SGLT2 Inhibitors in Patients with Chronic Kidney Disease and Heart Disease: A Literature Review

ABSTRACT

Sodium-glucose transport protein 2 inhibitors, commonly referred to as SGLT2i, are a group of prescription pharmaceuticals that are approved by the United States Food and Drug Administration for use with diet and exercise to lower blood glucose in adults with type 2 diabetes. Diabetes is a well-recognized major contributor to cardiovascular and renal disease burden. In addition to blood glucose control, SGLT2i have been shown to provide significant cardiovascular and renoprotective benefits in patients with and without diabetes. In this review, we describe current evidence related to the renal and cardiovascular benefits of using SGLT2i.

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INTRODUCTION

Sodium-glucose transporter 2 (SGLT2) is the major transport protein of the sodium-glucose transporter protein family and provides approximately 90% of glucose reabsorption from the kidneys. Inhibiting SGLT2 reduces blood glucose independently of insulin secretion and sensitivity. SGLT2 inhibitors (SGLT2i) are a class of pharmaceuticals that lower blood glucose by causing glucosuria, thereby inhibiting glucose reabsorption from glomerular filtration back into circulation. In addition, SGLT2i have been shown to provide significant cardiovascular and renal protection in patients with and without diabetes. In 2013, canagliflozin was the first SGLT2i approved by the United States (US) Food and Drug Administration (FDA) for the treatment of type 2 diabetes. Since then, several more SGLT2i have been approved (Table 1). Since their initial FDA approval for management of type 2 diabetes, SGLT2i have gained expanded approval for usage in conditions apart from diabetes. In this article, we note the evidence found in clinical trials that highlight the cardiovascular and renal benefits of this class of agents, especially with respect to heart failure and progression of kidney disease.

| SGLT2i             | TRADE NAME | FDA APPROVAL | LIMITATIONS OF USE                                      |
|--------------------|------------|--------------|---------------------------------------------------------|
| Canagliflozin      | Invokana   | As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Not for treatment of type 1 diabetes mellitus or DKA |
| Initial US approval: 2013 |            | To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease | |
| Dapagliflozin      | Farxiga    | To reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression | Not for treatment of type 1 diabetes mellitus; may increase the risk of DKA |
| Initial US approval: 2014 |            | To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction | Not for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m² |
| Empagliflozin      | Jardiance  | To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple CV risk factors | Not for use to improve glycemic control in adults with type 2 diabetes mellitus and an eGFR less than 45 mL/min/1.73 m² |
| Initial US approval: 2014 |            | As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Not for treatment of type 1 diabetes mellitus; may increase the risk of DKA |
| Ertugliflozin      | Steglatro  | As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Not for treatment of type 1 diabetes mellitus; may increase the risk of DKA |
| Initial US approval: 2017 |            |                                                          | |

Table 1 SGLT2i approved by the United States Food and Drug Administration. CV: cardiovascular; DKA: diabetic ketoacidosis; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; CKD: chronic kidney disease

SGLT2i IN OUTCOMES TRIALS

SGLT2i AND RENAL OUTCOMES

Several clinical trials have demonstrated the effects of SGLT2i on kidney disease, with effects on multiple kidney outcomes including albuminuria, doubling of serum creatinine, glomerular filtration rate (GFR) decline, kidney failure, and death. In the EMPA-REG trial, analysis of empagliflozin (an SGLT2i that received FDA approval in 2014) as a specific component of the secondary microvascular outcome decreased progression of renal disease in patients with type 2 diabetes mellitus (T2DM) and high cardiovascular risk compared to a placebo. The end points were worsening nephropathy, seen by doubling of serum creatinine levels, and initiation of renal replacement therapy, which demonstrated a significant relative risk reduction of 44% and 55%, respectively.

The benefit of canagliflozin on the kidney was seen in the CREDENCE trial, which included patients with T2DM with macroalbuminuria (urinary albumin/creatinine ratio > 300 mg/g and estimated GFR [eGFR] of 30–89 mL/min/1.73m²). This trial reported a relative risk reduction of 30% in progression to end-stage renal disease, doubling of serum creatinine level, or mortality from renal
or cardiovascular causes. The CANVAS trial showed a 25% risk reduction in the progression of albuminuria and a 40% risk reduction in the composite of 40% reduction in eGFR, renal replacement therapy, or renal death with the use of canagliflozin. The EMPEROR-REDUCED and VERTIS-CV trials, which studied heart failure and cardiovascular outcomes with empagliflozin and ertugliflozin, noted a similar risk reduction. The absolute difference in the eGFR in the empagliflozin group was higher by 1.73 mL/min/1.73m² than in the placebo group, and in the ertugliflozin group was higher by 2.55 mL/min/1.73m² than in the placebo group.

