

Impact of Sodium-Glucose Cotransporter 2 Inhibitors on Nonglycemic Outcomes in Patients with Type 2 Diabetes

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The efficacy of the sodium-glucose cotransporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin in reducing hyperglycemia in patients with type 2 diabetes is well documented. In addition, positive effects have been observed with these agents on nonglycemic variables, such as reductions in body weight and blood pressure, which may confer additional health benefits. SGLT2 inhibitors are also associated with evidence of renal-protecting benefits. Furthermore, during the landmark Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial, a substantial reduction in major adverse cardiovascular outcomes was demonstrated with empagliflozin therapy. In view of the complex pathogenesis of cardiovascular disease in patients with diabetes, a pharmacologic intervention for type 2 diabetes that produces a multifaceted reduction in cardiovascular disease risk, separate from glycemic control alone, would be advantageous. Although SGLT2 inhibitors are generally well tolerated, they are associated with an increased risk of genital mycotic infections, as well as the potential risk for serious adverse events such as dehydration, development of diabetic ketoacidosis, serious urinary tract infections, and bone fractures. The findings of ongoing research will help to determine the magnitude and clinical importance of these adverse events and whether the findings of EMPA-REG OUTCOME represent a class effect for SGLT2 inhibition or are specific to empagliflozin and will further elucidate the future role of SGLT2 inhibitors in the individualized management of patients with type 2 diabetes. In this article, we discuss the nonglycemic outcomes associated with SGLT2 inhibitor therapy in patients with type 2 diabetes as well as the clinical implications of these agents.

KEY WORDS SGLT2 inhibitors, cardiovascular risk, safety.

(*Pharmacotherapy* 2017;37(4):481–491) doi: 10.1002/phar.1903

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are glucose-lowering agents that target the kidney to reduce the reabsorption of glucose and promote urinary glucose excretion.¹ In

healthy individuals, effectively all of the glucose filtered by the kidney is reabsorbed and returned to the blood circulation, and a negligible amount is excreted in the urine.¹ Reabsorption of

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. The authors received no direct compensation related to the development of the manuscript. Writing support was provided by Debra Brocksmith, MB ChB, PhD, and Jennifer Garrett, MBBS, of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Dr Trujillo has disclosed advisory board membership for Sanofi; Dr Nuffer has no disclosures.

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glucose in the kidney is predominantly mediated by SGLT2, located in the early proximal tubule, with minor involvement by sodium-glucose cotransporter 1 (SGLT1), located in the late proximal tubule.¹ In patients with type 2 diabetes (T2D), the expression and activity of SGLT2 are increased in the presence of hyperglycemia, which results in additional glucose reabsorption and maintenance of elevated blood glucose concentration.¹ Thus, the rationale for the use of SGLT2 inhibitors in the treatment of patients with T2D is to reduce renal glucose reabsorption and increase urinary glucose excretion, and thereby reduce hyperglycemia. Pharmacologic inhibition of SGLT2 in the kidney reduces the capacity for renal glucose reabsorption by 30–50%.¹ The mechanism of SGLT2 inhibition occurs independently of insulin secretion and is not affected by pancreatic β -cell function or the degree of insulin resistance.¹ Consequently, SGLT2 inhibitors have the potential to be given at any stage of T2D progression and in combination with any class of glucose-lowering agent, including insulin.¹

Currently, three SGLT2 inhibitors are approved in the United States for the treatment of patients with T2D: canagliflozin,² dapagliflozin,³ and empagliflozin.⁴ These three agents also have marketing approval for use in the management of T2D in the European Union and in other parts of the world. Three additional SGLT2 inhibitors (ipragliflozin, luseogliflozin, and tofogliflozin) are approved and marketed in Japan, although they are not available in the United States at this time. Further SGLT2 inhibitors are currently in clinical development in the United States (e.g., ertugliflozin and sotagliflozin). A small number of phase 1 and 2 clinical trials to investigate the safety and efficacy of SGLT2 inhibitors in patients with type 1 diabetes (T1D) have been completed or are under way. In the 2016 American Diabetes Association (ADA) general recommendations for glucose-lowering therapy in patients with T2D, initial treatment with metformin (if not contraindicated) is preferred, and SGLT2 inhibitors are one of several second-line options for dual therapy with metformin, as well as a possible option for triple therapy.⁵ The current consensus statement from the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) for the management of T2D positions the use of SGLT2 inhibitors as one of several options for monotherapy in patients with contraindications or intolerance to

