# Sodium–Glucose Cotransporter 2 Inhibitor Protection Against Adverse Cardiovascular and Renal Outcomes in Patients With Type 2 Diabetes

Edward Shahady[1] and John L. Leahy[2]

**IN BRIEF** New treatments for type 2 diabetes are required to demonstrate cardiovascular safety in dedicated cardiovascular outcomes trials (CVOTs). This article reviews available evidence on cardiovascular, renal, and safety outcomes from CVOTs and real-world analyses of sodium–glucose cotransporter 2 inhibitors, along with considerations for their use in clinical practice.

## Introduction

Type 2 diabetes is strongly associated with increased risk of cardiovascular disease (CVD) and cardiovascular mortality (1–3). People who have had type 2 diabetes for ≥10 years are more than twice as likely to experience a cardiovascular event, including fatal and nonfatal myocardial infarction (MI), compared to people without diabetes (1). This elevated cardiovascular risk is the result of chronic hyperglycemia and other metabolic abnormalities, as well as comorbidities such as hypertension, dyslipidemia, and obesity (4–6). Additionally, within the broad scope of cardiovascular risk, small vessel changes, including arterial thickening, fibrosis, and endothelial dysfunction, can increase the risk of congestive heart failure (HF) in people with type 2 diabetes, even in the absence of coronary artery disease (CAD) (3).

There are many unanswered questions about the role of glucose-lowering therapies in preventing CVD. Early studies of traditional diabetes treatments found a lack of association between cardiovascular benefits and the use of sulfonylureas, insulin, and, to some extent, metformin. These findings initially shifted treatment strategies away from glycemic improvements and toward optimizing known CVD risk factors based on individual patient characteristics, including comorbid hypertension, dyslipidemia, and obesity; smoking; and duration of type 2 diabetes. However, the benefits of glycemic control on mitigating the risk of other complications has resulted in consistent recommendations for glucose lowering across clinical guidelines for diabetes management.

After the recent publication of results from cardiovascular outcomes trials (CVOTs), details are emerging on potential cardiovascular and renal benefits and risks associated with newer treatments for type 2 diabetes, including sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, that are beginning to be reflected in treatment guidelines (4,5,7). This article reviews available evidence on cardiovascular, renal, and safety outcomes from CVOTs and real-world analyses of SGLT2 inhibitors, along with considerations for their use in clinical practice.

## Pharmacologic Treatments for Type 2 Diabetes and Requirements for Cardiovascular Safety Studies

Beginning in the 1990s, several studies were conducted to evaluate the po-

[1]*Diabetes Master Clinician Program, Fernandina Beach, FL*

[2]*University of Vermont College of Medicine, Burlington, VT*

*Corresponding author: Edward Shahady, eshahady@att.net*

*https://doi.org/10.2337/cd18-0064*

tential of intensive glucose-lowering strategies to reduce cardiovascular risk in people with diabetes. Key early studies included the DCCT (Diabetes Control and Complications Trial) in patients with type 1 diabetes and the UKPDS (U.K. Prospective Diabetes Study) in patients with type 2 diabetes who were treated with insulin, metformin, and/or sulfonylureas (8–10). More recent pivotal studies have included ACCORD (Action to Control Cardiovascular Risk in Diabetes) (11), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (12), and VADT (Veterans Affairs Diabetes Trial) (13), which included patients treated with regimens that included thiazolidinediones (TZDs) as well as the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin and the GLP-1 receptor agonist exenatide.

Common themes that emerged from these studies were that no class of agents provided clear cardiovascular benefits (with the possible exception of metformin in the UKPDS), but that all classes of agents were generally safe and well tolerated, except for potential increased risks of worsening edema and HF with TZDs and risks of weight gain and serious hypoglycemia linked to increased cardiovascular mortality with sulfonylureas and insulin.

Subsequently, concerns about possible adverse cardiovascular outcomes with insulin due to increased hypoglycemia risk were essentially silenced by results from the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial (14). This study showed that, although rates of severe hypoglycemia were significantly higher with insulin glargine compared to standard care (1.00 vs. 0.31 per 100 person-years), rates were similar between the insulin and standard care groups for the composite of cardiovascular death, nonfatal MI, or nonfatal stroke and for the composite of these events plus a revascularization procedure and hospitalization for HF (14).

However, very public and sustained concerns about the potential for increased cardiovascular risks associated with diabetes therapies were raised after the publication of a meta-analysis showing a 43% increase in MI and a 64% increase in cardiovascular death with the TZD rosiglitazone (15). As a result of this report and subsequent U.S. Food and Drug Administration (FDA) advisory committee reviews, a boxed warning for myocardial ischemia was added to the rosiglitazone prescribing information, and access to rosiglitazone was restricted (16). In 2008, in part as a result of this experience with rosiglitazone, the FDA issued updated industry guidance requiring pre- and post-approval cardiovascular safety data for all new antidiabetic medications (16,17).

