disease.

The risk of the primary composite outcome was 30% lower in the canagliflozin group (HR 0.70, 95% CI 059–0.82, *P* < .001). One of the secondary composite outcomes, end-stage renal disease, doubling of creatinine, or renal

About one-third of patients with type 2 diabetes have cardiovascular disease

death, was reduced by 34% (HR 0.66, 95% CI 0.53–0.81, $P < .001$).

In addition, canagliflozin slowed the progression of chronic eGFR decline.[39] SGLT-2 inhibitors have been shown to induce an initial decline in eGFR but with subsequent return to baseline and then an overall preservation of eGFR over time.[40]

Of note, in the CREDENCE trial, patients whose eGFR was 30 to 44 mL/min/1.73 m^2 still benefited from canagliflozin; the primary outcome was reduced by 25% in this subgroup (HR 0.75, 95% CI 0.59–0.95), and the number needed to treat was 19. Initially, canagliflozin was contraindicated in patients with eGFR less than 45 mL/min/1.73 m^2. However, in January 2020, the 100-mg once-daily dose was approved for use in patients with eGFR 30 to 44 mL/min/1.73 m^2 with urinary albumin excretion less than 300 mg/day.

Canagliflozin is the only SGLT-2 inhibitor studied in a large trial with a primary renal outcome. The EMPA-REG OUTCOME and the DECLARE-TIMI 58 trials had prespecified secondary renal composite outcomes that showed favorable results for renal benefit, but it is prudent to note that the composite outcomes consisted of different criteria.

The EMPA-REG trial[41] found a 39% reduction compared with placebo for the renal composite outcome of progression to macroalbuminuria, a doubling of serum creatinine level accompanied by an eGFR of ≤ 45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.

The DECLARE-TIMI 58 trial[42] had a renal composite outcome consisting of sustained decrease in eGFR by at least 40% to less than 60 mL/min/1.73 m^2, end-stage renal disease, and renal death; there was a 47% reduction compared with placebo.

The VERTIS-CV trial[24] had a renal composite outcome that included renal death, renal replacement therapy, or doubling of serum creatinine. A statistically significant renal benefit was not found, although ertugliflozin did show a trend for reducing the rate of eGFR decline over time, similar to the other 3 SGLT-2 inhibitors.

Meta-analysis. In the meta-analysis by Zelniker et al[25] of the first 3 cardiovascular outcome trials (EMPA-REG OUTCOME,[21] CANVAS,[22] and DECLARE-TIMI 58[23]), the composite outcome of worsening renal function, end-stage renal disease, or renal death was reduced by 45%, suggesting a renal protective benefit of SGLT-2 inhibitors as a class.

The American Diabetes Association[43] currently recommends empagliflozin, canagliflozin, and dapagliflozin as second-line therapy after metformin in patients with type 2 diabetes and chronic kidney disease whose eGFR is at least 45 mL/min/1.73 m^2 (except for canagliflozin 100 mg, which can be used if eGFR is at least 30 mL/min/1.73 m^2 and urinary albumin excretion is more than 300 mg/day).

The CVD REAL 3 study[44] (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGTT-2 Inhibitors) evaluated the renal outcomes of SGLT-2 inhibitors in real-world clinical practice settings around the world. The rate of eGFR decline was significantly less in the SGLT-2 inhibitor group than with other glucose-lowering drugs, and the composite outcome of a 50% eGFR decline or end-stage renal disease was reduced by 51% (HR 0.49, 95% CI 0.35–0.67). These results were consistent across countries and baseline eGFR.

■ MECHANISM OF RENAL PROTECTION

The mechanism by which SGLT-2 inhibitors protect the kidneys is also not fully understood and is probably multifactorial.

A proposed mechanism is correction of glomerular hyperfiltration, which is a risk factor for progression of diabetic nephropathy.[45] SGLT-2 inhibitors inhibit uptake of glucose and sodium in the proximal tubule, leading to an increase in delivery of sodium to the distal tubule and juxtaglomerular apparatus. The juxtaglomerular apparatus perceives this increase in sodium as a decrease in glomerular perfusion, causing the afferent arteriole to vasoconstrict, which in turn attenuates the hyperfiltration.[46]

This afferent arteriolar constriction manifests as a transient reduction in eGFR of approximately 3 to 4 mL/min/1.73 m^2 in the first few weeks of SGLT-2 therapy and a reduction in albuminuria. Renal function subsequently stabilizes, and ultimately the progression of renal disease is slower with SGLT-2 inhibitors

SGLT-2 inhibitors have moderate benefits in preventing cardiovascular events and a robust benefit in preventing hospitalizations for heart failure

than with placebo in the long term. This effect was seen in the cardiovascular outcome trials of all 4 SGLT-2 inhibitors[39,41,42] as well as in the CVD REAL 3 study.[44]

An ongoing clinical trial is assessing the efficacy of empagliflozin in patients with chronic kidney disease. A trial evaluating dapagliflozin in patients with chronic kidney disease was recently terminated early due to the overwhelming benefit of dapagliflozin in this population. The results of this trial are of great interest, as they may further expand the utilization of this drug.