metformin and as one possible component of dual and triple therapy, either added to metformin, with or without other glucose-lowering agents, or in a regimen without metformin.⁶ In addition, the AACE/ACE treatment algorithm considers SGLT2 inhibitors to be an option for addition to basal insulin and as an alternative to prandial insulin when regimen intensification is required.⁶ According to meta-analyses of data from randomized controlled trials of canagliflozin, dapagliflozin, and empagliflozin, SGLT2 inhibitor monotherapy was associated with the following significant changes compared with placebo: reductions in glycated hemoglobin (Hb_{A1c}) of ~0.5–1.0%, reductions in body weight of ~1.6–2.8 kg, and reductions in systolic blood pressure (BP) of ~3.6–5.1 mm Hg.^{7–9} Compared with active comparators (metformin, sulfonylureas, and/or sitagliptin), these SGLT2 inhibitors showed similar or greater reductions in Hb_{A1c},^{7–9} as well as significant reductions in body weight^{7–9} and systolic BP.^{7, 9}

In patients with T1D and those with T2D, the association between improved glycemic control and the reduced risk of microvascular complications is well established. The efficacy of canagliflozin, dapagliflozin, and empagliflozin in lowering elevated blood glucose concentrations is well documented.^{2–4, 7–9} However, the positive effect observed with these SGLT2 inhibitors on nonglycemic factors, such as body weight and BP, as well as their potential role in protecting renal function, may confer additional health benefits to patients with T2D. Moreover, a substantial reduction in major adverse cardiovascular (CV) outcomes was demonstrated with empagliflozin therapy during the landmark Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial.¹⁰ CV outcome trials for other SGLT2 inhibitors are in progress.

In this article, we examine key data for the nonglycemic outcomes associated with SGLT2 inhibitor therapy in patients with T2D. Articles were retrieved through PubMed, Google, and Google Scholar searches that included terms related to CV risk factors or CV outcomes, renal protection, safety, bone mineral density, and ketoacidosis combined with terms for SGLT2 inhibitors, canagliflozin, dapagliflozin, or empagliflozin. The reference lists from retrieved articles, as well as those from relevant review articles, were also considered. Data from U.S. prescribing information (product label) for canagliflozin, dapagliflozin, and empagliflozin and

relevant drug safety information from the U.S. Food and Drug Administration (FDA) Web site were also used.

Cardiovascular Benefits of SGLT2 Inhibitors

In view of the complex pathogenesis of CV disease in patients with diabetes, a pharmacologic intervention for T2D that produces a multifaceted reduction in CV disease risk, separate from glycemic control alone, would be advantageous.¹¹ ADA guidelines for CV risk management note the benefit of addressing multiple CV risk factors simultaneously.¹² It is of interest, therefore, that SGLT2 inhibition appears to modify a range of nonglycemic CV risk factors that include BP, body weight and adiposity, and arterial stiffness.¹¹ These are summarized in Table 1.^{13–19}

Reduction in Blood Pressure

Studies of SGLT2 inhibitors using 24-hour ambulatory BP monitoring in hypertensive T2D populations have demonstrated that SGLT2 inhibitors are associated with reductions in systolic and diastolic BP and with no compensatory increase in heart rate.²⁰ The precise mechanism for the observed reductions in BP is not fully understood but is thought to be related to the effects of SGLT2 inhibition that lead to osmotic diuresis and mild natriuresis. The presence of nonreabsorbed glucose in the kidney tubule fluid, which is due to SGLT2 inhibition, leads to the excretion of glucose and water due to osmotic diuresis. This effect is consistent with the elevated urinary output (~110–470 mlday) that has been documented in patients treated with SGLT2 inhibitors.²¹ In addition, enhanced sodium excretion may contribute to reduced plasma volume and lower BP, although current clinical trial data to support this are limited. Despite the effects of SGLT2 inhibitor on diuresis and natriuresis, the observed frequencies of volume depletion–related adverse events (e.g., symptomatic hypotension) have been low in patients receiving SGLT2 inhibitor therapy.^{2–4} Patients who may be susceptible to volume depletion events include the following: the elderly, those with a low systolic BP, and/or those with renal impairment^{2–4} and/or those receiving diuretics or renin-angiotensin-aldosterone system blockers.² The BP reduction observed with SGLT2 inhibitors may also be related to the weight loss that is associated with treatment, although the BP-lowering

effect has been shown to occur earlier than any significant weight loss, so other mechanisms are likely to also play a role.²⁰

Reduction in Arterial Stiffness

BP reduction might also be related to the possible beneficial effects of SGLT2 inhibitors on the arterial wall. In a study of patients with T1D, empagliflozin administration was associated with a reduction in arterial stiffness.²² This change was not considered to be due to effects often associated with BP reduction, including changes in the renin-angiotensin-aldosterone system, or endothelial nitrous oxide activity.²² It is also possible that SGLT2 inhibition exerts an anti-inflammatory effect that could contribute to the observed reduction in arterial stiffness.²² Because arterial stiffness is a surrogate marker of renal and cardiac clinical outcomes, SGLT2 inhibitor–induced reduction in arterial stiffness may be an important mechanism by which these agents could provide cardiorenal protection, and further research is required in this area.²²