## What Are FDA-Mandated CVOTs?

The 2008 FDA guidance states that, for new antidiabetic therapies to be considered for approval for glucose lowering in type 2 diabetes, studies are required to show that use of these agents is not associated with increases in cardiovascular risk (17). Cardiovascular safety data must be provided showing that, compared to a control group, the upper bound of the two-sided 95% CI is <1.8 for the estimated risk ratio for a composite major adverse cardiovascular event (MACE) endpoint, which is usually defined as cardiovascular death, nonfatal MI, and nonfatal stroke (i.e., three-point MACE), but may also include additional elements such as hospitalization for unstable angina or revascularization procedures (referred to as MACE+). If the upper bound of this CI is between 1.3 and 1.8 in pre-approval studies, a subsequent post-approval study must be conducted with the same MACE endpoint to definitively show that the two-sided 95% CI for the estimated risk ratio is <1.3 (16–19). If the upper bound of the CI is >1.8, then approval cannot be granted. To ensure that the number of observed MACE outcomes is sufficient for statistical power and to provide a meaningful estimate of risk, the Phase 2 and Phase 3 clinical development programs for new antidiabetic agents must include patients at high risk for cardiovascular events such as elderly patients, those with advanced type 2 diabetes, and those with renal impairment (17).

The EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Out-come Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) with empagliflozin was the first of these CVOTs to demonstrate a cardiovascular benefit in patients with type 2 diabetes and high cardiovascular risk (20). Since then, consistent results have been reported with canagliflozin in the CANVAS (CANagliflozin cardioVascular Assessment Study) Program, suggesting a potential class effect for cardioprotection with SGLT2 inhibitors (21). In addition, positive cardiovascular outcomes have been reported in studies of the GLP-1 receptor agonists liraglutide and semaglutide (22,23).

## SGLT2 Inhibitors for the Treatment of Type 2 Diabetes

The kidneys are important regulators of glucose homeostasis. In healthy individuals, the kidneys metabolize ~10% of ingested sugars and provide ~25% of the glucose released into circulation through the process of gluconeogenesis (24,25). The kidneys also contribute to glucose conservation by controlling renal glucose reabsorption via SGLTs and glucose transporters (24,25). These transporters control how much glucose is filtered and reabsorbed by the kidneys. When the renal capacity to reabsorb glucose is reached, excess glucose is excreted in the urine (24,25). Paradoxically, people with type 2 diabetes will have a higher, rather than a lower, threshold for reabsorbing glucose compared to healthy individuals, thereby resulting in a larger amount of renal glucose reabsorption (24). For comparison,

in healthy people, urinary glucose excretion starts to occur when plasma glucose exceeds ~10 mmol/L (~180 mg/dL) compared to ~13.3 mmol/L (~240 mg/dL) in people with type 2 diabetes (24).

SGLT2 inhibitors block the reabsorption of glucose in the kidney by lowering the renal threshold for glucose excretion, which leads to urinary glucose excretion and reduced blood glucose levels (26–28). SGLT2 inhibition also promotes weight loss as a result of the loss of calories via urinary glucose excretion, as well as reduction in blood pressure as a result of enhanced salt and water excretion (24,29). Currently, four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) are approved in the United States as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (Table 1). These SGLT2 inhibitors have been associated with significant reductions in A1C, along with modest reductions in body weight and systolic blood pressure, in a broad range of patient populations, including older adults, patients with high baseline A1C, and patients with moderate renal impairment (29–32). In addition, SGLT2 inhibitors have been associated with reductions in arterial stiffness, adiposity, and oxidative stress, as well as favorable changes in energy metabolism in the heart, which may contribute to cardiovascular benefits (33,34). Because SGLT2 inhibitors act via an insulin-independent mechanism, they are effective at all stages of disease and in combination with other classes of type 2 diabetes medications, and they are associated with a low inherent risk of hypoglycemia (29,35–38).

