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REVIEW

Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes—cardiovascular and renal benefits in patients with chronic kidney disease

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Abstract

Purpose Sodium-glucose cotransporter 2 (SGLT2) inhibitors have important cardiovascular and renal benefits in adults with type 2 diabetes who have or are at high risk of cardiovascular and renal disease. These benefits are seen in patients with impaired renal function where the glucose-lowering effects are not observed. Here, we review the pharmacokinetics and pharmacology of SGLT2 inhibitors in relation to cardiovascular and renal outcomes in patients with chronic kidney disease (CKD).

Methods We searched PubMed and EMBASE for original research, meta-analyses and review articles relevant to the pharmacokinetics, and cardiac and renal outcomes of SGLT2 inhibitors published up until June 2019. Specialist society guidelines and publications were also consulted.

Results Renal impairment is currently a contraindication to SGLT2 inhibitor use largely due to limited anti-hyperglycaemic efficacy. However, in cardiovascular outcome trials, and a dedicated renal outcome trial, cardiovascular and renal benefits were seen in participants with CKD suggesting that mechanisms underlying the cardiovascular and renal benefits of SGLT2 inhibitors are likely largely independent of the glucose-lowering action of these agents.

Conclusions Despite minimal glycaemic benefits in patients with type 2 diabetes and stage 3 CKD, the cardiovascular and renal benefits of these agents are preserved in this group of patients. Whether these agents have cardiovascular and renal benefits in patients with stage 4 CKD and patients with non-diabetic CKD needs further research.

Keywords SGLT2 inhibitor · Pharmacokinetics · Cardiovascular outcomes · Efficacy · Safety · Chronic kidney disease

Introduction

Approximately 40% of patients with type 2 diabetes have chronic kidney disease (CKD) [1]. Patients with type 2 diabetes and CKD are a very high risk population for early cardiovascular disease (CVD) and mortality and end-stage renal disease [2]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a relatively new type 2 diabetes medication class, inhibit renal glucose reabsorption leading to glycosuria. The glycosuric effects of SGLT2 inhibitors are attenuated in patients with type 2 diabetes and CKD. Cardiovascular outcome trials (CVOTs) of three SGLT2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) have shown that this drug class has beneficial cardiovascular and renal effects in adults with type 2 diabetes who have CVD or are at high risk of CVD [3–7]. The first dedicated renal outcome trial to release results, CREDENCE, found that canagliflozin has renal and cardiovascular benefits in adults with type 2 diabetes and albuminuric CKD [8]. Thus, these drugs are emerging as important

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therapeutic agents for patients with type 2 diabetes and CKD. While these drugs are efficacious, SGLT2 inhibitors have rare, but potentially serious adverse effects, in particular diabetic ketoacidosis [9]. This review examines the clinical pharmacology of SGLT2 inhibitors with particular focus on cardiovascular and renal outcomes in patients with CKD and summarises the emerging safety issues.

Glucose reabsorption in the kidney—the role of sodium-glucose cotransporters (SGLTs)

Glucose is freely filtered in the glomerulus (approximately 180 g/day) [10]. In healthy adults, filtered glucose is completely reabsorbed by SGLT2 and SGLT1 located in the apical membrane of the proximal tubule. SGLT2 is responsible for approximately 97% of glucose reabsorption in the kidney [10]. When SGLT2 is inhibited, SGLT1 can reabsorb approximately 40–50% of glucose [10]. SGLT2 mRNA is exclusively expressed in the kidney, whereas SGLT1 mRNA is more widely expressed—most abundantly in the small intestine [11]. The renal transport maximum of glucose (T_{mG}) is approximately 11.1 mmol/L [10]. Glycosuria occurs when the plasma glucose exceeds T_{mG}.