When dapagliflozin was compared with placebo in patients with chronic kidney disease (CKD) with or without diabetes, the risk of eGFR decline of ≥ 50%, progression to end-stage renal disease, and renal or cardiovascular mortality was notably lower in the treatment group. The SCORED trial assessed cardiovascular outcomes in patients with diabetes and CKD (eGFR 25-60 mL/min/1.73m²) with or without albuminuria. While the primary and secondary end points had to be modified due to a change in trial sponsorship and early closure, sotagliflozin failed to show any significant changes in long-term dialysis, renal transplantation, the first occurrence of a sustained decrease of ≥ 50% in eGFR, or sustained eGFR of < 15 mL/min/1.73m².

**SGLT2i IN KIDNEY TRANSPLANT**

While SGLT2i offer renoprotection, a looming question remains regarding their efficacy and safety in patients who have undergone kidney transplantation. A review of the literature shows that the antihyperglycemic effect of SGLT2i in patients with kidney transplant was comparable to the effect previously demonstrated in large randomized controlled trials in non-kidney transplant patients. A summary of kidney-related outcomes from major SGLT2i trials is represented in Table 2.

**SGLT2i AND CARDIOVASCULAR OUTCOMES**

It is well established that diabetes is a major risk factor for cardiovascular disease (CVD), which affects about a third of individuals with T2DM. Additionally, at least half of the mortality in individuals with T2DM can be attributed to CVD. In recent years, several clinical trials have shown robust evidence regarding the benefits of SGLT2i with respect to cardiovascular outcomes. These studies have included patients with either preexisting heart disease or those with an elevated risk for heart disease. What is striking in these studies is that across different agents in this class, they show a uniform relative risk reduction in hospitalization for heart failure, and considerable heterogeneity exists when assessing the primary cardiovascular end point, which includes death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Only empagliflozin and canagliflozin have shown clinically significant benefits with regard to the primary outcome. Empagliflozin is the only agent to show significant risk reduction for death from cardiovascular or any cause. Ertugliflozin shows no clinically significant benefit in any of the primary or secondary outcomes studied, but it did show a statistically significant risk of hospitalization for heart failure (Table 3). Sotagliflozin also showed a 26% reduction in the modified primary end points. Importantly, as with most SGLT2i drug trials, the benefit in the primary outcomes was likely secondary to the reduction in hospitalization for heart failure. Table 3 shows a summary of cardiovascular outcome trials for SGLT2i.

**HEART FAILURE OUTCOMES**

Further trials including patients with heart failure have helped to better delineate these outcomes. Empagliflozin showed an overall risk reduction in the primary outcomes of cardiovascular death or hospitalization for heart failure of anywhere from 21% to 25% in patients with either heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Ertugliflozin showed similar outcomes in patients with HFpEF, with a 26% overall risk reduction. Although a study of sotagliflozin ended early due to lack of funding from the sponsor, it showed a 33% risk reduction with a median follow-up of only 9 months. Moreover, the CANVAS program reduced the overall risk of heart failure events but had no clear difference in effects on patients with HFrEF versus HFpEF. It is important to recognize that in these studies, no death benefit was noted except in the dapagliflozin study.

A meta-analysis of more than 20,000 patients from 15 randomized controlled trials noted a 31% reduction in hospitalization for heart failure and a 61% reduction in urgent visits for heart failure. Additionally, Cardoso et al. noted a 14% reduction in all-cause mortality and a similar reduction in cardiovascular mortality. These findings were significantly lower in individuals treated with SGLT2i across subgroups of age, sex, race, renal function, and heart failure functional classification. Another meta-analysis by McGuire et al. studied over 46,000 patients from six trials and noted a 32% risk reduction in hospitalization for heart failure and, despite significant heterogeneity of associations with outcomes, a 15% risk reduction for cardiovascular death.

These studies and meta-analyses may indicate an improvement in quality of life and functional status, due to a uniform risk reduction in hospitalization for heart failure, whereas mortality benefits show only some heterogeneity among studies. Additional studies with dapagliflozin and canagliflozin have assessed and reported quality of life outcomes. The PRESERVED-HF trial assessed the primary end point of Kansas City Cardiomyopathy Questionnaire Clinical
| TRIAL                | DRUG       | NO. OF PARTICIPANTS | PERCENTAGE OF PARTICIPANTS WITH CKD, eGFR < 60 mL/min/1.73m² | PRIMARY OUTCOME^ | PROGRESSION OF ALBUMINURIA | COMPOSITE OF 40% REDUCTION IN eGFR, RENAL REPLACEMENT THERAPY OR RENAL DEATH | DOUBLING OF SERUM CREATININE | ESRD: eGFR < 15, CHRONIC DIALYSIS, KIDNEY TRANSPLANTATION | DECLINE IN eGFR OF ≥50% | ABSOLUTE DIFFERENCE IN eGFR, (STUDY DRUG-PLACEBO, mL/min/1.73m²) | INCIDENT OR WORSENING NEPHROPATHY |
|---------------------|------------|---------------------|----------------------------------------------------------------|------------------|-----------------------------|--------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------|--------------------------------|
| EMPA-REG OUTCOME    | Empagliflozin | 7,020               | 25.9                                                          | Table 3          | 38% RRR                     | 44% RRR                                                                     | 46% RRR                       |                                                                               | 39% RRR                        |                                                                               |
| CANVAS              | Canagliflozin | 10,142              | 20.1                                                          | Table 3          | 27% RRR                     | 40% RRR                                                                     |                                                                               |                                                                               |                               |                                                                               |
| CREDENCE            | Canagliflozin | 4,401               | 59.9                                                          | Table 3          | 30% RRR                     | 40% RRR                                                                     | 32% RRR                       |                                                                               |                               |                                                                               |
| EMPEROR-REDUCED     | Empagliflozin | 3,730               | 48.2                                                          | Table 4          | 50% RRR                     |                                                                               | 1.73 (1.1–2.37)               |                                                                               |                               |                                                                               |
| VERTIS-CV           | Ertugliflozin | 8,246               | 21.9                                                          | Table 3          | 21% RRR                     | 34% RRR                                                                     | NS                            | 2.55 (1.5–3.61)                                                              |                               |                                                                               |
| DAPA-CKD            | Dapagliflozin | 4,304               | 89.5                                                          | Table 3          | 39% RRR                     |                                                                               | 36% RRR                       | 47% RRR                                                                     |                               |                                                                               |
| SCORED              | Sotagliflozin | 10,584              | 100                                                           | Table 3          | NS*                         |                                                                               |                               |                                                                               |                               |                                                                               |