SGLT2 inhibitors are generally safe and well tolerated, with increased incidence of adverse events that are related to the mechanism of SGLT2 inhibition, including genital mycotic infections, urinary tract infections (UTIs), volume depletion–related adverse events (e.g., hypotension and dehydration), and osmotic diuresis–

**TABLE 1. Prescribing Guidelines and CVOT Details for Approved SGLT2 Inhibitors in the United States**

| Drug | Trade Name | Indications | Dosing | Precautions | CVOT Details |
|---|---|---|---|---|---|
| Canagliflozin (69) | Invokana® | • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes | • Recommended starting dose is 100 mg QD, taken before the first meal of the day<br>• Dose can be increased to 300 mg QD in patients tolerating the 100 mg dose and who have an eGFR ≥60 mL/min/1.73 $m^2$ and require additional glycemic control | • Not for treatment of type 1 diabetes or DKA<br>• Should not be used in patients with an eGFR <45 mL/min/1.73 $m^2$<br>• Monitor patients for risk of lower limb amputation and signs of hypotension, ketoacidosis, acute kidney injury/impaired renal function, hyperkalemia, urosepsis and pyelonephritis, hypoglycemia, genital mycotic infections, bone fracture, and increased LDL-C | • CANVAS Program (21) (CANVAS: NCT01032629; CANVAS-R: NCT01989754)<br>• *n* = 10,142<br>• Inclusion criteria: adults with type 2 diabetes and either ≥30 years of age with a history of CVD (secondary CVD prevention, 66%) or ≥50 years of age with CV risk factors but no history of CVD (primary CVD prevention, 34%)<br>• Median follow-up: 2.4 years; mean follow-up: 3.6 years<br>• Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke (HR 0.86 for canagliflozin vs. placebo) |

*TABLE CONTINUED ON P. 214* →

**TABLE 1. Prescribing Guidelines and CVOT Details for Approved SGLT2 Inhibitors in the United States, *continued from p. 213***

| Drug | Trade Name | Indications | Dosing | Precautions | CVOT Details |
|---|---|---|---|---|---|
| Dapagliflozin (70) | Farxiga® | • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes | • Recommended starting dose is 5 mg QD, taken in the morning<br>• Dose can be increased to 10 mg QD in patients tolerating dapagliflozin who require additional glycemic control | • Not for treatment of type 1 diabetes or DKA<br>• Not recommended in patients with an eGFR persistently <60 mL/min/1.73 $m^2$<br>• Monitor patients for signs of hypotension, ketoacidosis, acute kidney injury/impaired renal function, urosepsis and pyelonephritis, hypoglycemia, genital mycotic infections, increased LDL-C, and bladder cancer | • DECLARE TIMI 58 (71) (NCT01730534)<br>• *n* = 17,160<br>• Inclusion criteria: ≥40 years of age with a history of CVD (secondary CVD prevention, 41%) or ≥55 years of age (men) or ≥60 years of age (women) with CV risk factors (primary CVD prevention, 59%)<br>• Anticipated completion in 2018<br>• Co-primary endpoint: *1*) composite of CV death, nonfatal MI, or nonfatal stroke; *2*) hospitalization for HF or CV death |
| Empagliflozin (72) | Jardiance® | • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes<br>• To reduce the risk of CV death in adults with type 2 diabetes and established CVD | • Recommended dose is 10 mg QD, taken in the morning<br>• Dose can be increased to 25 mg QD | • Not for treatment of type 1 diabetes or DKA<br>• Should not be used in patients with eGFR <45 mL/min/1.73 $m^2$<br>• Monitor patients for signs of hypotension, ketoacidosis, acute kidney injury/impaired renal function, urosepsis and pyelonephritis, hypoglycemia, genital mycotic infections, hypersensitivity reactions, and increased LDL-C | • EMPA-REG OUTCOME (20) (NCT01131676)<br>• *n* = 7,020<br>• Inclusion criteria: ≥18 years of age with a history of CVD<br>• Median follow-up: 3.1 years<br>• Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke (HR 0.86 for empagliflozin vs. placebo) |

*TABLE CONTINUED ON P. 215 →*

**TABLE 1. Prescribing Guidelines and CVOT Details for Approved SGLT2 Inhibitors in the United States, *continued from p. 214***

| Drug | Trade Name | Indications | Dosing | Precautions | CVOT Details |
|---|---|---|---|---|---|
| Ertugliflozin (45) | Steglatro™ | • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes | • Recommended dose is 5 mg QD, taken in the morning<br>• Dose can be increased to 15 mg QD in patients needing additional glycemic control | • Not for treatment of type 1 diabetes or DKA<br>• Should not be used in patients with eGFR <30 mL/min/1.73 $m^2$<br>• Initiation not recommended in patients with eGFR ≥30 and <60 mL/min/1.73 $m^2$<br>• Monitor patients for signs of hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, lower limb amputation, hypoglycemia, genital mycotic infections, and increased LDL-C | • VERTIS-CV (73) (NCT01986881)<br>• *n* = 8,000 (estimated)<br>• ≥40 years of age with a history of CVD<br>• Anticipated completion in 2019<br>• Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke |

*CV, cardiovascular; HR, hazard ratio; LDL-C, LDL cholesterol; QD, once daily.*

related adverse events (e.g., increased thirst and increased urination) (39). There have been concerns about possible associations between SGLT2 inhibitors and increased risk of normoglycemic diabetic ketoacidosis (DKA), bone fractures, and acute kidney injury, but these events are usually infrequent (40–42). Recently, a signal for increased risk of amputation was identified with canagliflozin in the CANVAS Program involving high-risk patients, with ertugliflozin in Phase 3 studies (including interim data from an ongoing CVOT) (43), and with other SGLT2 inhibitors in an analysis of a World Health Organization safety case reports database (21,44,45). These findings are discussed in detail later in this article.

