CONTACT HOUR: 2.0 HRS

A review of the expanding applications of SGLT2 inhibitors in chronic kidney disease and heart disease

By Yuki Meng and Marisa Battistella

LEARNING OBJECTIVES

1. To discuss the cardiac and kidney outcomes associated with sodium glucose cotransporter 2 inhibitors (SGLT2i) in patients with chronic kidney disease (CKD)
2. To describe the cardio-renoprotective effects of SGLT2i
3. To summarize the adverse effects associated with SGLT2i

BACKGROUND

Sodium glucose cotransporter 2 (SGLT2) is a key protein that reabsorbs about 90% of glucose in the proximal convoluted tubule of the kidneys (Kalra, 2014). By inhibiting SGLT2, blood glucose levels can be reduced independent of insulin. SGLT2 inhibitors (SGLT2i) belong to a drug class that lowers blood glucose by facilitating excretion of glucose in the urine, thus preventing its reabsorption in the kidneys back into circulation (Kalra, 2014). Since the approval of the first SGLT2i, canagliflozin, by the United States (US) Food and Administration (FDA) in 2013 and subsequently by Health Canada in 2014, SGLT2i have transformed the clinical management of type 2 diabetes mellitus (T2DM). Additional advantages of SGLT2i, irrespective of T2DM, have continued to surface with demonstrated cardiovascular and kidney benefits in people with heart failure (HF), chronic kidney disease (CKD), and atherosclerotic cardiovascular disease (ASCVD).

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At present, there are three SGLT2i available in Canada: canagliflozin, dapagliflozin, and empagliflozin. The labeled indications and doses are listed in Table 1. In this review, we summarize the latest evidence of the cardiovascular and kidney protective benefits of SGLT2i with a focus on CKD with or without T2DM. We offer an overview of cardiorenal efficacy outcomes from key landmark SGLT2i trials in CKD and HF, implications for practice, and safety considerations of SGLT2i.

CARDIORENAL PROTECTIVE MECHANISM OF SGLT2 INHIBITORS

SGLT2i have pleiotropic properties – that is, they exert their cardiorenal protective effects through several different mechanisms. The key kidney mechanism offered by SGLT2 inhibition is believed to be mediated by the restoration of the tubulo-glomerular feedback. Reducing reabsorption of sodium and glucose at the proximal tubules via SGLT2 inhibition leads to increased sodium delivery to the macula densa cells in the distal kidney tubules. Increased sodium concentration sensed by these specialized cells leads to activation of the tubulo-glomerular feedback, which causes vasoconstriction of the afferent arterioles. As a result, intraglomerular pressure and kidney hyperfiltration are reduced, which manifests as decreased albuminuria, a marker of kidney disease progression (Dharia et al., 2023). Other potential mechanisms include reducing pro-inflammatory and oxidative pathways that can cause cardiac and kidney tissue injury (Dharia et al., 2023). The central cardiovascular action of SGLT2i is less understood, although there are several proposed mechanisms as well. Some theories include the influence SGLT2i on cardiac energy metabolism and cardiac muscle cell contractility (Braunwald, 2022). Glucose lowering and blood pressure lowering properties of SGLT2i typically require a period of time to observe clinical benefits. It is believed that the cardio-protection offered by SGLT2i is beyond these known benefits as reduction in HF hospitalization is seen relatively early in clinical trials and in a heterogeneous population of varying degrees in kidney function, heart function (i.e., ejection fraction), and diabetes status (Kansara et al., 2022).

Table 1

Approved Dosing of SGLT2 Inhibitors Based on Kidney Function and Indication

	Canagliflozin (Invokana®)[1]	Dapagliflozin (Forxiga®)[2]	Empagliflozin (Jardiance®)[3]
Approved indications based on current Canadian product monographs	• T2DM • Diabetic nephropathy with urine ACR > 33.9 mg/mmol)	• T2DM • HFrEF • CKD	• T2DM • HF
Usual dose or eGFR 60	100–300 mg daily	T2DM: 5–10 mg once daily HFrEF: 10 mg daily CKD: 10 mg daily	T2DM: 10–25 mg daily HF: 10 mg daily
eGFR 46 to 59	100 mg once daily	CKD and HFrEF: no dose adjustment necessary	No dose adjustment necessary
eGFR 30 to 45		T2DM: not recommended for use	
eGFR 20 to 29*	Not recommended for use†	CKD and HFrEF: no dose adjustment necessary	T2DM: not recommended for use† HF: no dose adjustment necessary
eGFR 20*	Not recommended for use	CKD and HFrEF (eGFR < 25): not recommended for use†	T2DM: contraindicated HF: not recommend for use