Place of SGLT2 inhibitors in the management of type 2 diabetes

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released guidelines in late 2018 for the management of hyperglycaemia in type 2 diabetes [12]. Metformin remains as first-line pharmacological therapy because of its glucose-lowering efficacy, good safety profile and low cost [12]. SGLT2 inhibitors are listed as appropriate second-line agents; however, there are certain clinical settings where SGLT2 inhibitors are preferred to other anti-hyperglycaemic agents, most notably those with established atherosclerotic coronary artery disease and concomitant cardiac failure, as well as CKD [12–14].

Pharmacokinetics of SGLT2 inhibitors—empagliflozin, dapagliflozin, canagliflozin and ertugliflozin

Pharmacokinetics in people without renal or hepatic impairment

Important pharmacokinetic parameters for empagliflozin, dapagliflozin, canagliflozin and ertugliflozin are provided in Table 1. These SGLT2 inhibitors are rapidly absorbed [15–18]. The area under the concentration-time curve (AUC) and peak plasma concentrations (C_{max}) increase approximately proportionally with dose over the therapeutic dose ranges [15, 19, 23, 24]. The major pathway of metabolism is glucuronidation and the glucuronides are inactive [15–18]. Overall, the pharmacokinetic parameters between SGLT2 inhibitors are similar, although empagliflozin has a greater fraction of the parent drug excreted unchanged in the urine (f_e) compared with dapagliflozin, canagliflozin or ertugliflozin (Table 1) [18, 20, 21]. There are no grounds, based on pharmacokinetic profiles alone, for differentiating between class members in clinical practice.

Pharmacokinetics in people with renal or hepatic impairment

Pharmacokinetic studies of SGLT2 inhibitors in people with renal and hepatic impairment have largely been limited to single-dose studies [22, 25–29], but population pharmacokinetic models for dapagliflozin [30], empagliflozin [31] and canagliflozin [32] including these patient populations have been developed. Empagliflozin, dapagliflozin, canagliflozin and ertugliflozin exposure increases with worsening renal impairment; however, AUC does not exceed two-fold that of subjects with normal renal function [22, 25, 26, 33]. Similarly, in subjects with mild, moderate and severe hepatic impairment, increases in empagliflozin and dapagliflozin exposure were less than two-fold that of subjects with normal hepatic function [27, 28]. In single dose studies of canagliflozin in subjects with mild and moderate hepatic impairment, and ertugliflozin in subjects with moderate hepatic impairment, canagliflozin and ertugliflozin exposure, respectively, was comparable to subjects with normal hepatic function [22, 29]. These data do not identify a class member that is obviously preferred in patients with CKD.

Pharmacodynamics

Urinary glucose excretion

SGLT2 inhibitors inhibit up to 40–60% of glucose reabsorption [21, 23]. The renal transport maximum of glucose is reduced in a concentration-dependent manner [34]. Urinary glucose excretion induced by SGLT2 inhibitors is reduced with increasing severity of renal impairment, and this reduction is more marked in stage 4 CKD (estimated glomerular filtration rate (eGFR) 15 to < 30 mL/min/1.73 m^2) compared with stage 2 or 3 CKD (eGFR 60 to < 90 or 30 to < 60 mL/min/1.73 m^2, respectively) [22, 25, 26, 33].

Metabolic responses to SGLT2 inhibitor use

SGLT2 inhibitor use results in a decrease in plasma insulin concentration and an increase in plasma glucagon

Table 1 Therapeutic dose range and pharmacokinetic parameters of empagliflozin, dapagliflozin, canagliflozin and ertugliflozin [15–22]

	Empaglilfozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Therapeutic dose range (mg per day)	10–25	10	100–300	5–15
Time to maximum plasma concentration—t_{max} (hours)	~1.5	~1	~1.5	~1
Terminal half-life—$t_{1/2}$ (hours)	~13	~14	14–15	~17
Plasma protein binding (%)	80–86	~91	~99	~94
Fraction of parent drug excreted unchanged in the urine—f_e (%)	~18	<2.5	< 1	1.5

"~" approximately

concentration [35]. Free fatty acid suppression post-meal is also impaired [35]. Perhaps paradoxically, endogenous glucose production is increased [35]. Corresponding to the decrease in insulin-to-glucagon ratio and increase in free fatty acids, the concentration of beta-hydroxybutyrate is increased [36]. These effects are driven by the hypoglycaemic actions and are muted as renal function declines.