Table 2 Summary of renal outcomes trials of SGLT2 inhibitors. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; RRR: relative risk reduction.

^ Primary outcomes varied between different studies. CREDENCE: Composite of end-stage kidney disease (dialysis, transplantation, eGFR < 15 mL/min/1.73m²), doubling of serum creatinine or death from renal or cardiovascular causes; DAPA-CKD: composite of first occurrence of any of decline of at least 50% in eGFR, onset of end-stage kidney disease (dialysis, kidney transplantation or eGFR < 15 mL/min/1.73m²), or death from renal or cardiovascular causes.

* NS not significant for first occurrence of a sustained decrease of ≥50% in eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of ≤15 mL/min/1.73m² for ≥30 days.

| TRIAL                | DRUG       | NO. OF PARTICIPANTS | MEDIAN FOLLOW-UP, YEARS | MALE GENDER STUDY POPULATION, % | STUDY ARM/PLACEBO ARM | PREEXISTING CVD, % | PREEXISTING HEART FAILURE, % | CKD WITH eGFR <60 mL/min/1.73m², % | PRIMARY OUTCOME^ | HOSPITALIZATION FOR HEART FAILURE | DEATH FROM CV CAUSES | DEATH FROM ANY CAUSE |
|---------------------|------------|---------------------|-------------------------|-------------------------------|----------------------|---------------------|-----------------------------|----------------------------------|------------------|-------------------------------|---------------------|---------------------|
| EMPA-REG, 2015      | Empagliflozin | 7020               | 3.1                     | 71.2/72                       | >99                  | 10.1                | 25.9                        | 14% RRR                          | 35% RRR          | 38% RRR                      | 32% RRR              | 32% RRR              |
| CANVAS, 2017        | Canagliflozin | 10,142             | 126.1 weeks             | 64.9/63.3                    | 65.5                 | 14.4                | 20.1                        | 14% RRR                          | 33% RRR          | NS                            | NS                  | NS                  |
| DECLARE-TIMI 58, 2018 | Dapagliflozin | 17,160             | 4.2                     | 63.1/62.1                    | 40.6                 | 10.0                | 7                           | NS*                             | 27% RRR          | NS                            | NS                  | NS                  |
| VERTIS-CV, 2020     | Ertugliflozin | 8,246              | 3.0                     | 70.3/69.3                    | 100                  | 23.7                | 21.9                        | NS*                             | 30% RRR          | NS                            | NS                  | NS                  |
| SCORED, 2020        | Sotagliflozin | 10,584             | 16 months               | 55.7/54.5                    | At least 22%        | 31%                 | 100                         | 26% RRR                          | 33% RRR          | NS                            | NS                  | NS                  |

Table 3 Summary of cardiovascular outcome trials of SGLT2i.

^ Primary outcome = death from cardiovascular causes, nonfatal MI, or nonfatal stroke; RRR: relative risk reduction; NS: not significant, * significant for noninferiority.
Summary Score (KCCQ-CS) and 6-minute walk test (6MWT) in 324 patients with HFpEF after 12 weeks of treatment with dapagliflozin. The study reported a 5.8-point improvement in KCCQ-CS and an improvement of 20.1 meters in the 6MWT, both statistically significant, while noticing reduced weight, but no differences were reported in the N-terminal pro-B-type natriuretic peptide (NT-proBNP), BNP levels, or other secondary end points. The CHIEF-HF trial, which was conducted entirely virtually, assessed the primary outcome of change in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 12 weeks in 476 participants who were randomized to either canagliflozin or placebo. The change in score was 4.3 points higher with canagliflozin than with placebo, independent of ejection fraction or diabetes status. While this study has its limitations due to being virtual, the improvement in the clinical outcome is significant and may be extrapolated more widely (Table 4).