CKD=chronic kidney disease; HF=heart failure; HFrEF=heart failure, reserved ejection fraction; T2DM=type 2 diabetes mellitus
[1]Janssen Inc. (2023); [2]AstraZeneca Inc., 2021; [3]Boehringer Ingelheim Ltd., 2023
*Do not initiate but can continue to use down to dialysis or kidney transplantation.
†KDIGO guideline recommends the use of SGLT2i among all patients with T2DM and CKD (based on albuminuria or low eGFR without albuminuria) with an eGFR of at least 20 mL/min/1.73 m^2 (Grade 1A) (Navaneethan et al., 2022).

OUTCOME TRIALS

Several large-scale clinical trials have provided compelling insights into the effects of SGLT2i on both CKD and HF. In trials with the CKD population, important kidney outcomes include cardiovascular or kidney death and kidney disease progression (i.e., eGFR decline, increased serum creatinine, development of end-stage kidney disease (ESKD) at which point dialysis or kidney transplantation is required). In HF trials, key efficacy outcomes include cardiovascular death and hospitalization due to HF.

SGLT2i and Kidney Outcomes

Given the high prevalence of CKD, affecting 1 in 10 individuals in Canada, and nearly 40% of the cases being associated with T2DM (Kidney Foundation, 2023), the CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trial was a well-received landmark study aimed at expanding our knowledge of SGLT2i in the setting of CKD. Of note, approximately 60% of individuals with CKD do not have T2DM as the primary etiology; instead, their kidney dysfunction may be attributed to other causes or risk factor such as hypertension, autoimmune diseases, obstructive uropathy, and more (Kidney Foundation, 2023; Chen et al., 2019). Published in 2019, CREDENCE was the first large-scale study to examine the kidney outcomes of SGLT2i specifically in diabetic CKD (Perkovic et al., 2019). People with diabetic CKD with significant albuminuria (estimated glomerular filtration rate [eGFR] greater than or equal to 30 mL/min/1.73 m^2 and urine ACR greater than or equal to 30 mg/mmol) were randomized to canagliflozin 100 mg daily or placebo. At a median follow-up of 2.6 years, the primary outcome, which was a combined risk of CKD progression or death from a cardiovascular or kidney cause, was significantly reduced by canagliflozin treatment versus placebo.

Following the CREDENCE trial, the DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease) trial, published in 2020, sought to examine the efficacy and safety of SGLT2i in a broader range of people with CKD, including those without T2DM (Heerspink et al., 2020). Notably, 60% of the participants in the DAPA-CKD trial did not have T2DM, and the primary causes of CKD comprised hypertension and glomerular disease, among other factors. Similarly, dapagliflozin 10 mg daily was associated with a significant advantage in reducing CKD progression, as well as cardiovascular or kidney mortality, compared to placebo. The positive outcome was largely driven by slowing CKD progression, which was defined as decline of eGFR greater than or equal to 50%. Most recently published at the end of 2022, the EMPA-KIDNEY (Empagliflozin in Patients with Chronic Kidney Disease) trial further strengthened the preceding evidence of SGLT2i in slowing kidney disease progression. EMPA-KIDNEY had 6,609 participants and was the largest trial to include people with CKD without diabetes and eGFR as low as 20 mL/min/1.73 m^2 or had moderate albuminuria with urine ACR of at least 20 mg/mmoL (The EMPA-KIDNEY Collaborative Group, 2023). Compared to placebo, empagliflozin 10 mg daily significantly reduced the risk of CKD progression and cardiovascular mortality. The benefits of empagliflozin were generally consistent among patients with or without diabetes and regardless of the initial eGFR. The cardiorenal benefits were less pronounced in patients with low to moderate albuminuria (i.e., urine ACR less than 30 mg/mmol). Nevertheless, the accumulating evidence clearly indicates substantial kidney protection and preservation of function through the utilization of SGLT2i in people with CKD.

Implications for Practice

Irrespective of diabetes status, people with CKD with eGFR as low as 20 mL/min/1.73 m^2 or severely increased albuminuria (urine ACR of at least 30 mg/mmol), SGLT2i is the recommended drug therapy to slow the advancement of kidney disease. By employing this treatment, the aim is to increase the duration between the onset of CKD and the development of ESKD where kidney replacement therapy (i.e., dialysis or kidney transplantation) may become necessary.