Effect of SGLT2 inhibitors on glycaemic control, weight and blood pressure

In a network meta-analysis of randomised controlled trials (RCTs) of at least 24 weeks, empagliflozin, dapagliflozin and canagliflozin reduced HbA1c (glycated haemoglobin) by 0.6–0.9% (6.6–9.8 mmol/mol) and fasting plasma glucose by 1.1–1.9 mmol/L compared with placebo [37]. SGLT2 inhibitors reduced body weight by 1.6–2.5 kg and systolic and diastolic blood pressure by 2.8–4.9 and 1.5–2.0 mmHg, respectively, compared with placebo [37].

In patients with stage 3 CKD, SGLT2 inhibitors have attenuated glycaemic effects but preserved blood pressure and body weight-lowering effects [38–41]. There are very limited data regarding the efficacy of SGLT2 inhibitors in patients with stage 4 CKD. The EMPA-REG RENAL trial evaluated the efficacy and safety of empagliflozin versus placebo as an add-on to existing anti-hyperglycaemia treatment in participants with type 2 diabetes and stage 2, 3 and 4 CKD [42]. As there were a small number of participants with stage 4 CKD, efficacy measures in this participant group were analysed descriptively. In participants with stage 4 CKD, empagliflozin 25 mg did not reduce HbA1c at weeks 24 and 52, but clinically meaningful reductions in blood pressure and body weight were noted at these time points.

Dual SGLT1 and SGLT2 inhibition may have greater anti-hyperglycaemic efficacy compared with selective SGLT2 inhibition in patients with type 2 diabetes and CKD due to inhibition of SGLT1-mediated intestinal glucose absorption. In a relatively small study of patients with type 2 diabetes and stage 3 or 4 CKD, 7 days of sotagliflozin, a dual SGLT1/SGLT2 inhibitor resulted in significantly lower postprandial glucose levels compared with placebo [43]. A phase 3 trial examining the glycaemic effects of sotagliflozin in patients with type 2 diabetes and stage 3 CKD (ClinicalTrials.gov Identifier: NCT03242252) will provide further knowledge on the efficacy of the dual SGLT1/SGLT2 inhibitor in this patient group.

Effect of SGLT2 inhibitors on haematocrit, uric acid and lipids

SGLT2 inhibitors induce osmotic diuresis, reflected by an increase in haematocrit [3]. In addition, a meta-analysis of 62 RCTs involving type 2 diabetes patients found that SGLT2 inhibitors lowered serum uric acid on average by 38 μmol/L (0.038 mmol/L) compared with control [44]. However, a reduced effect in patients with longer duration of type 2 diabetes and a higher baseline HbA1c was observed, and there was no significant reduction in serum uric acid in patients with eGFR < 60 mL/min/1.73 m^2. SGLT2 inhibitor use is associated with a small increase in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels [3, 5]. It is not plausible that the small rise in LDL induces atherosclerosis. There are insufficient studies examining these indices to indicate the effects in severe CKD patients that might contribute to the positive CVD outcomes in these patients.

Cardiovascular outcome trials (CVOTs) of SGLT2 inhibitors—focus on cardiovascular and renal outcomes in patients with CKD

The EMPA-REG OUTCOME trial, the CANVAS Program and the DECLARE-TIMI 58 trial were RCTs examining the cardiovascular effects of empagliflozin, canagliflozin and dapagliflozin, respectively, in participants with type 2 diabetes receiving standard care [3, 5, 6]. These CVOTs were undertaken to assess cardiovascular safety as part of the United States Food and Drug Administration (FDA) regulatory requirements and to assess efficacy and safety outcomes. Supplementary Table 1 outlines the inclusion criteria, study populations, primary outcomes and the cardiovascular and renal outcomes of these trials. Of note, the inclusion criteria of the trials differed in regard to participants' cardiovascular status and renal function (Supplementary Table 1). A meta-