These studies indicate that SGLT2i not only improve cardiac outcomes as measured in clinical trials but likely contribute to an improved quality of life, with improved walk scores and fewer symptoms associated with heart failure.

**EFFECTS OF SGLT2i APART FROM GLUCOSURIA**

**RENAI E EffecTSS**

SGLT2i help to restore the tubulo-glomerular feedback by increasing sodium chloride transport to macula densa, which causes the release of vasoactive substances including adenosine. Adenosine locally binds to receptors, causing afferent arteriole constriction; this leads to decreases in glomerular perfusion and filtration, which otherwise cause progressive glomerular injury. In contrast, a study in patients with T2DM also shows that SGLT2i causes efferent arteriole dilatation, which reduces GFR. Proximal tubular cells require high oxygen consumption for energy and adenosine triphosphate (ATP)-dependent reabsorption of electrolytes and other organic molecules. Glucose reabsorption via SGLT2 increases in patients with T2DM due to hyperglycemia, which results in hyperfiltration and increased luminal glucose load. As a result, the oxygen demand of tubular cells increases, leaving the proximal tubule relatively hypoxic. SGLT2i decrease the reabsorption of sodium and glucose, thus reducing proximal tubular workload and overcoming the hypoxia.

In early experimental and human diabetes studies, glucose metabolic flux increases in the kidney cortex due to increased glucose uptake in proximal tubular cells, which can lead to mitochondrial dysfunction. SGLT2 inhibition reduces progression of mitochondrial dysfunction and alleviates hypoxia and ATP depletion. In addition, the favorable effect of SGLT2i versus a diuretic in promoting fluid shift, especially from the renal interstitium, and decreased energy consumption by proximal tubular cells may alleviate cortical and outer medullary hypoxia. Alternate mechanisms of action may include increased circulating ketones, causing a shift from glucose to lipid oxidation that, together with an increase in the glucagon-to-insulin ratio, provide increased ketone production, improved myocardial energetics, improved ionic hemostasis, altered adipokine regulation, and autophagy.

**CARDIOVASCULAR EFFECTS**

Although the causes for heterogeneity in several cardiovascular outcomes remain unexplained, a common theme across this family of hypoglycemic pharmacotherapy is its significant benefit in hospitalization for heart failure. Given that benefits to heart failure hospitalization have been noted rather early in the studies, the effects are

| TRIAL                | DRUG     | NO. OF PARTICIPANTS | MEDIAN FOLLOW-UP | MALE GENDER STUDY POPULATION, %, STUDY ARM/PLACEBO ARM | PRE-EXISTING CVD, % | PRE-EXISTING HEART FAILURE, % | CKD WITH eGFR <60 ML/MIN/1.73 m², % | PRI-MARY OUTCOME^^ | HOSPITALIZATION FOR HEART FAILURE | DEATH FROM CV CAUSES | DEATH FROM ANY CAUSE |
|----------------------|----------|---------------------|------------------|--------------------------------------------------------|---------------------|-----------------------------|-----------------------------------|---------------------|----------------------------------|---------------------|---------------------|
| DAPA-HF, 2019        | Dapagliflozin | 4,744               | 18.2 months      | 76.2/77                                                | 56.4^               | 100                         | 40.6                              | 26% RRR              | 30% RRR                        | 18% RRR              | 17%                   |
| EMPEROR-Reduced, 2020| Empagliflozin | 3,730               | 16 months        | 76.5/75.6                                              | 51.8^               | 100                         | 48.2                              | 25% RRR              | 31% RRR                        | NS                  | NS                   |
| EMPEROR-Preserved, 2021 | Empagliflozin | 5,988               | 26.2 months      | 55.4/55.3                                              | 35.4^               | 100                         | 49.9                              | 21% RRR              | 29% RRR                        | NS                  | NS                   |
| SOLOIST-WHF, 2020    | Sotagliflozin | 1,222               | 9.0 months       | 67.4/65.1                                              | 58.3^               | 100                         | NA                                | 33% RRR              | 36% RRR                        | NS                  | NS                   |

Table 4 Summary of heart failure outcomes trials of SGLT2i. CVD: cardiovascular disease; CKD: chronic kidney disease; eGFR: estimate glomerular filtration rate; RRR: relative risk reduction; NS: not significant.