## Cardiovascular and Renal Outcomes From CVOTs of SGLT2 Inhibitors

To date, the completed CVOTs of empagliflozin (EMPA-REG OUTCOME) (20) and canagliflozin (CANVAS Program) (21) have demonstrated cardiovascular and renal benefits in patients with type 2 diabetes and a history of or high risk for CVD. Data from ongoing CVOTs of other SGLT2 inhibitors, including dapagliflozin (DECLARE-TIMI 58 [Dapagliflozin Effect on Cardiovascular Events]; NCT01730534) and ertugliflozin (VERTIS CV [Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess Cardiovascular Outcomes Following Treatment With Ertugliflozin (MK-8835/PF-04971729) in Subjects With Type 2 Diabetes Mellitus and Established Vascular Disease]; NCT01986881) will confirm whether cardiovascular and renal benefits are class effects (Table 1). The ongoing CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; NCT02065791) trial will also provide data on cardiovascular and renal outcomes and safety with canagliflozin in patients with type 2 diabetes and chronic kidney disease (46).

### EMPA-REG OUTCOME

The EMPA-REG OUTCOME trial evaluated the effects of empagliflozin compared to placebo on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care (20,47). Eligible participants were ≥18 years of age, with a BMI ≤45 kg/m$^2$, estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m$^2$, and history of a cardiovascular event, including MI, multi- or single-vessel CAD, unstable angina, stroke, or peripheral artery disease (20).

A total of 7,020 patients participated in the study and were followed for a median of 3.1 years (20). Risk of the primary three-point MACE endpoint of the composite of cardiovascular death, nonfatal MI, or nonfatal stroke was significantly reduced by 14% with empagliflozin compared to placebo (20). This decrease in MACE risk was driven by a 38% reduction in the risk of cardiovascular death with empagliflozin compared to placebo (20). Notably, reductions in risk of cardiovascular death occurred within just a few weeks of treatment initiation with empagliflozin, and mortality benefits were sustained throughout the trial (20). Compared to placebo, empagliflozin was also associated with a 35% reduction in hospitalization for HF, a 34% reduction in the composite of HF hospitalization or cardiovascular death, and a 39% reduction in the composite of hospitalization for HF or death from HF (48). Effects of empagliflozin on HF outcomes occurred early and were sustained throughout the trial (48).

The EMPA-REG OUTCOME trial also explored the effects of empagliflozin on a number of renal-related parameters; however, several of these renal outcomes were not adjudicated (49). Treatment with empagliflozin was associated with an initial reduction in eGFR that stabilized over time, compared to a steady eGFR decline with placebo. The eGFR reduction with empagliflozin was reversed upon cessation of study drug (49). Key renal benefits observed with empagliflozin compared to placebo included a 39% reduction in the risk of incident or worsening nephropathy and a 38% reduction in progression to macroalbuminuria (49). A 46% reduction in risk was also observed with empagliflozin compared to placebo for the composite endpoint of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m$^2$, initiation of renal replacement therapy, or renal death (49).

The safety and tolerability profile of empagliflozin in EMPA-REG OUTCOME was generally consistent with previous studies. Genital mycotic infections and urosepsis were more common with empagliflozin than with placebo, and no other safety imbalances were observed, including for fracture or amputation; however, amputation events were not collected systematically (20).

### CANVAS Program

The CANVAS Program consisted of two double-blind, randomized, placebo-controlled trials of canagliflozin, CANVAS and CANVAS-R (21,50–52). The design of CANVAS-R was nearly identical to CANVAS to allow for an analysis of combined data from both studies to satisfy the FDA post-marketing requirement for cardiovascular safety. Both CANVAS and CANVAS-R enrolled adults with type 2 diabetes (A1C ≥7.0% and ≤10.5%) who were either ≥50 years of age and had ≥2 risk factors for (but no history of) CVD (primary CVD prevention; 34%) or were ≥30 years of age with a history of CVD (secondary CVD prevention; 66%) (21,50–52). The inclusion of the primary CVD prevention cohort in the CANVAS Program is an important distinction from EMPA-REG OUTCOME, which only enrolled patients with a history of CVD. All participants had eGFR >30 mL/min/1.73 m$^2$. Patients in both studies were randomized to receive once-daily canagliflozin or matching placebo (21,52).