Reductions in Body Weight and Body Fat and Changes in Lipid Parameters

Weight losses associated with SGLT2 inhibitor treatment were sustained during clinical trials of up to 104 weeks.^{18, 23, 24} Weight loss is related to SGLT2 inhibitor–induced urinary glucose excretion, which results in the loss of approximately 200 kcal/day.²⁵ SGLT2 inhibition also causes a mild osmotic diuresis, which can lead to some degree of weight reduction. However, the majority of the observed weight loss arises from a reduction in body fat mass,^{16, 18} which might be explained by a shift in substrate utilization from carbohydrates to lipids.²⁶

Clinical trials investigating SGLT2 inhibitors (as monotherapy and combination therapy) reported small increases in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, and small decreases in triglyceride levels.²⁷ The significance of these changes in terms of CV disease risk is currently unclear.

Effect on Overall Cardiovascular Risk

As the reported clinical effects of SGLT2 inhibitors include reduction of hyperglycemia, weight loss, and BP reduction, treatment would be expected to confer CV benefits.²⁸ However, the effect of SGLT2 inhibitors on CV outcomes

Table 1. Nonglycemic Cardiovascular Risk Factors Modified by SGLT2 Inhibitor Treatment

Risk Factor	Canagliflozin		Dapagliflozin		Empagliflozin	
	100 mg	300 mg	5 mg	10 mg	10 mg	25 mg
Blood pressure (mm Hg)						
Systolic	-3.7 ^a	-5.4 ^a	-1.4 ^b	-2.7 ^b	-2.6 ^c	-3.4 ^c
Diastolic	-1.6 ^a	-2.0 ^a	-1.0 ^b	-1.3 ^b	-0.6 ^c	-1.5 ^c
Body weight (kg)	-1.9 ^a	-2.9 ^a	-0.6 ^b	-1.0 ^b	-1.93 ^c	-2.15 ^c
Visceral adiposity	-7.4% vs glimepiride (6 or 8 mg once/day) ^d	-8.3% vs glimepiride (6 or 8 mg once/day) ^d	Not reported ^e	-258.4 cm ³ placebo-corrected change (at week 24) ^e	Not reported ^f	-18.8 cm ² vs glimepiride (1-4 mg once/day) in abdominal visceral adipose tissue (at week 104) ^f
Blood lipid levels						
Low-density lipoprotein cholesterol	+2.0% ^{a,h}	+6.1% ^{a,h}	Not reported ^g	-0.9% ^{g,h}	+0.03 mmol/L ^c	+0.07 mmol/L ^c
High-density lipoprotein cholesterol	+6.8% ^{a,h}	+6.1% ^{a,h}	Not reported ^g	+6.7% ^{g,h}	+0.07 mmol/L ^c	+0.09 mmol/L ^c
Triglyceride	-5.4% ^{a,h}	-10.2% ^{a,h}	Not reported ^g	-0.2% ^{g,h}	-0.23 mmol/L ^c	-0.11 mmol/L ^c

Data are placebo-subtracted mean changes from baseline with sodium-glucose cotransporter 2 (SGLT2) inhibitor monotherapy unless otherwise specified. Data are from patients who received approved doses (i.e., according to current U.S. labels) in the primary study cohort.

^aA 26-week randomized double-blind placebo-controlled phase 3 trial (n=584) of canagliflozin 100 or 300 mg, or placebo once/day.¹³

^bA 24-week randomized double-blind placebo-controlled phase 3 trial (n=485) of dapagliflozin 2.5, 5, or 10 mg, or placebo once/day.¹⁴

^cA 24-week randomized double-blind placebo-controlled phase 3 trial (n=899) of empagliflozin 10 or 25 mg, sitagliptin 100 mg, or placebo once/day.¹⁵

^dA 52-week randomized double-blind active-controlled phase 3 noninferiority trial (N=1450) of canagliflozin 100 or 300 mg, or glimepiride 6 or 8 mg once/day.¹⁶

^eDouble-blind, placebo-controlled, phase 3 trial (n=182) of dapagliflozin 10 mg or placebo once/day added to open-label metformin for a 24-week double-blind treatment period followed by a 78-week extension period (site and patient blinded).¹⁷

^fRandomized active-controlled double-blind phase 3 trial (n=1549) of empagliflozin 25 mg or glimepiride as add-on to metformin.¹⁸

^gReview of the cardiovascular effects of dapagliflozin.¹⁹

^hData are percent mean changes.