^:^ Primary outcome = composite of adjudicated CV death or worsening/hospitalization for heart failure; #: ischemic cardiomyopathy.
likely not associated with the glucose-lowering properties and changes with blood pressure and cholesterol due to SGLT2i therapy, which often take a long time to yield any beneficial effects. Additionally, these benefits are noted in patients with or without diabetes and irrespective of ejection fraction and across a spectrum of renal function. SGLT2i cause glucosuria and natriuresis, which facilitate improvement in ventricular loading by reducing preload; ensuing osmotic diuresis also contributes. It is theorized that SGLT2i may influence cardiac energy metabolism by shifting cardiac energy reliance from non-esterified fatty acids and glucose to ketones; ketones may increase the mechanical efficiency of the failing heart and are considered a “super fuel” for the failing myocardium. Another interesting hypothesis is that inhibition of Na+/H+ exchanger (NHE) 1 and NHE3 by SGLT2i in both the kidney and the heart may be a common mechanism through which these agents offer cardioprotection and renoprotection. Some experimental models and preliminary studies have shown antiﬁbrotic properties of dapagliflozin and empagliflozin, respectively. It has been suggested that SGLT2i may restore the inflammatory adipokine balance, but this theory has not yet been conﬁrmed. Though the exact process remains unknown, it has been observed that SGLT2i decrease inflammatory markers, including nuclear factor-kB, interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), and many other factors in investigational models of diabetes. Similarly, a decrease in serum tumor necrosis factor receptor 1, IL-6, urine IL-6, and MCP-1 was seen in patients with T2DM on SGLT2i. SGLT2i also reduced uric acid levels in patients with T2DM, thus reducing the inﬂammatory effects of uric acid that contribute to diabetic kidney disease. Joshi et al. highlighted the potential mechanisms by classifying them as conventional and novel. The understood conventional mechanisms can be described as diuresis and blood pressure reduction, weight loss, blood glucose control, and hemoconcentration, while the novel mechanisms comprise the improved myocardial energetics, ionic hemostasis, autophagy, and altered adipokine regulation described above.

THE ROLE OF SGLT2i IN PRIMARY PREVENTION

EFFECT ON LIPIDS
A meta-analysis of 48 randomized controlled trials revealed that SGLT2i significantly increased total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and non-HDL-cholesterol. Additionally, SGLT2i administration significantly decreased triglyceride levels. No significant alteration in LDL/HDL ratio was found after SGLT2i treatment. The dapagliflozin trial demonstrated significant benefit of raising HDL cholesterol level for improving reverse cholesterol transport. Overall, the effects of SGLT2i on dyslipidemia in both human and animal studies are inconclusive.

EFFECT ON WEIGHT
SGLT2i promote weight loss via glucosuria (average 70 grams of glucose per day or 270 kcal) and negative energy balance, leading to significant weight loss. SGLT2i use is associated with a reduction of major adverse cardiovascular events through clinically significant weight loss. Compared with placebo, results of network meta-analyses show reductions of body weight for all SGLT2i treatments of about 1.5 kg to 2 kg, depending on the dose.

PREVENTION OF DIABETES
A prespecified pooled analysis of the DAPA-CKD and DAPA-HF trials showed that dapagliflozin reduced the incidence of new-onset diabetes by approximately one-third. Among people with prediabetes, the number needed to treat was 50 patients per year to prevent one case of new-onset diabetes (absolute risk reduction of 2 events per 100 patient-years). Several mechanisms have been proposed, including protection of pancreatic beta cells from glucose toxicity. Indirect mechanisms could include decrease in insulin resistance through weight loss and improvement of hepatic insulin sensitivity. SGLT2i may thus play a role in the primary prevention of cardiovascular and kidney disease.

SGLT2i SAFETY CONCERNS AND ADVERSE EFFECTS
Severe adverse effects of SGLT2i are rare but have been reported through clinical trials and post-marketing data, as highlighted below.

HYPOGLYCEMIA
SGLT2i used as a monotherapy are all associated with a low risk of developing hypoglycemia. However, the risk is higher when SGLT2i are utilized as an add-on therapy with sulfonylurea or insulin.

MYCOTIC INFECTIONS OF PERINEUM AND URINARY TRACT INFECTIONS (UTIS)
The risk for genital candidiasis increases with the development of glycosuria in poorly controlled hyperglycemia. The most common adverse event of SGLT2i as a group, compared with placebo groups, is mycotic infections, particularly among females. A metaanalysis found that the risk of mycotic genital infections is lower when SGLT2i is combined with dipeptidyl peptidase-4 (DPP-
4) inhibitors than when they are used as a monotherapy or as an adjunct to metformin.\textsuperscript{56} Necrotizing fasciitis of the perineum, called Fournier’s gangrene, is a significant adverse event, although post-marketing case reviews show a lower incidence than initially reported.\textsuperscript{57}

**DIABETIC KETOACIDOSIS AND EUGLYCEMIC DIABETIC KETOACIDOSIS**

The use of SGLT2i has been associated with an increased risk of diabetic ketoacidosis (DKA). The rates of DKA in major trials were 0.1% to 0.5% over 4 to 8 years.\textsuperscript{58} The FDA and European Medicines Agency issued safety reports on DKA risk in patients treated with SGLT2i who showed DKA-like symptoms.\textsuperscript{59} Considering the insulin-independent inhibition of glycemia, DKA may present with mildly elevated or even normal blood glucose levels, leading to delayed diagnosis and management under the term euglycemic DKA (EDKA).\textsuperscript{60} The risk of EDKA is significantly higher in the clinical settings of acute illness, fasting, perioperative states, or excess alcohol consumption.