The CANVAS Program included 10,142 participants who were followed for a mean of 3.6 years (21). The risk of the three-point MACE primary endpoint of the composite of cardiovascular death, nonfatal MI, or nonfatal stroke was significantly reduced by 14% with canagliflozin compared to placebo (21). Additionally, compared to placebo, treatment with canagliflozin was associated with a 33% reduction in risk of hospitalization for HF and a 22% reduction in the composite of cardiovascular death or hospitalization for HF (21). Similar to observations with empagliflozin, the cardiovascular benefits observed with canagliflozin occurred early in the course of the CANVAS Program, and the benefits were sustained over time (21).

Canagliflozin treatment was associated with increased regression and decreased progression of albuminuria, in addition to reductions in urinary albumin-to-creatinine ratio, especially in patients with baseline micro- or macroalbuminuria (21,53). Consistent with previous Phase 3 studies, eGFR levels initially declined with canagliflozin and stabilized over time, whereas progressive eGFR decline was seen with placebo in the CANVAS Program (53). In a 30-day off-treatment eGFR assessment performed in CANVAS-R, the eGFR decline seen with canagliflozin was reversed upon study drug discontinuation (53).

Renal events in the CANVAS Program were prespecified and adjudicated (21,53). For the composite of 40% reduction in eGFR, end-stage kidney disease (defined as the composite of maintenance of dialysis, renal transplantation, or sustained eGFR <15 mL/min/1.73 m$^2$), or renal death, canagliflozin was associated with a 40% reduction in risk compared to placebo (21). In addition, risk for the composite of doubling of serum creatinine, end-stage kidney disease, or renal death was 47% lower with canagliflozin versus placebo (53).

The safety and tolerability profile of canagliflozin in the CANVAS

Program was generally similar to profiles reported in previous studies, with fewer serious adverse events compared to placebo and no signals for increased risks of cancer, DKA, hyperkalemia, acute kidney injury, pancreatitis, or UTI (21). Rates of all types of fractures (15.4 vs. 11.9 patients per 1,000 patient-years) and of low-trauma fractures (11.6 vs. 9.2 patients per 1,000 patient-years) were higher with canagliflozin than with placebo in the overall population (21). However, there was evidence of heterogeneity in fracture data between CANVAS and CANVAS-R; specifically, fracture risk was higher with canagliflozin than with placebo in CANVAS, but not in CANVAS-R. A new safety signal for increased risk of lower-extremity amputation was identified in the CANVAS Program. The observed amputation risk was about twofold higher with canagliflozin than with placebo (6.3 and 3.4 per 1,000 patient-years, respectively) (21). Amputations were primarily at the level of the toe or metatarsal (accounting for 71% of amputations). Patients with a history of amputation or peripheral vascular disease had the highest risk of amputation in both the canagliflozin and placebo arms (21).

### *Real-World Data on Cardiovascular Outcomes*

Although clinical studies are the gold standard in determining the efficacy and safety of new drugs, they may have limited generalizability to broader patient populations (i.e., patients encountered in actual clinical practice settings). Therefore, in addition to the dedicated CVOTs with SGLT2 inhibitors, researchers are collecting cardiovascular outcomes data in real-world settings. In the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors), which included >300,000 patients across six countries (United States, United Kingdom, Germany, Sweden, Denmark, and Norway), SGLT2 inhibitors provided a significant 39% reduction in hospitalization for HF, a 51% reduction in death from any cause, and a 46% reduction in risk of the composite of hospitalization for HF and all-cause mortality compared to other type 2 diabetes treatments (54). Similar results were observed in the subsequent CVD-REAL 2 study in six additional countries (South Korea, Japan, Singapore, Israel, Australia, and Canada), which found that risk of death was reduced by 49% and risk of hospitalization for HF was reduced by 36% with SGLT2 inhibitors compared to other therapies (55). Significantly reduced risks were also observed with SGLT2 inhibitors versus comparators for MI and stroke (55).

The EASEL (Evidence for cArdiovascular outcomes with Sodium glucose co-transporter 2 inhibitors in the rEal worLd) study was a population-based cohort study of patients with type 2 diabetes and established CVD, based on data from 25,258 propensity-matched patients included in the U.S. Department of Defense Military Health System (56). In this study, compared to non-SGLT2 inhibitors, initiation of SGLT2 inhibitors was associated with a 33% lower risk of the composite of all-cause mortality, nonfatal MI, and nonfatal stroke and a 43% lower risk for the composite of all-cause mortality and hospitalization for HF (56). In a separate observational analysis of data from a large U.S. claims database, canagliflozin was shown to reduce the risk of hospitalization for HF by 30% compared to DPP-4 inhibitors, 39% compared to GLP-1 receptor agonists, and 49% compared to sulfonylureas (57).

