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.
pential 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 an 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, 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            | • Not for treatment of type 1 diabetes or DKA                                                     | • DECLARE TIMI 58 (71) (NCT01730534)                                                                 |
|                     |            |                                                                              | • Dose can be increased to 10 mg QD in patients tolerating dapagliflozin who require additional glycemic control | • Not recommended in patients with an eGFR persistently <60 mL/min/1.73 m²                           | • n = 17,160                                                                                      |
|                     |            |                                                                              |                                                                       | • 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 | • 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%) |
|                     |            |                                                                              |                                                                       |                                                                                                   | • Anticipated completion in 2018                                                                   |
|                     |            |                                                                              |                                                                       |                                                                                                   | • 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 | • Recommended dose is 10 mg QD, taken in the morning                   | • Not for treatment of type 1 diabetes or DKA                                                     | • EMPA-REG OUTCOME (20) (NCT01131676)                                                             |
|                     |            | • To reduce the risk of CV death in adults with type 2 diabetes and established CVD | • Dose can be increased to 25 mg QD                                  | • Should not be used in patients with eGFR <45 mL/min/1.73 m²                                     | • n = 7,020                                                                                      |
|                     |            |                                                                              |                                                                       | • 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 | • Inclusion criteria: ≥18 years of age with a history of CVD                                       |
|                     |            |                                                                              |                                                                       |                                                                                                   | • Median follow-up: 3.1 years                                                                      |
|                     |            |                                                                              |                                                                       |                                                                                                   | • Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke (HR 0.86 for empagliflozin vs. placebo) |                                                                                                   |

*TABLE CONTINUED ON P. 215*
There have been concerns about possible associations between SGLT2 inhibitors and increased risk of normal glycemic 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 CREDEENCE (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/m², estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m², 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 m², 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 m². 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 m²), 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.

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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.

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