analysis of the three CVOTs found a significant reduction in the risk of a major adverse cardiac event (composite of cardiovascular death, myocardial infarction or stroke) in participants with atherosclerotic CVD (hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.80–0.93), as well as a significant and approximate 30% relative risk reduction in hospitalisation for heart failure in both participants with atherosclerotic CVD, and participants with multiple risk factors [7]. In this meta-analysis, the reduction in hospitalisation for heart failure with SGLT2 inhibitor use was most apparent in participants with worse baseline renal function (40% reduction if eGFR < 60 mL/min/1.73 m^2, 31% if eGFR 60 to < 90 mL/min/1.73 m^2 and a non-significant 12% reduction if eGFR ≥ 90 mL/min/1.73 m^2) [7]. The lowest eGFR group had a greater reduction in major adverse cardiovascular events compared with the other two eGFR groups; however, the risk reduction trend across these subgroups was not significant. Although not explicitly reported, the improvement in HbA1c is expected to be least in these groups who most likely experienced the greatest reduction in major adverse cardiovascular events, reinforcing the hypothesis that the glycaemic and cardiovascular benefits of the SGLT-2 inhibitors are independent.

In the CVOTs, empagliflozin, canagliflozin and dapagliflozin were found to have important renoprotective effects (Supplementary Table 1) [4–6]. These renoprotective effects included a significant reduction in progression of albuminuria [4, 5]. Interestingly, in the meta-analysis of CVOTs of SGLT2 inhibitors, there was a significant reduction in a composite renal outcome of worsening of renal function, end-stage renal disease or renal death across all baseline eGFR categories. However, the reduction in this outcome was greatest in participants with baseline eGFR ≥ 90 mL/min/1.73 m^2 (56% reduction compared with a 44% and 33% reduction for participants with eGFR 60 to < 90 and < 60 mL/min/1.73 m^2, respectively, p value for risk reduction trend across subgroups = 0.026) [7].

Dedicated renal outcome trials of SGLT2 inhibitors in patients with CKD

The CREDENCE trial was a multicenter RCT done to examine the effects of canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric CKD (eGFR 30 to < 90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) > 300 to 5000 mg/g) [8]. Approximately 60% of participants had an eGFR of 30 to < 60 mL/min/1.73 m^2 (part of a prespecified plan). Participants were required to be taking the maximum tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). The trial was stopped early after a planned interim analysis due to prespecified efficacy criteria being achieved. The median follow-up time was 2.6 years. The canagliflozin group had a significant 30% lower relative risk of the primary composite outcome of end-stage kidney disease, doubling of the serum creatinine level or renal or cardiovascular death compared with the placebo group (HR 0.70, 95% CI 0.59–0.82). Furthermore, participants in the canagliflozin group had a lower risk of a composite of cardiovascular death, myocardial infarction or stroke (HR 0.80, 95% CI 0.67–0.95), as well as hospitalisation for heart failure (HR 0.61, 95% CI 0.47–0.80). These impressive findings occurred despite modest differences between the groups in glycaemic control and body weight (overall mean differences in HbA1c and body weight between the canagliflozin and placebo group throughout the trial were − 0.25% and − 0.80 kg, respectively). Additionally, while the canagliflozin group had a greater mean reduction in eGFR during the first 3 weeks of treatment compared with the placebo group (− 3.72 vs. − 0.55 mL/min/1.73 m^2), thereafter the reduction in eGFR was lower in the canagliflozin group (− 1.85 vs. − 4.59 mL/min/1.73 m^2/year).