It is now recommended in the updated clinical practice guideline by Kidney Disease Improving Global Outcomes (KDIGO) on T2DM management in CKD to initiate SGLT2i therapy, irrespective of blood glucose control status, in those with an eGFR of at least 20 mL/min/1.73 m^2 (Navaneethan et al., 2023). This recommendation emphasizes that the benefits of SGLT2i treatment can be obtained even in the absence of T2DM.

SGLT2i and Cardiovascular and Heart Failure Outcomes

Since the initial trials investigating the use of SGLT2i in T2DM, there has been a consistent demonstration of the advantageous effects on heart failure (HF) outcomes across different agents in this class. A majority of SGLT2i clinical trials have presented compelling evidence regarding their advantages with respect to cardiovascular outcomes. These trials encompass patients with known CVD and those with CVD risk factors. Although a consistent benefit has been observed in reducing HF hospitalization, there is variability when it comes to assessing the primary composite outcome, which includes cardiovascular mortality, myocardial infarction, or stroke (Kansara et al., 2022). For instance, only canagliflozin and empagliflozin have shown significant benefits in the primary outcome, and empagliflozin is the only agent to demonstrate significant benefit in cardiovascular and all-cause mortality.

However, it appears most of the cardiovascular benefit derived from SGLT2i are primarily attributed by reduction in HF hospitalization. Several dedicated HF trials, such as DAPA-HF (Dapagliflozin in Patients with Heart Failure with Reduced Ejection Fraction), DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction), EMPEROR-Reduced (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure), and EMPEROR-Preserved (Empagliflozin in Heart Failure with a Preserved Ejection Fraction), have demonstrated this significant advantage with dapagliflozin and empagliflozin (McMurray et al., 2019; Packer et al., 2020; Anker et al., 2021; Solomon et al., 2021). Of note, the background standard therapy of renin-angiotensin-aldosterone system inhibitors, beta-blockers, mineralocorticoid receptor and diuretics were well optimized. Prominently, this advantage of reduced HF hospitalization holds true regardless of left ventricular ejection fraction percentage or the presence of T2DM.

Implications for Practice

SGLT2i is now considered first-line therapy in the management of HF with reduced ejection fraction (HFrEF), mid-range ejection fraction (HFmEF), and preserved ejection fraction (HFpEF) in addition to standard therapies. The Canadian Cardiovascular Society recently updated their guidelines to include SGLT2i as part of the guideline-directed medical therapies for HF (Mancini et al., 2022).

ADVERSE EFFECTS AND RISKS OF SGLT2 INHIBITORS

Overall, SGLT2i are well tolerated and have a low risk of severe adverse effects. More prevalent adverse effects include mycotic genital infection, transient rise in serum creatinine, and increased urinary volume and frequency. Less common or rare adverse effects are urinary tract infection (UTI), diabetic ketoacidosis (DKA), and lower limb amputation. Key monitoring and safety considerations are described below.

Genitourinary Infections

The most common adverse effect of SGLT2i is mycotic genital infection owing to their glucosuric action. This side effect may occur more commonly in T2DM and females (Kansara et al., 2022; Krishnan et al., 2023). Individuals initiating SGLT2i should be counselled on proper hygiene practices and monitoring for signs and symptoms of infection. Typically, the infection is managed with a short course of topical or oral antifungal agents, and SGLT2i discontinuation is not necessary. UTIs are far less common and data from a meta-analysis of randomized controlled trials suggest no increased risk with SGLT2i use (Li et al., 2017). A handful of cases of serious UTIs have been reported in patients with obstructive urologic conditions (U.S. Food and Drug Administration, 2022).

Initial Rise in Serum Creatinine

There is an expected rise in serum creatinine (i.e., dip in eGFR) during the first few weeks of initiating therapy, which is due to the drug class's underlying mechanism of action of reducing intraglomerular pressure (Heerspink et al., 2021). The creatinine stabilizes and returns to closer to baseline values after two to four weeks. An eGFR decline of up to 30% may be acceptable with close monitoring. In both DAPA-CKD and EMPA-KIDNEY trials, dapagliflozin and empagliflozin groups had an initial acute eGFR decline but then had a slower rate of decline compared to placebo in the long-term compared to placebo (Heerspink et al., 2020; The EMPA-KIDNEY Collaborative Group, 2023).