## Summary of Cardiovascular and Renal Outcomes With SGLT2 Inhibitors and Other Treatments for Type 2 Diabetes

The EMPA-REG OUTCOME trial was groundbreaking because it was the first FDA-mandated CVOT to provide evidence that treatment of type 2 diabetes may improve cardiovascular and renal outcomes in patients with high levels of cardiovascular risk (20). Findings from the CANVAS Program are equally important because evidence of cardiovascular and renal benefits seen with canagliflozin suggests a possible class effect for SGLT2 inhibitors, and the results were observed in a broader patient population, including primary CVD prevention, with longer follow-up time than in the EMPA-REG OUTCOME trial (21). Notably, SGLT2 inhibitors are the only class of drugs approved to treat type 2 diabetes that have provided statistically significant and clinically important reductions in the risk of hospitalization for HF (19). Additional research is needed to explain the mechanism of improved cardiovascular and renal outcomes with SGLT2 inhibitors, although it has been hypothesized that changes in renal hemodynamics and/or cardiac energy metabolism may contribute (58–61).

In 2018, for the first time, the American Diabetes Association (ADA) *Standards of Medical Care in Diabetes* included cardiovascular effects as key drug-specific and patient factors to consider when selecting appropriate pharmacologic therapies in adults with type 2 diabetes (5). This most recent iteration of the ADA guidelines also includes the specific recommendation to add an agent proven to reduce MACE and/or cardiovascular mortality as second-line therapy in combination with metformin for patients with atherosclerotic CVD. Agents with confirmed benefits include canagliflozin, empagliflozin, and liraglutide; metformin and pioglitazone are classified as having potential cardiovascular benefits (5). The impact of these changes will become apparent over time, but based on these updated recommendations, there is potential for clinicians to implement newer antidiabetic medications with cardiovascular benefits, such as SGLT2 inhibitors, as earlier lines of treatment. However, it will remain important for

clinicians to optimize therapy based on patient characteristics and preferences, overall benefits and risks, and consideration of external factors (e.g., formulary restrictions).

The emergence of a safety signal for amputation with SGLT2 inhibitors warrants clinical consideration. In the CANVAS Program, there was about a twofold increase in the rate of lower-extremity amputation with canagliflozin relative to placebo in high-risk patients with type 2 diabetes, and this was replicated in a real-world population of high-risk patients with type 2 diabetes and confirmed in an analysis of amputation reports in the FDA Adverse Event Reporting System (21,56,62). Most patients with amputations had preexisting amputation risk factors, such as gangrene, foot ulcer, ischemic limb, or previous amputation (63). No imbalance in amputation risk was seen in a pooled analysis of Phase 3 canagliflozin studies (not part of the CANVAS Program) that was representative of a general type 2 diabetes population with lower cardiovascular risk (~6.6% of patients had established CVD) or in a real-world analysis of a general type 2 diabetes population with low cardiovascular risk (64). The EMPA-REG OUTCOME trial did not report an imbalance in amputation risk, but that study did not systematically collect adequate data to confirm or refute this risk (65). An increased amputation risk has been reported for ertugliflozin based on data from its Phase 3 clinical trial program, including interim data from an ongoing CVOT (43), suggesting a potential class effect for SGLT2 inhibitors (45). Increased amputation risk has also been observed with empagliflozin and dapagliflozin, as well as canagliflozin, in an analysis of a World Health Organization safety case reports database (44). Moving forward, longer-term studies of SGLT2 inhibitors that prospectively and systematically collect amputation events will be beneficial to confirm whether amputation is a risk throughout the class.

The mechanism associated with the increased risk of amputation is not known, but clinicians may consider implementing a suitable alternative treatment in patients with a history of amputation or peripheral vascular disease or in patients who develop an amputation-preceding event (e.g., lower-extremity skin ulcer, infection, osteomyelitis, or gangrene) (66–68). Clinicians should also encourage patients taking SGLT2 inhibitors to remain hydrated and to engage in good foot care practices to minimize their risk of amputation. As with any treatment decisions, practitioners should weigh the balance of benefits and risks associated with SGLT2 inhibitors.

In summary, the requirement for CVOTs of new antidiabetic therapies has provided the medical community with high-quality data indicating that treatment with SGLT2 inhibitors (specifically empagliflozin and canagliflozin) can significantly improve cardiovascular and renal outcomes and provide unique benefits related to reductions in adverse HF outcomes in patients with type 2 diabetes who are at high risk for CVD. These results, along with favorable results from trials of other classes of drugs, have led to updates to type 2 diabetes treatment guidelines to place greater emphasis on the prevention of serious and potentially fatal cardiovascular events.