With regard to the effect of SGLT2 inhibitors on albuminuria in patients with type 2 diabetes and CKD, in the CREDENCE trial, there was a 31% reduction in the mean UACR during follow-up in the canagliflozin group [8]. The recent DELIGHT trial primarily examined the albuminuria-lowering effect of dapagliflozin with and without saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor in patients with type 2 diabetes, eGFR 25–75 mL/min/1.73 m^2 and UACR 30–3500 mg/g [45]. After 24 weeks of treatment, the dapagliflozin and dapagliflozin-saxagliptin group had a 21% and 38%, respectively, greater reduction in mean UACR change from baseline compared with placebo. These reductions in UACR were not fully mediated by changes in glycaemic or blood pressure control.

The CREDENCE and DELIGHT trials have important implications for the population of patients with diabetic CKD, especially given that prior to these findings, ACE inhibitors or ARBs were the only approved treatment for renoprotection in patients with type 2 diabetes and CKD. There are dedicated renal outcome trials underway for empagliflozin and dapagliflozin (EMPA-KIDNEY and Dapa-CKD (ClinicalTrials.gov Identifiers: NCT03594110 and NCT03036150), respectively). These trials will also provide insight into the effects of empagliflozin and dapagliflozin, respectively, in patients with non-diabetic CKD as diabetes is not an inclusion criterion. With regard to patients with CKD, an area warranting further research is individual variability in response to SGLT2 inhibitors (cardiovascular, renal and glycaemic effects) and factors predicting response.

Mechanisms mediating cardiovascular benefits with use of SGLT2 inhibitors

As discussed above, in patients with CKD, SGLT2 inhibitors have attenuated glycaemic benefits but preserved cardiovascular benefits [7, 46]. Hence, mechanisms mediating

cardiovascular benefits are likely largely independent of the glucose-lowering action of these agents. Proposed mechanisms include

- *Natriuresis and osmotic diuresis*: leading to a reduction in preload [47]. By reducing blood pressure and arterial stiffness, SGLT2 inhibitors may also reduce afterload [48, 49]. Natriuresis increases sodium delivery to the macula densa, which activates tubuloglomerular feedback, resulting in afferent arteriolar vasoconstriction and a reduction in intraglomerular pressure [50], likely mediating renal benefits of SGLT2 inhibitors.
- *Inhibition of the sodium-hydrogen exchanger in the myocardium* [51, 52]: overactivity of this exchanger leads to an increase in cytoplasmic sodium and calcium (through the sodium-calcium exchanger) resulting in myocardial dysfunction, hypertrophy, apoptosis and failure [53].
- *Use of ketone bodies for cardiac metabolism*: as detailed above, SGLT2 inhibitor use results in an increase in beta-hydroxybutyrate concentration [35]. It is hypothesised that beta-hydroxybutyrate is freely taken up by the heart and oxidised in preference to fatty acids due to reduced oxygen consumption, leading to improved cardiac efficiency in the impaired myocardium [54].
- *Reduced cardiac fibrosis*: in rat models of post-myocardial infarction, dapagliflozin administration was associated with attenuated myofibroblast infiltration and cardiac fibrosis [55].
- *Favourable changes in adipose tissue inflammatory cytokines*: this is a proposed mechanism but further studies are needed to confirm this hypothesis [56].

Safety considerations with use of SGLT2 inhibitors

Table 2 provides information on adverse events reported in the EMPA-REG OUTCOME trial, the CANVAS Program and the DECLARE-TIMI 58 trial.

Genitourinary infections

SGLT2 inhibitors are associated with an increased risk of genital infections in both men and women (Table 2) [3, 5, 6]. With regard to rates of urinary tract infections, there was no significant difference between the SGLT2 inhibitor and placebo groups in the three CVOTs [3, 5, 6]. In 2015, the FDA issued a warning about the risk of serious urinary tract infections with SGLT2 inhibitors due to 19 cases of life-threatening urosepsis and pyelonephritis reported between March 2013 and October 2014 [57].

Fournier's gangrene (necrotising fasciitis of the perineum)

In 2018, the FDA issued a warning concerning reports of Fournier's gangrene in patients taking an SGLT2 inhibitor based on 12 cases up to May 2018 [58]. However, in the DECLARE-TIMI 58 trial, there was one case of Fournier's gangrene in the dapagliflozin group, compared with five cases in the placebo group.