◼ EFFECT ON METABOLIC OUTCOMES

SGLT-2 inhibitors have been shown to promote weight loss and lower blood pressure. Taking these drugs as monotherapy for 24 to 26 weeks, patients lost approximately 2.3 to 3.5 kg. Systolic blood pressure decreased by 1.4 to 3.7 mm Hg, and diastolic blood pressure decreased by 0.6 to 2.0 mm Hg.[5–8] Reductions in weight and blood pressure persist in patients with eGFR less than 60 mL/min/1.73 m^2 even when the glucose-lowering effect of SGLT-2 inhibitors is attenuated.[47]

SGLT-2 inhibitors have not been approved for use solely as weight-loss medications. However, when they are used in combination with other antiobesity medications they seem to have an additive effect on weight loss and blood pressure compared with SGLT-2 inhibitor monotherapy.

Hollander et al[48] compared the effect of canagliflozin, phentermine, canagliflozin and phentermine combined ("can-phen"), and placebo in patients without type 2 diabetes. Patients lost an average of 0.6 kg on placebo, 1.9 kg on canagliflozin, 4.1 kg on phentermine, and 7.3 kg on can-phen over 26 weeks. Compared with placebo, can-phen produced a statistically significant weight loss of 6.9% (P < .001). In addition, there was a statistically significant reduction in systolic blood pressure in the can-phen group compared with placebo (difference of –4.2 mm Hg, P = .015).

Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists has been studied in patients with type 2 diabetes, with the primary outcome of glycemic control and secondary outcomes including changes in weight and blood pressure.

A meta-analysis[49] of 4 large, randomized controlled trials showed that patients who received combination therapy lost significantly more weight than those who received SGLT-2 inhibitor monotherapy (difference = –1.61 kg, P = .01), and they had significantly reduced systolic blood pressure (difference = –3.32 mm Hg, P < .001).[49] Hemoglobin A_{1c} reduction was also greater in the combination therapy group compared with monotherapy (difference = –0.74%, P < .001).

◼ STUDIES IN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD is a chronic liver disease that can ultimately progress to liver cirrhosis, and there are no FDA-approved pharmacotherapies for it to date. Such treatments are needed, especially considering that the prevalence of NAFLD is high in the type 2 diabetes population.

Empagliflozin, dapagliflozin, and canagliflozin have been studied for their effect on NAFLD. Overall, they have been shown to decrease alanine aminotransferase and improve steatosis and fibrosis along with reducing hemoglobin A_{1c} and body weight.[50] Further randomized controlled trials are needed to evaluate the benefit of SGLT-2 inhibitors in NAFLD in patients with and without diabetes.

The mechanism by which SGLT-2 inhibitors improve NAFLD remains unclear. A popular theory is that a chronic inflammatory state underlies type 2 diabetes and its complications, and patients with NAFLD show significant increases in inflammatory markers as well.[51] Therefore, it is speculated that SGLT-2 inhibitors have several features that can provide anti-inflammatory benefits to improve NAFLD. One feature is the reduction in weight as well as subcutaneous and visceral fat,[52] as weight reduction is known to reduce inflammatory markers.[53]

In addition, SGLT-2 inhibitors decrease serum uric acid levels.[21] Uric acid has been associated with oxidative stress and vascular injury in in-vitro and animal studies[54] leading to the hypothesis that lowering of serum uric acid may improve the inflammatory state. Fralick et al[55] showed that SGLT-2 inhibitors

To date, no treatments have been shown to lower mortality in heart failure with preserved ejection fraction

decreased the rate of gout in patients with type 2 diabetes compared with those who were prescribed a GLP-1 receptor agonist.

Bottom line. SGLT-2 inhibitors should be considered in patients with type 2 diabetes who are also overweight or obese. They may also have an added benefit of improving NAFLD. In cases in which further hemoglobin A_{1c} reduction and weight loss is preferred, combination therapy with GLP-1 receptor agonists is a reasonable option. In those without type 2 diabetes, canagliflozin plus phentermine seems to have a synergistic effect in promoting significant weight loss. Subsequent studies evaluating the combination of other SGLT-2 inhibitors and phentermine and assessing the effect of this combination therapy in the type 2 diabetes population is of interest.