## Acknowledgments

Medical writing support was provided by Cherie Koch, PhD, of MedErgy and funded by Janssen Scientific Affairs.

## Duality of Interest

E.S. has served on advisory boards for Janssen and Novo Nordisk. J.L.L. has served on advisory boards for Janssen, Merck, Novo Nordisk, and Sanofi.

## Author Contributions

Both authors reviewed the literature and wrote, reviewed, and edited the manuscript. E.S. is the guarantor of this work and, as such, had full access to all references cited and takes responsibility for the accuracy of content.

## References

1. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med 2011;171:404–410

2. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–78

3. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus: mechanisms, management, and clinical considerations. Circulation 2016;133:2459–2502

4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2018 executive summary. Endocr Pract 2018;24:91–120

5. American Diabetes Association. *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41:S1–S159

6. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet 2012;380:601–610

7. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2018;42(Suppl. 1):S1–S326

8. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986

9. U.K. Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853

10. U.K. Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865

11. ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559

12. ADVANCE Collaborative Group. Intensive blood glucose control and vascular

outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572

13. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139

14. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328

15. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471

16. Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs–insights from the rosiglitazone experience. N Engl J Med 2013;369:1285–1287

17. U.S. Food and Drug Administration. Guidance for industry: diabetes mellitus: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/%20Guidances/UCM071627.pdf2008. Accessed 16 March 2018

18. Smith RJ, Goldfine AB, Hiatt WR. Evaluating the cardiovascular safety of new medications for type 2 diabetes: time to reassess? Diabetes Care 2016;39:738–742

19. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a Diabetes Care Editors' Expert Forum. Diabetes Care 2018;41:14–31

20. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

21. Neal B, Perkovic V, Mahaffey KW, et al., on behalf of the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657

22. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844

23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322

24. Wilding JP. The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. Metabolism 2014;63:1228–1237

25. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med 2010;27:136–142

26. DeFronzo RA, Hompesch M, Kasichayanula S, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 2013;36:3169–3176

27. Rosenstock J, Aggarwal N, Polidori D, et al., for the Canagliflozin DIA2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232–1238

28. Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab 2010;95:34–42

29. Rosenthal N, Meininger G, Ways K, et al. Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. Ann N Y Acad Sci 2015;1358:28–43

30. Cinti F, Moffa S, Impronta F, et al. Spotlight on ertugliflozin and its potential in the treatment of type 2 diabetes: evidence to date. Drug Des Devel Ther 2017;11:2905–2919

31. White JR Jr. Empagliflozin, an SGLT2 inhibitor for the treatment of type 2 diabetes mellitus: a review of the evidence. Ann Pharmacother 2015;49:582–598

32. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. Cardiovasc Diabetol 2015;14:142

33. Pfeifer M, Townsend RR, Davies MJ, Vijapurkar U, Ren J. Effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on blood pressure and markers of arterial stiffness in patients with type 2 diabetes mellitus: a post hoc analysis. Cardiovasc Diabetol 2017;16:29

34. Cavaiola TS, Pettus J. Cardiovascular effects of sodium glucose cotransporter 2 inhibitors. Diabetes Metab Syndr Obes 2018;11:133–148

35. Neumiller JJ, White JR Jr, Campbell RK. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. Drugs 2010;70:377–385

36. Chao EC, Henry RR. SGLT2 inhibition: a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010;9:551–559

37. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci 2011;32:63–71

38. Matthews DR, Zinman B, Tong C, Meininger G, Polidori D. Glycaemic efficacy of canagliflozin is largely independent of baseline beta-cell function or insulin sensitivity. Diabet Med 2016;33:1744–1747

39. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium–glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. Diabetes Care 2015;38:2344–2353

40. U.S. Food and Drug Administration. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available from www.fda.gov/downloads/Drugs/DrugSafety/UCM446954.pdf. Accessed 22 March 2018

41. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. Available from www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed 22 March 2018

42. U.S. Food and Drug Administration. FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Available from www.fda.gov/Drugs/DrugSafety/ucm505860.htm. Accessed 22 March 2018

43. U.S. Food and Drug Administration. Ertugliflozin new drug application clinical review. Available from www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209803,209805,209806Orig1s000MedR.pdf. Accessed 4 June 2018

44. Khouri C, Cracowski JL, Roustit M. SGLT-2 inhibitors and the risk of lower-limb amputation: is this a class effect? Diabetes Obes Metab 2018;20:1531–1534