was unknown until the publication of the EMPA-REG OUTCOME trial in September 2015.¹⁰ During the EMPA-REG OUTCOME trial, patients with T2D and at high risk of CV events were randomized and treated with empagliflozin 10 or 25 mg or placebo in addition to the standard of care. The primary outcome was a composite of CV death, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. Overall, 7020 patients were enrolled and treated, median treatment time was 2.6 years, and there were a total of 772 outcome events. The primary outcome occurred in a significantly lower proportion of patients receiving empagliflozin versus those receiving placebo (10.5% vs 12.1%; hazard ratio [HR] 0.86, 95.02% confidence interval [CI] 0.74–0.99, $p < 0.001$ for noninferiority, $p = 0.04$ for superiority). The main secondary outcome, which was a composite of the primary outcome plus hospitalization for unstable angina, also occurred less frequently among patients receiving empagliflozin versus those receiving placebo (12.8% vs 14.3%; HR 0.89, 95% CI 0.78–1.01, $p < 0.001$ for noninferiority, $p = 0.08$ for superiority). The rate of myocardial infarction (fatal or nonfatal, excluding silent myocardial infarction) was not significantly reduced with empagliflozin versus placebo (4.8% vs 5.4%; HR 0.87, 95% CI 0.70–1.09, $p = 0.23$). Similarly, the rate of stroke (fatal or nonfatal) was not significantly reduced with empagliflozin compared with placebo (3.5% vs 3.0%; HR 1.18, 95% CI 0.89–1.56, $p = 0.26$). However, when compared with placebo, there was a 38% relative risk (RR) reduction in CV mortality in the empagliflozin group (3.7% for empagliflozin vs 5.9% for placebo; HR 0.62, 95% CI 0.49–0.77, $p < 0.001$), a 35% RR reduction in hospital admission for heart failure (2.7% for empagliflozin vs 4.1% for placebo; HR 0.65, 95% CI 0.50–0.85, $p = 0.002$), and a 32% RR reduction in death from any cause (5.7% for empagliflozin vs 8.3% for placebo; HR 0.68, 95% CI 0.57–0.82, $p < 0.001$). Of interest, separation between the empagliflozin and placebo event curves occurred early in the trial.

The EMPA-REG OUTCOME trial was the first dedicated CV outcome study to show that a glucose-lowering agent decreased CV mortality and all-cause mortality, in addition to reducing hospitalization for heart failure in patients with T2D at high risk of CV events.¹⁰ Importantly, the reduction in the primary composite outcomes was driven by a reduction in mortality. The mechanisms underlying the observed CV

effects of empagliflozin remain speculative at present, but the study authors suggested that several mechanisms might be responsible, including changes in arterial stiffness, changes in cardiac function and oxygen demand, cardiorenal effects, reduced albuminuria, and reduced uric acid level, as well as the established effects on lowering hyperglycemia, weight, BP, and body fat mass.¹⁰ The observed reductions in CV events and CV mortality are not fully explained by a reduction in standard CV risk factors, and commentators have speculated on various possible mechanisms.²⁹ Recently, a mechanism involving a change in substrate use in the myocardial cells from glucose or fatty acids to ketones was postulated.²⁶ This potential shift in substrate might improve the metabolic efficiency of the myocardium, which, in conjunction with a reduction in BP and a mild diuresis, could produce a cardioprotective effect.³⁰ The unclear mechanism of CV benefit, as well as the lack of benefit on myocardial infarction and stroke, warrants further investigation.

Cardiovascular outcome trials for canagliflozin (CANVAS; ClinicalTrials.gov identifier NCT01032629), dapagliflozin (DECLARE-TIMI58; ClinicalTrials.gov identifier NCT01730534), and ertugliflozin (VERTIS CV; ClinicalTrials.gov identifier NCT01986881) are ongoing. Final data from the CANVAS trial are due later in 2017, whereas the DECLARE and VERTIS trials are both expected to be reported in 2019.

Renal Effects of SGLT2 Inhibitors

Chronic kidney disease (CKD) is common in patients with T2D, with an estimated prevalence of 43.5%, according to data from U.S. National Health and Nutrition Examination Survey 1999–2012 (CKD was defined by either estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m² or urinary albumin excretion ≥ 30 mg/g).³¹ Because the mechanism of action of SGLT2 inhibitors requires adequate renal function for effective reduction of hyperglycemia, these agents are contraindicated in people with severe renal impairment. Thus, the current U.S. prescribing information for SGLT2 inhibitors recommends that these agents not be used in patients with impaired renal function.^{2–4} Specifically, SGLT2 inhibitors are contraindicated in patients with an eGFR of < 30 ml/minute/1.73 m².^{2–4} Initiation or continued treatment with canagliflozin or empagliflozin is not recommended if eGFR is persistently < 45 ml/minute/1.73 m².^{2, 4} No

dosage adjustment is needed for empagliflozin if eGFR is ≥ 45 ml/minute/1.73 m²,⁴ whereas the dose of canagliflozin is limited to 100 mg once/day in patients with moderate renal impairment or CKD with an eGFR of 45 to < 60 ml/minute/1.73 m².² Dapagliflozin should not be initiated if the eGFR is < 60 ml/minute/1.73 m² and is not recommended if eGFR is persistently between 30 and < 60 ml/minute/1.73 m².³ Renal function should be assessed before the initiation of SGLT2 inhibitor therapy and subsequently monitored on a regular basis.²⁻⁴