■ ADVERSE EFFECTS OF SGLT-2 INHIBITORS

Several adverse events related to the use of SGLT-2 inhibitors have been reported. Some are drug-specific and others are class-specific.[21–23]

Fractures, amputations with canagliflozin. The hazard ratio for the risk of fractures with canagliflozin was 1.26 (95% CI 1.04–1.52), and the hazard ratio for the risk of amputations was 1.97 (95% CI 1.41–2.75) in the CANVAS trial.[22] However, the hazard ratios for these 2 events were not significant in the CREDENCE trial.[39] Moreover, the increased risk for fractures and amputations has not been seen in randomized control trials of empagliflozin, dapagliflozin, and ertugliflozin. Thus, the FDA removed the boxed warning about the amputation risk with canagliflozin in August 2020.[56]

Genital infections. As a class, SGLT-2 inhibitors increase the risk of genital infections.[8,21–23] Urinary tract infections were generally not significantly increased as a class, but an increase in female urinary tract infections was seen with empagliflozin.[21]

Fournier gangrene. In a postmarketing analysis based on the FDA adverse event reporting system and published case reports, SGLT-2 inhibitors as a class were associated with an increased risk of Fournier gangrene: 55 cases of Fournier gangrene were identified from March 2013 to January 2019: 21 cases were attributed to canagliflozin, 16 to dapagliflozin, and 18 to empagliflozin.[57] This increased risk of Fournier gangrene has not been shown in any of the randomized clinical trials, but due to the severe and fatal nature of this infection, it is crucial to have a high index of suspicion for it in order to detect these cases in the early stages.

Diabetic ketoacidosis. SGLT-2 inhibitor-associated diabetic ketoacidosis may present atypically (ie, with a lower-than-expected glucose level) which can result in missed diagnoses and delays in treatment.[58]

A proposed mechanism of SGLT-2 inhibitor-associated diabetic ketoacidosis is that the increased urinary excretion of glucose suppresses insulin secretion by the beta cells which in turn decreases the antilipolytic activity of insulin. This stimulates production of free fatty acids that are then converted to ketone bodies.[59] In addition, the decrease in insulin activity increases the activity of carnitine palmitoyl-transferase I (CPT-I) through inhibition of acetyl-CoA carboxylase. CPT-I promotes the transport of fatty acids into the mitochondria which ultimately increases ketone body production.[59] There is also evidence that SGLT-2 inhibitors increase glucagon secretion. As glucagon suppresses acetyl-CoA carboxylase, CPT-I activity is increased, leading to ketone body production.[60]

According to the American Association of Clinical Endocrinologists position statement on SGLT-2 inhibitors and diabetic ketoacidosis, this complication occurs infrequently, and the benefits of SGLT-2 inhibitors clearly outweigh the risk, so continued use of SGLT-2 inhibitors in type 2 diabetes is recommended.[58] However, evidence is emerging that surgery may increase the risk of ketoacidosis in patients taking SGLT-2 inhibitors.[61]

In March 2020, the FDA approved a label change for all SGLT-2 inhibitors on the market, recommending temporary discontinuation of the drug before scheduled surgery. Empagliflozin, canagliflozin, and dapagliflozin should be discontinued 3 days before scheduled surgery and ertugliflozin should be discontinued 4 days before. The drug can be reinitiated after surgery when oral intake has returned to baseline.[62]

Benefit outweighs risk. SGLT-2 inhibitors have an abundance of additional benefits

Early diabetic kidney disease shortens life by 16 years

TABLE 3

Risks and benefits of SGLT-2 inhibitors

	Benefits					Risks	
	Hemoglobin A_{1c}	Weight and blood pressure	Heart failure hospitalizations	Cardiovascular events	Progression of renal disease	Fracture, amputation	Genital infection
Empagliflozin	Decrease	Decrease	Decrease	Decrease	Decrease	No change	Increase
Canagliflozin	Decrease	Decrease	Decrease	No change	Decrease	No change[a]	Increase
Dapagliflozin	Decrease	Decrease	Decrease	No change	Decrease	No change	Increase
Ertugliflozin	Decrease	Decrease	Decrease	No change	No change	No change	Increase

[a]Changed from "increases risk" to "no change" after the removal of the black box warning by the US Food and Drug Administration.

aside from improving glycemic control. Based on the safety data we have thus far, the risk-benefit ratio unquestionably favors the use of SGLT-2 inhibitors, and they should be recommended for any patient with type 2 diabetes who does not have any absolute contraindications (**Table 3**). Relative contraindications may include recurrent urinary tract or genital infections. For canagliflozin, risk factors for amputation such as prior history of amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers should be considered before initiation and then monitored for signs and symptoms of foot infections if initiated. Fournier gangrene is a severe and fatal infection; any patient on an SGLT-2 inhibitor should be counseled about the symptoms, and providers need to have heightened awareness of the possibility of Fournier gangrene in order to detect this condition early.