**AMPUTATION**

In the CANVAS clinical trial, canagliflozin showed an increased risk of toe and foot amputation. The higher risk of amputation seems inconsistent, as it was reported only in the CANVAS trial but not in empagliflozin or dapagliflozin trials, nor in the subsequent CREDENCE trial with canagliflozin.\textsuperscript{61} However, the true risk of this complication as a causation or even a consistent correlation is not clear.\textsuperscript{62}

**FRACTURES**

SGLT2i are associated with a small increase in fractures, as noted in the CANVAS study thus far,\textsuperscript{31} but other SGLT2i randomized clinical trials and meta-analyses have failed to show an increase in fractures. A recent study based on real-world, population-based Medicare data noted no increase in risk of fractures in patients treated with SGLT2i compared to patients treated with either DPP-4 or glucagon-like peptide-1 receptor agonists.\textsuperscript{63} However, it is expected to be an uncertain complication in future trials.\textsuperscript{64}

**USE IN CHRONIC KIDNEY DISEASE/RISK OF ACUTE KIDNEY INJURY**

Data on using SGLT2i in severe or end-stage renal failure are scarce. Some studies have suggested that SGLT2i may prevent the development of acute kidney injury (AKI) despite adverse events related to hypovolemia.\textsuperscript{64,65} The mechanism may be reduced renal hyperfiltration, though an initial and transient decline in eGFR usually follows SGLT2i commencement. In summary, SGLT2i is clinically safe to use in patients with diabetes who have mild to moderate renal failure. The safety of use in patients with eGFR less than 30 is less clear.

**CONCLUSION**

Although SGLT2i were developed as antihyperglycemic agents, a growing body of evidence demonstrates consistent reductions in risks for secondary kidney disease end points (albuminuria and a composite of serum creatinine doubling or eGFR decline, kidney failure, or death) and reductions in CVD events. Although not as robust, there are emerging data on using SGLT2i in patients who have received a kidney transplant. In addition to glycemic benefits, nonglycemic mechanisms are involved in the pathogenesis of CKD and CVD. Due to significant benefits seen, use of SGLT2i in appropriate patient populations is encouraged. With the increasing use of these agents in patients with non-diabetes CVD (particularly heart failure) and CKD to prevent progression, it is of the utmost importance to identify potential significant adverse effects, such as EDKA and genitourinary infections. Although not common, these adverse effects can lead to significant morbidity and in some cases mortality. Therefore, efforts to disseminate awareness and recognition of these adverse effects is imperative since the increased use of these agents is expected to continue.

**KEY POINTS**

• Sodium-glucose transporter 2 inhibitors (SGLT2i), a group of medications that were initially approved to treat type 2 diabetes, are increasingly used for indications such as heart failure and chronic kidney disease prevention in patients without diabetes.

• There are significant data regarding the cardiovascular and renal benefits of these medications in patients with or without diabetes, such as decreased progression of renal disease in patients with type 2 diabetes and high cardiovascular risk, and decreased risk of cardiovascular death or hospitalization for heart failure.

• Significant adverse effects have been shown in clinical trials and are seen in clinical practice. Of particular concern are euglycemic diabetic ketoacidosis (DKA), genitourinary infections including severe infections, and reports of limb amputations.

• Clinicians need to be aware of potential adverse effects of using SGLT2i in patients who may be at high risk of infection, DKA, or limb amputation.
COMPETING INTERESTS

The authors have no competing interests to declare.

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REFERENCES

1. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clin Diabetes. 2014 Jan;32(1):4-11. doi: 10.2337/diaclin.32.1.4
2. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res. 2015 Mar;12(2):78-89. doi: 10.1177/1479164114561992
3. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015 Jan;75(1):33-59. doi: 10.1007/s40265-014-0337-y
4. Bonora BM, Avogaro A, Fadini GP. Extraglycemic Effects of SGLT2 Inhibitors: A Review of the Evidence. Diabetes Metab Syndr Obes. 2020 Jan 21;13:161-174. doi: 10.2147/DMSO.S233538
5. Tuttle KR, Brosius FC 3rd, Cavender MA, et al. SGLT2 Inhibition for CKD and Cardiovascular Disease in Type 2 Diabetes: Report of a Scientific Workshop Sponsored by the National Kidney Foundation. Am J Kidney Dis. 2021 Jan;77(1):94-109. doi: 10.1053/j.ajkd.2020.08.003
6. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):323-34. doi: 10.1056/NEJMoa1515920
7. Sarraju A, Li J, Cannon CP, et al. Effects of canagliflozin on cardiovascular, renal, and safety outcomes in participants with type 2 diabetes and chronic kidney disease according to history of heart failure: Results from the CREDENCE trial. Am Heart J. 2021 Mar;233:141-148. doi: 10.1016/j.ahj.2020.12.008
8. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446. doi: 10.1056/NEJMoab2024816
9. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021 Jan 14;384(2):129-139. doi: 10.1056/NEJMoab2030186
10. Halden TAS, Kvitne KE, Midvedt K, et al. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. Diabetes Care. 2019 Jun;42(6):1067-1074. doi: 10.2337/dc19-0093
11. AlKindi F, Al-OMaryy HL, Hussain Q, Al Hakim M, Chaaban A, Boobes Y. Outcomes of SGLT2 Inhibitors Use in Diabetic Renal Transplant Patients. Transplant Proc. 2020 Jan-Feb;52(1):175-178. doi: 10.1016/j.transproceed.2019.11.007
12. Patel N, Hindli J, Farouk SS. Sodium-Glucose Cotransporter 2 Inhibitors and Kidney Transplantation: What Are We Waiting For? Kidney360. 2021 Apr 22;2(7):1174-1178. doi: 10.34067/KID.0000732021
13. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018 Jun 8;17(1):83. doi: 10.1186/s12933-018-0728-6
14. Sarwar N, Gao P, Seshasai SRK, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010 Jun 26;375(9733):2215-22. doi: 10.1016/S0140-6736(10)60484-9
15. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720
16. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925
17. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038
18. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190
19. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303
20. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021 Jan 14;384(2):117-128. doi: 10.1056/NEJMoa2030183
21. Cardoso R, Graffunder FP, Ternes CMP, et al. SGLT2 inhibitors decrease cardiovascular death and heart failure
hospitalizations in patients with heart failure: A systematic review and meta-analysis. EClinicalMedicine. 2021 Jun 5;36:100933. doi: 10.1016/j.eclinm.2021.100933

22. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021 Feb 1;6(2):148-158. doi: 10.1001/jamacardio.2020.5111

23. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021 Nov;27(11):1954-1960. doi: 10.1038/s41591-021-01536-x

24. Spertus JA, Birmingham MC, Nassif M, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat Med. 2022 Apr;28(4):809-813. doi: 10.1038/s41591-022-01703-8

25. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016 Sep 6;134(10):752-772. doi: 10.1161/CIRCULATIONAHA.116.021887

26. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017 Feb;60(2):215-225. doi: 10.1007/s00125-016-4157-3

27. Tonneijck L, Musket MHA, Smits MM, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017 Apr;28(4):1023-1039. doi: 10.1681/ASN.2016060666

28. Vallon V, Thomson SC. The tubular hypothesis of nephron filtration and diabetic kidney disease. Nat Rev Nephrol. 2020 Jun;16(6):317-336. doi: 10.1038/s41581-020-0256-y

29. Corrigendum to “van Bommel EJM, Musket MHA, van Baar MJ, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial.” Kidney Int. 2020 May;97(5):1061. doi: 10.1016/j.kint.2020.03.009

30. Wang C, Zhou Y, Kong Z, et al. The renoprotective effects of sodium-glucose cotransporter 2 inhibitors versus placebo in patients with type 2 diabetes with or without prevalent kidney disease: A systematic review and meta-analysis. Diabetes Obes Metab. 2019 Apr;21(4):1018-1026. doi: 10.1111/dom.13620

31. Layton AT, Vallon V. SGLT2 inhibition in a kidney with reduced nephron number: modeling and analysis of solute transport and metabolism. Am J Physiol Renal Physiol. 2018 May 1;314(5):F969-F984. doi: 10.1152/ajprenal.00551.2017

32. Sas KM, Kayampilly P, Byun J, et al. Tissue-specific metabolic reprogramming drives nutrient flux in diabetic complications. JCI Insight. 2016 Sep 22;1(15):e86976. doi: 10.1172/jci.insight.86976

33. Hallow KM, Helminger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab. 2018 Mar;20(3):479-487. doi: 10.1111/dom.13126

34. Daniele G, Xiong J, Solis-Herrera C, et al. Dapagliflozin Enhances Fat Oxidation and Ketone Production in Patients With Type 2 Diabetes. Diabetes Care. 2016 Nov;39(11):2036-2041. doi: 10.2337/dc15-2688

35. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018 Oct;61(10):2108-2117. doi: 10.1007/s00125-018-4670-7

36. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017 Mar;104:298-310. doi: 10.1016/j.freeradbiomed.2017.01.035

37. Kang S, Verma S, Hassanabad AF, et al. Direct Effects of Empagliflozin on Extracellular Matrix Remodelling in Human Cardiac Myofibroblasts: Novel Translational Clues to Explain EMPA-REG OUTCOME Results. Can J Cardiol. 2020 Apr;36(4):543-553. doi: 10.1016/j.jcc.2019.08.033

38. Han JH, Oh TJ, Lee G, et al. The beneficial effects of empagliflozin, an SGLT2 inhibitor, on atherosclerosis in ApoE-/- mice fed a western diet. Diabetologia. 2017 Feb;60(2):364-376. doi: 10.1007/s00125-016-4158-2

39. Vallon V, Gerasimova M, Rose MA, et al. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. Am J Physiol Renal Physiol. 2014 Jan;306(2):F194-204. doi: 10.1152/ajprenal.00520.2013

40. Dekkers CCJ, Petrykiv S, LaVerman GB, et al. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. Diabetes Obes Metab. 2018 Aug;20(8):1988-1993. doi: 10.1111/dom.13301