Following postmarketing reports of acute kidney injury with canagliflozin and dapagliflozin, the FDA reinforced the existing warning in the drug labels of these agents to include information on this potential risk.³² Before initiating therapy with either of these SGLT2 inhibitors, the FDA advises that health care professionals should consider whether patients have risk factors for kidney injury (including reduced blood volume, chronic kidney insufficiency, heart failure, and concomitant medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs).³² The FDA further advises that the SGLT2 inhibitor agent should be discontinued promptly if acute kidney injury occurs.³²

SGLT2 inhibition has been evaluated in clinical trials of patients with T2D and CKD (stages 1-4).³³⁻³⁸ Two studies of SGLT2 inhibition in patients with T2D and stage 3 CKD showed that canagliflozin was associated with reductions in Hb_{A1c}, BP, and body weight and was generally well tolerated in this vulnerable population.^{34, 35} In both analyses (one 26-week study³⁴ and one analysis of four studies of 18-26 weeks' duration³⁵), eGFR declined ~10-15% during the initial weeks of therapy but then returned toward baseline levels by the end of each study. Similar findings have been observed with dapagliflozin treatment in patients with moderate renal impairment, where initial reductions in eGFR were not sustained and, although no improvement in glycemic control was observed, reductions in BP and weight were achieved during 104 weeks of treatment.³⁸ Empagliflozin treatment in patients with stage 2 and stage 3 CKD achieved reductions in Hb_{A1c}, but no change in Hb_{A1c} was observed in patients with stage 4 CKD who received treatment with empagliflozin.³⁷ However, reductions in BP and weight were observed with empagliflozin treatment in patients with stages 2, 3, and 4 CKD.³⁷ A pooled analysis of data from four 24-

week, placebo-controlled studies of empagliflozin showed that treatment was also associated with decreases in eGFR and increases in serum creatinine concentration, with the greatest changes being reported in patients with moderate renal impairment at baseline.⁴ The short-term changes in eGFR observed with all of these agents suggest an early hemodynamic effect of treatment that becomes attenuated over time and do not suggest the development of progressive renal injury.³⁴⁻³⁷ However, an increased incidence of kidney-related adverse events (e.g., increased serum creatinine concentration, reduced eGFR, renal failure, and impairment of renal function) was reported with canagliflozin versus placebo in patients with stage 3 CKD.³⁵

The SGLT2 inhibitors are associated with evidence of renal benefits. Of interest is the fact that renal hyperfiltration, a marker of diabetic nephropathy, has been shown to decrease in normotensive, normoalbuminuric patients with T1D following SGLT2 inhibitor therapy with empagliflozin 25 mg once/day for 8 weeks.³⁹ In clinical studies, canagliflozin therapy was associated with a reduction in the albumin:creatinine ratio, a change suggesting prevention of renal injury progression.³⁴ Dapagliflozin had no adverse effect on albuminuria in a pooled analysis of 12 randomized controlled trials.³⁶ Similarly, urinary albumin:creatinine ratios improved after 52 weeks of empagliflozin therapy, compared with placebo, for patients with stage 2 or 3 CKD.³⁷ The EMPA-REG OUTCOME trial also investigated prespecified renal outcomes in patients with T2D and high CV risk, including incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of the serum creatinine concentration, initiation of renal replacement therapy, or death from renal disease), and incident albuminuria (defined as urinary albumin:creatinine ratio ≥ 30 mg/g).⁴⁰ Empagliflozin treatment was associated with a statistically significant RR reduction of 39% in incident or worsening nephropathy versus placebo (rates were 12.7% vs 18.8%, respectively).⁴⁰ There was no significant difference in the rate of incident albuminuria between the treatment groups (~51% for each). However, progression to macroalbuminuria, a component of incident or worsening nephropathy, showed a statistically significant RR reduction of 38% for empagliflozin versus placebo (rates were 11.2% vs 16.2%, respectively). Patients in the empagliflozin group also had a significantly lower risk of developing clinically important renal outcomes, including

doubling of serum creatinine concentrations and initiation of replacement therapy, compared with those in the placebo group.