■ REVIEW OF THE GUIDELINES

In 2020, diabetes treatment algorithms were issued by the American Diabetes Association[43] and the American Association of Clinical Endocrinologists.[63]

American Diabetes Association
- In patients who have established ASCVD, high ASCVD risk (age ≥ 55 with coronary, carotid, or lower extremity artery stenosis > 50%, or left ventricular hypertrophy), heart failure, or chronic kidney disease, SGLT-2 inhibitors are considered for use as second-line therapy (first-line is met-

formin) regardless of baseline hemoglobin A_{1c}. The 3 SGLT-2 inhibitors with cardiovascular and renal benefits are empagliflozin, canagliflozin, and dapagliflozin.
- In patients whose hemoglobin A_{1c} is above their individual target and who do not have established ASCVD, high ASCVD risk, heart failure, or chronic kidney disease, SGLT-2 inhibitors are considered for use as second-line therapy.

American Association of Clinical Endocrinologists
- In patients with established ASCVD, high ASCVD risk, or chronic kidney disease, SGLT-2 inhibitors and GLP-1 receptor agonists are recommended as first-line therapy independent of glycemic control.
- If entry hemoglobin A_{1c} is less than 7.5%, monotherapy is recommended with metformin, a GLP-1 receptor agonist, or a SGLT-2 inhibitor (strength of the recommendation is equal).
- For those with stage 3 chronic kidney disease, canagliflozin is recommended.
- For those with heart failure with reduced ejection fraction, dapagliflozin is recommended.
- If entry hemoglobin A_{1c} is 7.5% to 9.0% or higher or if uncontrolled on monotherapy, dual therapy is recommended with SGLT-2 inhibitor and GLP-1 receptor agonists as the top choices in the hierarchy along with metformin. The 2 drug classes are also the top choices for triple therapy.

A trial of dapagliflozin in chronic kidney disease was recently terminated early due to benefit

Bottom line

SGLT-2 inhibitors are recommended for use as either first-line or second-line therapy regardless of baseline hemoglobin A_{1c} in patients who have established ASCVD, high ASCVD risk, chronic kidney disease, or heart failure. They are also recommended for use in those who would benefit from weight loss and in those whom prevention of hypoglycemia is a priority according to the ADA.

■ FUTURE DIRECTIONS

Use in type 1 diabetes? Currently, SGLT-2 inhibitors as a class are not recommended for use in type 1 diabetes. Large, randomized, placebo-controlled studies have been undertaken with dapagliflozin,[64] empagliflozin,[65] and canagliflozin[66] as adjunct therapy to insulin in patients with type 1 diabetes. Common results included reduction in hemoglobin A_{1c} and weight without increases in hypoglycemia events. However, the incidence of diabetic ketoacidosis was higher in the SGLT-2 inhibitor groups in all 3 studies.[64–66] None of these drugs have been approved by the FDA for use in type 1 diabetes. Future studies involving type 1 diabetes and SGLT-2 inhibitors include adjunctive use with closed-loop insulin pumps and combination therapy with GLP-1 receptor agonists.

Sotagliflozin is an SGLT-1 and SGLT-2 dual inhibitor being studied for treatment of type 1 diabetes and type 2 diabetes. Besides the distal segment of the proximal tubule of the kidneys, SGLT-1 is also located in the proximal intestine, and inhibition results in reduced glucose absorption and delays postprandial hyperglycemia. In a phase 3 clinical trial,[67] its efficacy and safety were tested as an add-on therapy to insulin in patients with type 1 diabetes. Although the drug was effective in improving glycemic control, the rate of diabetic ketoacidosis was higher compared with placebo.[67] Sotagliflozin was rejected by the FDA as adjunct therapy for type 1 diabetes. There is currently an ongoing clinical trial studying the efficacy of sotagliflozin in type 2 diabetes. ■

■ DISCLOSURES

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SGLT-2 inhibitors for type 2 diabetes

In the January 2021 issue, in Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. Cleve Clin J Med 2021; 88(1):47–58. doi:10.3949/ccjm.88a.20088, a sentence on page 52 con-tained an error: "However, in January 2020, the 100-mg once-daily dose was approved for use in patients with eGFR 30 to 44 mL/min/1.73 m^2 with urinary albumin excretion less than 300 mg/day." The 100-mg once-daily dose was approved for use in patients with eGFR 30 to 44 mL/min/1.73 m^2 with urinary albumin excretion **more than** 300 mg/day. This has been corrected online.