45. Merck Sharp & Dohme. STEGLATRO™ (ertugliflozin) [package insert]. Whitehouse Station, N.J., Merck Sharp & Dohme, December 2017

46. Jardine MJ, Mahaffey KW, Neal B, et al. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale and design. Am J Nephrol 2017;46:462–472

47. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). Cardiovasc Diabetol 2014;13:102

48. Fitchett D, Zinman B, Wanner C, et al.; EMPA-REG OUTCOME® Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. Eur Heart J 2016;37:1526–1534

49. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334

50. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the CANagliflozin cardioVascular Assessment Study (CANVAS): a randomized placebo-controlled trial. Am Heart J 2013;166:217–223

51. Neal B, Perkovic V, Matthews DR, et al.; CANVAS-R Trial Collaborative Group. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R):

a randomized, placebo-controlled trial. Diabetes Obes Metab 2017;19:387–393

52. Neal B, Perkovic V, Mahaffey KW, et al. Optimizing the analysis strategy for the CANVAS program: a pre-specified plan for the integrated analyses of the CANVAS and CANVAS-R trials. Diabetes Obes Metab 2017;19:926–935

53. Perkovic V, Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691–704

54. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study. Circulation 2017;136:249–259

55. Kosiborod M, Lam CSP, Kohsaka S, et al.; CVD-REAL Investigators Study Group. Lower cardiovascular risk associated with SGLT-2i in >400,000 patients: the CVD-REAL 2 Study. J Am Coll Cardiol 2018;71:2628–2639

56. Udell JA, Yuan Z, Rush T, Sicignano NM, Galitz M, Rosenthal N. Cardiovascular outcomes and risks after initiation of a sodium glucose co-transporter 2 inhibitor: results from the EASEL population-based cohort study (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World). Circulation 2018;137:1450–1459

57. Patorno E, Goldfine AB, Schneeweiss S, et al. Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study. BMJ 2018;360:k119

58. Abdul-Ghani M, Del Prato S, Chilton R, Defronzo RA. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME study. Diabetes Care 2016;39:717–725

59. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. Diabetes Care 2016;39:1108–1114

60. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. Diabetes Care 2016;39:1115–1122

61. Aubert G, Martin OJ, Horton JL, et al. The failing heart relies on ketone bodies as a fuel. Circulation 2016;133:698–705

62. Fadini GP, Avogaro A. SGLT2 inhibitors and amputations in the U.S. FDA Adverse Event Reporting System. Lancet Diabetes Endocrinol 2017;5:680–681

63. Fulcher G, Matthews DR, de Zeeuw D, Perkovic VH, Neal B, Ferrannini E. CANagliflozin cardioVascular assessment study (CANVAS). Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes in Lisbon, Portugal, 11–15 September 2017

64. Yuan Z, Defalco FJ, Ryan PB, et al. Risk of lower extremity amputations in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors in the United States: a retrospective cohort study. Diabetes Obes Metab 2018;20:582–589

65. European Medicines Agency. PRAC concludes that diabetes medicine canagliflozin may contribute to risk of toe amputation: risk may also apply to other medicines in the same class. Available from www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500221431.pdf. Accessed 8 June 2018

66. Tanaka A, Shimabukuro M, Okada Y, et al. Rationale and design of a multicenter placebo-controlled double-blind randomized trial to evaluate the effect of empagliflozin on endothelial function: the EMBLEM trial. Cardiovasc Diabetol 2017;16:48

67. Ryder REJ, DeFronzo RA. What now on the CANVAS of diabetes medications with cardiovascular protection? Could metformin, pioglitazone, SGLT2 inhibitors and liraglutide complement each other to save lives? Br J Diabetes 2017;17:89–92

68. Janssen-Cilag International. Invokana (300 mg film-coated tablets) [package insert]. Beerse, Belgium, Janssen-Cilag International NV, 2017

69. Janssen Pharmaceuticals. INVOKANA® (canagliflozin) [package insert]. Titusville, N.J., Janssen Pharmaceuticals, July 2017

70. AstraZeneca. FARXIGA® (dapagliflozin) [package insert]. Wilmington, Del., AstraZeneca Pharmaceuticals, October 2017

71. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: participants' baseline characteristics. Diabetes Obes Metab 2018;20:1102–1110

72. Boehringer Ingelheim Pharmaceuticals. JARDIANCE® (empagliflozin) [package insert]. Ridgefield, C, Boehringer Ingelheim Pharmaceuticals, December 2017

73. ClinicalTrials.gov. Cardiovascular outcomes following ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease, the VERTIS CV study (MK-8835-004). Available from clinicaltrials.gov/ct2/show/NCT01986881. Accessed 19 January 2018