The beneficial effects of SGLT2 inhibitors on renal function are thought to result from the reduction of proximal tubular reabsorption of sodium due to SGLT2 inhibition, which causes tubuloglomerular feedback (via increased sodium delivery to the macula densa), afferent vasoconstriction, and decreased hyperfiltration.^{33, 40} These effects on hyperfiltration have been shown to occur independently of the glucose-lowering effects of SGLT2 inhibitors.³³ Other factors might also play a role in the reduction of progression of renal disease with these agents, including reduction of arterial stiffness and vascular resistance,^{22, 39} decreases in serum uric acid levels, and modulation of systemic and renal neurohormonal systems.^{33, 40}

Two dedicated renal protection studies using SGLT2 inhibitors are under way: a study of the effects of canagliflozin on renal end points in adults with T2D (CANVAS-R, ClinicalTrials.gov identifier NCT01989754), and an evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy (CREDENCE, ClinicalTrials.gov identifier NCT02065791). The results of these trials are expected to be reported later in 2017 and in 2020, respectively. A study to evaluate the effect of dapagliflozin on blood glucose level and renal safety in patients with T2D and moderate renal impairment, CKD stage 3A, (DERIVE, ClinicalTrials.gov identifier NCT02413398) is also under way and expected to report later in 2017.

SGLT1 Inhibition

Sodium-glucose cotransporter 1 is expressed in the intestine and plays a central role in the intestinal absorption of glucose and the release of incretin hormones. Animal studies have shown that the inhibition of SGLT1 promotes the secretion of glucagon-like peptide-1 (GLP-1) through increased glucose concentrations in the distal part of the small intestine.⁴¹ The glucose-lowering effects of GLP-1 are well documented and include increasing the glucose-dependent secretion of insulin and inhibiting gastric emptying and glucagon secretion. SGLT1 appears to be upregulated in subjects with T2D, compared with subjects without diabetes, which results in an increased capacity for intestinal absorption of monosaccharides, although the underlying mechanism is not yet understood.⁴²

Sodium-glucose cotransporter 2 inhibitors with a high selectivity for SGLT2 (vs SGLT1) may be associated with a greater gastrointestinal tolerability versus agents with low selectivity,⁴³ as SGLT1 inhibition may reduce the absorption of monosaccharides in the small intestine, resulting in these sugars reaching the large intestine and leading to intestinal water retention and the risk of diarrhea. A comparison of the *in vitro* potency of several SGLT2 inhibitors showed that empagliflozin had the highest selectivity for SGLT2 over SGLT1 (> 2500-fold) versus agents including tofogliflozin (> 1875-fold), dapagliflozin (> 1200-fold), ipragliflozin (> 550-fold), and canagliflozin (> 250-fold), suggesting that empagliflozin might have superior gastrointestinal tolerability compared with less selective agents.⁴³ However, data from recent animal studies suggest that in patients with T2D, complete renal and/or partial intestinal inhibition of SGLT1, in addition to SGLT2 inhibition, may confer benefits by improving glucose control beyond that of SGLT2 inhibition alone and, potentially, without causing gastrointestinal adverse effects.⁴⁴ A rationale for dual inhibition relates to the expectation that SGLT1 inhibition will reduce postprandial glucose levels by reducing the uptake of glucose from the gut. A dual SGLT2/SGLT1 inhibitor, sotagliflozin, is currently in clinical development. Further research will determine the clinical utility of this approach in the management of T2D.

Safety and Tolerability of SGLT2 Inhibitors Related to Mechanism of Action

Many safety and tolerability issues relate to the mechanism of SGLT2 inhibition but are not strictly nonglycemic *per se*, although the clinical relevance of these adverse effects will be considered in this section.

Genital Mycotic Infections and Urinary Tract Infections

Sodium-glucose cotransporter 2 inhibitor therapy is associated with an increased risk of genital mycotic infections.⁷⁻⁹ This is likely to be related to the presence of urinary glucose, although no definitive dose relationship between incidence of infection and SGLT2 inhibitor treatment has been established to date. Genital mycotic infections associated with SGLT2 inhibitors occurred more commonly in females and patients with a history of such infections.²⁻⁴ These infections

were usually of mild to moderate severity^{7, 45} and responded to standard therapy.⁷

The potential risk of urinary tract infections (UTIs) associated with SGLT2 inhibitor therapy is small, and clinical data are not consistent. Pooled data from randomized controlled trials showed that UTIs occurred in 3.8% of patients receiving placebo versus 5.9% and 4.4% of those receiving canagliflozin 100 mg and 300 mg once/day, respectively.² Similar rates of UTIs were reported for dapagliflozin (3.7% for placebo vs 5.7% and 4.3% for dapagliflozin 5 mg and 10 mg once/day, respectively).³ Rates of UTIs for empagliflozin 25 mg once/day and placebo were equal (7.6% for each vs 9.3% for empagliflozin 10 mg once/day).⁴

Postmarketing reports of cases of potentially fatal urosepsis and pyelonephritis that developed from UTIs in patients receiving SGLT2 inhibitors have led to a new warning from the FDA (December 2015) about the possibility of severe urinary tract infection and pyelonephritis with these agents.⁴⁶ Health care professionals have been advised to evaluate patients for signs and symptoms of UTIs and treat such infections promptly, if indicated.