Hypoglycaemia

There was no significant increased risk of hypoglycaemia in the SGLT2 inhibitor group compared with the placebo group in the three trials [3, 5, 6].

Volume depletion and acute kidney injury

By inducing osmotic diuresis, SGLT2 inhibitors may contribute to volume depletion and postural hypotension, particularly in the elderly and individuals taking diuretics [59].

In 2015/2016, the FDA issued a warning about the risk of acute kidney injury with canagliflozin and dapagliflozin based on 101 cases from March 2013 to October 2015, some requiring hospitalisation and dialysis [60]. In approximately half of the cases, the acute kidney injury occurred within 1 month of commencing a SGLT2 inhibitor and most cases improved after discontinuation. Some patients were dehydrated, hypotensive or were taking potentially nephrotoxic medications. A propensity-matched analysis of SGLT2 inhibitor users and non-users in two different cohorts demonstrated no increased risk of acute kidney injury with SGLT2 inhibitor therapy—in fact, there was a trend toward decreased risk with SGLT2 inhibitor use [61]. Consistent with this finding, in the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials, there was a significantly lower rate of acute kidney injury in the SGLT2 inhibitor group compared with the placebo group (Table 2) [3, 6].

Diabetic ketoacidosis (DKA)

In the CVOTs, participants randomised to SGLT2 inhibitor had 2–3 times the risk of DKA compared with participants randomised to placebo (Table 2) [3, 5–7]. A register-based cohort study using nationwide data from Sweden and Denmark comparing new users of SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists found a similar doubling in the risk of DKA with the use of SGLT2 inhibitors relative to GLP-1 receptor agonists (1.3 events/1000 patient-years among SGLT2 inhibitor users) [62]. A common precipitating factor to DKA is absolute or relative insulin deficiency—this includes known or undiagnosed type 1 diabetes and insulin dose reduction or cessation [7, 9]. In the DECLARE-TIMI 58 trial, > 80% of participants who

Table 2 Adverse events reported in the cardiovascular outcome trials of SGLT2 inhibitors–comparison of the adverse event rate in the SGLT2 inhibitor versus the placebo group [3, 5, 6]

Adverse event	EMPA-REG OUTCOME	CANVAS program	DECLARE-TIMI 58
Genital infection	~4× increase in events consistent with genital infection ($P < 0.001$)	~4× increased event rate of mycotic genital infection in women ($P < 0.001$)	~8× increase in genital infections that led to discontinuation of study drug or were considered to be serious adverse events (0.9% vs. 0.1%, $P < 0.001$)
Urinary tract infection (UTI)	No significant difference in events consistent with UTI	No significant difference in event rate of UTI	No significant difference in UTIs that led to discontinuation of study drug or were considered to be serious adverse events
Hypoglycaemia	No significant difference	No significant difference	Reduction in major hypoglycaemic events (0.7% vs. 1.0%, $P = 0.02$)
Volume depletion	No significant difference in events consistent with volume depletion	~1.4× increased event rate of volume depletion ($P < 0.01$)	No significant difference in symptoms of volume depletion
Acute kidney injury	1.0% vs. 1.6% ($P < 0.05$)	3.0% vs. 4.1% ($P = 0.33$)	1.5% vs. 2.0% ($P = 0.002$)
Diabetic ketoacidosis	0.1% vs. < 0.1% ($P > 0.05$)	0.6 vs. 0.3 participants/1000 patient-years ($P = 0.14$)	0.3% vs. 0.1% ($P = 0.02$)
Amputation	No significant difference	Increased event rate of lower-limb amputation (6.3 vs. 3.4 participants/1000 patient-years, $P < 0.001$)	No significant difference
Fracture	No significant difference	Increased event rate of all fracture (15.4 vs. 11.9 participants/1000 patient-years, $P = 0.02$). Trend towards increased event rate of low-trauma fracture (11.6 vs. 9.2 participants/1000 patient-years, $P = 0.06$)	No significant difference