Increased Urinary Frequency and Volume

SGLT2i can cause osmotic diuresis induced by glucosuria. This can lead to increased frequency and volume of urination. In T2DM, urinary frequency and voiding symptoms improve with better glycemic control.

Ketoacidosis and Acute Illness

SGLT2i have been associated with an increased risk of DKA, a serious complication of diabetes characterized by high circulating levels of ketones and glucose. However, the risk of ketoacidosis among patients without diabetes is extremely rare with only one event out of over 30,000 participants observed based on pooled data from a large meta-analysis of SGLT2i landmark trials (Nuffield Department of Population Health Renal Studies Group, 2022). Nevertheless, it is important to note that in certain situations such as acute illness (e.g., diarrhea, vomiting), fasting, surgery, excessive alcohol consumption, or a significant change in insulin dosage, the risk of ketoacidosis becomes significantly higher. In these cases, ketoacidosis may manifest even with mildly elevated or normal blood glucose levels, referred to as euglycemic DKA. This can lead to a delay in diagnosis and treatment since blood

glucose levels may appear to be under control (Kansara et al., 2022). An important patient counselling point is sick day management in which SGLT2i are temporarily held in the setting of an acute illness or volume depletion to lessen the risk of ketoacidosis and acute kidney injury (Morris, 2022).

Lower Limb Amputation

An increased risk of lower limb amputation (toe or metatarsal) was observed in the CANVAS (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) trial (Neal et al., 2017). This was not a significant risk found in subsequent trials and the U.S. FDA removed the original boxed warning based on further evaluation (U.S. FDA, 2020). The small risk may be more relevant in T2DM, and frequent foot examinations are recommended.

ACTIVE AREAS OF RESEARCH

SGLT2i in Dialysis

Currently, SGLT2i use in dialysis is contraindicated given insufficient data and limited research. However, this remains an active area of research and there are ongoing randomized controlled trials such as DAPA-HD (SGLT2 Inhibition in Hemodialysis) and SDHF (The Safety of Dapagliflozin in Hemodialysis Patients with Heart Failure) (Paschen et al., 2022; Gu et al., 2022). In practice, if a patient has initiated SGLT2i treatment but the eGFR drops below 20 mL/min/1.73 m^2, the medication may still be continued and only stopped if the patient is preparing to go on dialysis or receive kidney transplantation.

SGLT2i in Transplant Recipients

There is insufficient data and limited research to support use at this moment. In a recent systematic review of 17 studies of kidney and heart transplant recipients, primarily retrospective and observational in design, the authors concluded that the current understanding of cardiovascular and kidney benefits of SGLT2i in the transplant population remains inconclusive (Lin et al., 2023). It is an active area of research with ongoing randomized, controlled trials such as INFINITI2019 (Efficacy, Mechanisms and Safety of SGLT2 Inhibitors in Kidney Transplant Recipients) and CREST-KT (Cardiorenal Effects of SGLT2 Inhibition in Kidney Transplant Recipients) (Singh et al., 2021; Wolf, 2022). It remains to be seen whether SGLT2i are safe and effective in kidney transplant recipient (Kansara et al., 2022; Lin et al., 2023).

SUMMARY

From its initial beginnings as anti-hyperglycemic agents in the management of T2DM, the clinical application of SGLT2i has rapidly expanded within a decade in establishing its place as standard therapy in HF to increasing uptake of its use in CKD irrespective of diabetes. Evidence from clinical trials demonstrates the superiority of SGLT2i in reducing risks of kidney disease progression, including reducing albuminuria, slowing eGFR decline and serum creatinine rise, and prolonging the time to ESKD requiring kidney replacement therapy. Initiating an SGLT2i may now be considered with eGFR as low as 20 mL/min/1.73 m^2 or severe albuminuria with urine ACR of 30 mg/mmol or greater. In addition to the kidney benefits, SGLT2i have been shown to reduce the risk of HF hospitalization in patients with HF irrespective of ejection fraction or diabetes status. In addition to glucosuria, SGLT2i can improve glomerular hemodynamics, counteract inflammatory and oxidative pathways, and improve energy metabolism. These cardiorenal mechanisms appear to modify the pathogenesis of cardiovascular and kidney diseases. To minimize the chances of complications like DKA and acute kidney injury, it is advisable to temporarily hold SGLT2i treatment if a patient is facing an acute illness or is at risk of fluid loss. Educating patients on sick day management is pertinent. The clinical utilization of SGLT2i is projected to further expand in the context of increasing indications and a broader spectrum of application in cardiovascular and kidney diseases.

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