Diabetic Ketoacidosis

Postmarketing reports of serious cases of diabetic ketoacidosis (DKA) resulting in emergency department visits or hospitalization have been recorded for a small number of patients treated with SGLT2 inhibitors; most patients had T2D but some cases of DKA in patients with T1D were also reported, implying off-label use.⁴⁷ Some of these cases of DKA have occurred in patients without significant hyperglycemia and were therefore diagnosed as “euglycemic diabetic ketoacidosis.”^{47–50} Published case reports have also documented episodes of DKA in patients receiving SGLT2 inhibitors in patients with T1D⁴⁸ (i.e., off-label use) and T2D.^{48, 50–52} These reports indicate that the occurrence of DKA is rare and is possibly triggered by factors such as acute febrile illness, reduced calorie intake, reduced insulin dose, and causes of pancreatic insufficiency.⁴⁶ The FDA issued a warning to alert patients and health care professionals to be aware of signs and symptoms of DKA, regardless of ambient plasma glucose levels, and the U.S. product labeling for dapagliflozin, canagliflozin, and empagliflozin was subsequently updated (December 2015).⁴⁶

In a retrospective analysis of data based on 17,596 participants in the canagliflozin clinical trials program, serious adverse events of DKA and related events were reported in four (0.07%), six (0.11%), and two (0.03%) patients with T2D treated with canagliflozin 100 and 300 mg and comparator, respectively (corresponding incidence rates of 0.522, 0.763, and 0.238 per 1000 patient-years).⁴⁹ Data from > 18,000 patients in the dapagliflozin clinical trial program indicate that < 0.1% of patients with T2D experienced DKA events.⁵³ For empagliflozin, eight DKA events were reported among > 13,000 patients with T2D, with no imbalance between events reported for empagliflozin and placebo.⁵³ In a conference convened by the AACE/ACE to discuss the issue of SGLT2 inhibitor-associated DKA, experts concluded that “the prevalence of DKA is infrequent and the risk-benefit ratio overwhelmingly favors continued use of SGLT2 inhibitors with no changes in current recommendations.”⁵⁴

Mechanisms proposed to explain SGLT2 inhibitor-associated DKA include the promotion of renal tubular reabsorption of acetoacetate and the promotion of glucagon secretion with a reduction of endogenous insulin secretion that leads to increased ketone body production.⁵⁵ SGLT2 inhibitor-associated euglycemic DKA is pathophysiologically similar to DKA, except that the urinary glucose excretion induced by SGLT2 inhibitors results in a lowering of plasma glucose levels and increases the likelihood of ketogenesis.⁵³

Bone Safety

The U.S. product label for canagliflozin cites pooled data from nine clinical trials (mean treatment duration 85 weeks) that reported incidence rates of adjudicated bone fractures of 1.4 and 1.5 per 100 patient-years for the canagliflozin 100-mg and 300-mg groups, respectively, versus 1.1 per 100 patient-years for the comparator group.² Fractures occurred as early as 12 weeks after the start of study drug treatment, were often related to minor trauma (e.g., falls), and affected the arms.² In a similar pooled analysis of placebo- and active-controlled studies of canagliflozin, the overall data showed an increase in bone fracture risk for canagliflozin versus the noncanagliflozin treatment groups (2.7% vs 1.9%, respectively).⁵⁶ This was driven by findings from interim results from the

Canagliflozin Cardiovascular Assessment Study (CANVAS) study, which showed a significant increase in fracture risk for canagliflozin-treated patients versus those receiving placebo (4.0% vs 2.6%, respectively), starting within the first few weeks of treatment.⁵⁶ In the CANVAS study, this equated to about six additional fracture cases per 1000 patient-years for canagliflozin versus placebo.⁵⁶ The increased fracture risk in the CANVAS trial was observed in a subset of patients who were older and had a higher baseline CV risk, lower baseline eGFR, and higher baseline use of diuretics than the overall study population. The authors postulated that the increased in fractures might be due to non-treatment-related factors, such as falls; however, the underlying cause of the apparent increased fracture risk with canagliflozin is currently unknown. In a separate analysis, the effects of canagliflozin on bone mineral density (BMD) were investigated in patients with T2D (aged 55–80 years) who received canagliflozin (100 or 300 mg) or placebo for 104 weeks.⁵⁷ Dual-energy X-ray absorptiometry revealed small but statistically significant reductions in BMD at the hip (placebo-subtracted changes of –0.9% and –1.2% for the 100- and 300-mg dose groups, respectively) but no change at other sites (neck of femur, lumbar spine, distal forearm). The FDA issued a revision to the U.S. product label of canagliflozin in September 2015 to include a warning about risks of bone fracture and decreased BMD.⁵⁸