41. Heerspink HJL, Perco P, Mulder S, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia. 2019 Jul;62(7):1154-1166. doi: 10.1007/s00125-019-4859-4

42. Zoppini G, Tarberger G, Chanchol M, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. Diabetes Care. 2012 Jan;35(1):99-104. doi: 10.2337/dc11-1346

43. Zhao Y, Xu L, Tian D, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018 Feb;20(2):458-462. doi: 10.1111/dob.13101
44. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021 Feb 26;107(13):1032-1038. doi: 10.1136/heartjnl-2020-318060

45. Sánchez-García A, Simental-Mendoza M, Millán-Alanís JM, Simental-Mendoza LE. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: A systematic review and meta-analysis of 48 randomized controlled trials. Pharmacol Res. 2020 Oct;160:105068. doi: 10.1016/j.phrs.2020.105068

46. Storgaard H, Gluud LL, Bennett C, et al. Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. PLoS One. 2016 Nov 11;11(11):e0166125. doi: 10.1371/journal.pone.0166125

47. Adingupu DD, Göpel SO, Göpel J, et al. SGLT2 inhibition with empagliflozin improves coronary microvascular function and cardiac contractility in prediabetic ob/ob -/- mice. Cardiovasc Diabetol. 2019 Feb 7;18(1):16. doi: 10.1186/s12933-019-0820-6

48. Kario K, Ferdinand KC, O’Keefe JH. Control of 24-hour blood pressure with SGLT2 inhibitors to prevent cardiovascular disease. Prog Cardiovasc Dis. May-Jun 2020;63(3):249-262. doi: 10.1016/j.pcad.2020.04.003

49. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs. 2019 Feb;79(3):219-230. doi: 10.1007/s40265-019-1057-0

50. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab. 2016 Aug;18(8):783-94. doi: 10.1111/dom.12670

51. Cai X, Yang W, Gao X, et al. The Association Between the Dosage of SGLT2 Inhibitor and Weight Reduction in Type 2 Diabetes Patients: A Meta-Analysis. Obesity (Silver Spring). 2018 Jan;26(1):70-80. doi: 10.1002/oby.22066

52. Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy Balance After Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015 Sep;38(9):1730-5. doi: 10.2337/dc15-0355

53. Rosing P, Inzucchi SE, Vart P, et al. Dapagliflozin and new-onset type 2 diabetes in patients with chronic kidney disease or heart failure: pooled analysis of the DAPA-CKD and DAPA-HF trials. Lancet Diabetes Endocrinol. 2022 Jan;10(1):24-34. doi: 10.1016/S2213-8587(21)00295-3

54. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan;44(Suppl 1):S111-S124. doi: 10.2337/dc21-5009

55. Nicolle LE, Capuano G, Ways K, Usiskin K. Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study. Curr Med Res Opin. 2012 Jul;28(7):1167-71. doi: 10.1185/03007995.2012.689956

56. Zhou Y, Geng Z, Wang X, Huang Y, Shen L, Wang Y. Meta-analysis on the efficacy and safety of SGLT2 inhibitors and incretin based agents combination therapy vs. SGLT2i alone or add-on to metformin in type 2 diabetes. Diabetes Metab Res Rev. 2020 Feb;36(2):e3223. doi: 10.1002/dmrr.3223

57. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier Gangrene Associated With Sodium-Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. Ann Intern Med. 2019 Jun 4;170(11):764-769. doi: 10.7326/M19-0085

58. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357. doi: 10.1056/NEJMoa1812389

59. Dardi I, Kouvatsos T, Jobbour SA. SGLT2 inhibitors. Biochem Pharmacol. 2016 Feb 1;101:27-39. doi: 10.1016/j.bcp.2015.09.005

60. Somagutta MR, Agadi K, Hange N, et al. Euglycemic Diabetic Ketoacidosis and Sodium-Glucose Cotransporter-2 Inhibitors: A Focused Review of Pathophysiology, Risk Factors, and Triggers. Cureus. 2021 Mar 3;13(3):e13665. doi: 10.7759/cureus.13665

61. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925

62. Vlachopoulos C, Terentes-Printzios D, Tsiofus K. Do SGLT2 inhibitors increase the risk of amputation? Make haste slowly. Eur Heart J. 2021 May 7;42(18):1739-1741. doi: 10.1093/eurheartj/ehaa1022

63. Zhuo M, Hawley CE, Paik JM, et al. Association of Sodium-Glucose Cotransporter-2 Inhibitors With Fracture Risk in Older Adults With Type 2 Diabetes. JAMA Netw Open. 2021 Oct 1;4(10):e2130762. doi: 10.1001/jamanetworkopen.2021.30762

64. Scheen AJ. Efficacy and safety profile of SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease. Expert Opin Drug Saf. 2020 Mar;19(3):243-256. doi: 10.1080/14740338.2020.1733967

65. Menne J, Dumann E, Haller H, Schmidt BMW. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: A systematic review and meta-analysis. PLoS Med. 2019 Dec 9;16(12):e1002983. doi: 10.1371/journal.pmed.1002983