For dapagliflozin and empagliflozin, there is no apparent relationship between drug administration and the occurrence of bone fractures.^{45, 59} An analysis of pooled data from patients treated with empagliflozin (> 9000 patient-years' exposure) showed that the occurrence of bone fractures was similar for patients treated with empagliflozin (1.7% [10 mg] and 1.3% [25 mg]) compared with placebo (1.8%).⁴⁵ Similarly, an evaluation of bone formation, reabsorption, and BMD after 50 weeks of therapy showed no significant changes in these markers for patients who received dapagliflozin versus placebo.⁵⁹

Sodium-glucose cotransporter 2 inhibition may have an adverse effect on bone turnover by increasing renal tubular reabsorption of phosphate and parathyroid hormone secretion, which has the potential to increase the secretion of FGF-23 (a regulator of phosphate homeostasis) from osteocytes, leading to bone resorption. It is also possible that SGLT2 inhibition could lead

to a reduction in mean concentrations of 1,25-dihydroxyvitamin D, which could reduce calcium absorption from the gut and impair the calcification of bones.⁶⁰ Further research is needed to determine any relationship between SGLT2 inhibition and bone metabolism and whether particular patient groups might be identified as having an elevated risk of adverse bone effects. Until then, the clinical significance of bone fractures and BMD changes reported with canagliflozin remains unclear.

Clinical Implications and Place of SGLT2 Inhibitors in T2D Therapy

Sodium-glucose cotransporter 2 inhibitors offer a new treatment option for patients with T2D that will facilitate the individualized treatment recommended by current management guidelines.^{5, 6} At present, there are relatively few published studies that compare SGLT2 inhibitors with other agents used for the management of T2D (in particular, GLP-1 receptor agonists). Current evidence suggests that the average A1C reduction that could be achieved with SGLT2 inhibitors would be expected to be in the range of 0.5–1.0%.^{7–9} However, other factors are also important in the management of T2D, including weight reduction and the need for well-tolerated treatment with a low risk of hypoglycemia, in addition to the convenience of once-daily oral dosing.⁵ In addition, SGLT2 inhibitors offer other potential benefits, including BP reduction,²⁰ CV risk reduction,¹⁰ and possible renal protective effects.^{34, 36, 37, 40} Although SGLT2 inhibitors are generally well tolerated, attention must be paid to the possible risk of serious adverse events,^{2–4} including dehydration, development of DKA,⁴⁶ serious UTIs,⁴⁶ and bone fractures,⁵⁸ as well as the risk of less serious but more common adverse events such as genital mycotic infection. These possible risks must be carefully weighed against the potential benefits for each patient. Patients should be educated about possible adverse effects, how to lower the risk of adverse effects, common symptoms associated with adverse effects, and what to do if adverse effects occur. Patients should be encouraged to drink plenty of water and maintain good hygiene habits, and to contact a health care provider if symptoms of dehydration, genital mycotic infections, or UTIs occur. For DKA, patients should know the common symptoms (nausea, vomiting, abdominal pain, tiredness,

breathing difficulty) and should know that DKA in this setting can occur even if glucose levels are < 250 mg/dl (13.9 mmol/L). If such symptoms arise, patients should stop taking their SGLT2 inhibitor agent and contact their health care provider immediately.

Although the SGLT2 inhibitors are a relatively new class of glucose-lowering agents, several questions remain about their place in clinical practice. First, based on strong evidence of a reduction in CV risk with empagliflozin in patients at high baseline risk of CV events in the EMPA-REG OUTCOME trial,¹⁰ could these study results be extrapolated to a larger population who fit the study inclusion criteria and who could be considered for SGLT2 inhibitor therapy as a second-line agent, over other treatment options? A second question is, are the findings of EMPA-REG OUTCOME represent a class effect for SGLT2 inhibition or are specific to empagliflozin? Third, a similar question applies to the occurrence of serious adverse events associated with SGLT2 inhibitors, as well as the magnitude and clinical importance of these adverse events in the T2D patient population—are these events specific to an individual drug or to the whole drug class? The findings of ongoing research will help to further elucidate the future role of SGLT2 inhibitors in the individualized management of patients with T2D.

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