"~" approximately, "×" times, *UTI* urinary tract infection

developed DKA were using insulin at baseline [6]. Other precipitating factors include ketosis-promoting states such as surgery, infection (demonstrated in case studies by Isaac et al. [63]), very low carbohydrate diets and alcohol abuse [9, 64]. In a review of 105 cases of SGLT2 inhibitor-associated DKA, 35% of cases were relatively euglycaemic, defined as an admission plasma glucose < 11.1 mmol/L [9]. The majority of cases were severe and all required hospitalisation. The duration of SGLT2 inhibitor treatment before the onset of DKA was very variable. There have been at least three deaths due to SGLT2 inhibitor-associated DKA [63, 64].

Amputation and fracture

The CANVAS Program was the only CVOT to demonstrate an increased risk of predominantly distal amputation and fracture in the SGLT2 inhibitor group compared with the placebo group (Table 2) [3, 5, 6]. This increased risk was not observed in the CREDENCE trial [8]. In the CANVAS Program, 71% of affected participants had their highest amputation at the level of the toe or metatarsal [5]. The Swedish and Danish cohort study found a 2.3 increase in the risk of lower limb amputation among SGLT2 inhibitor users relative to GLP-1 receptor agonist users [62]. The vast majority of SGLT2 inhibitor users were taking dapagliflozin or empagliflozin, and therefore, this finding differs with the results of the DECLARE-TIMI 58 and EMPA-REG OUTCOME trials. The Swedish and Danish cohort study found no difference between SGLT2 inhibitor users and GLP-1 receptor agonist users with regard to the risk of bone fracture.

Safety of SGLT2 inhibitors in patients with CKD

In post hoc subgroup analyses of the EMPA-REG OUTCOME trial and the CANVAS Program, rates of adverse events were similar in participants with eGFR < 45, 45 to < 60 and ≥ 60 mL/min/1.73 m^2 at baseline [46, 65]. In the CREDENCE trial, as expected, there was a higher rate of genital infections and DKA in the canagliflozin group (rate of DKA in the canagliflozin vs. placebo group 2.2 vs. 0.2 per 1000 patient-years) [8]. The rate of DKA in the canagliflozin group in this trial was higher compared with the SGLT2 inhibitor groups in the three CVOTs [7]. This is possibly due to the CREDENCE trial having a greater proportion of participants using insulin at baseline compared with the CVOTs (all but 1 of the 12 participants who developed DKA in the CREDENCE trial had insulin treatment at baseline). There was a non-significant greater event rate of volume depletion in the canagliflozin group (28.4 vs. 23.5 per 1000 patient-years). The rate of acute kidney injury in the canagliflozin group in the CREDENCE trial was not increased compared with the placebo group (HR 0.85, 95% CI 0.64–1.13). There

was no significantly increased risk of amputation or fracture. While there is no clear evidence of an increased fracture risk with SGLT2 inhibitor use in patients with CKD, a post hoc analysis of a randomised crossover trial in patients with type 2 diabetes and early-stage CKD (eGFR ≥ 45 mL/min/1.73 m^2 and UACR 100–3500 mg/g) found dapagliflozin use to be associated with increases in serum phosphate, parathyroid hormone and fibroblast growth factor 23 (FGF23) [66]. Further research is warranted in this area. Furthermore, larger trials in patients with stage 4 CKD are required to better define the safety profile of SGLT2 inhibitors in this population.

Contraindications and precautions for SGLT2 inhibitor use

Table 3 lists contraindications and precautions for SGLT2 inhibitor use [67–70]. Renal impairment is a 'contraindication' largely because the anti-hyperglycaemic efficacy of SGLT2 inhibitors is dependent on renal function [67–69]. As discussed above, this is not the same with regard to the cardiovascular and renal effects of SGLT2 inhibitors. If a patient is using insulin, their insulin dose may need to be reduced at the time of SGLT2 inhibitor prescription to minimise the risk of hypoglycaemia. However, caution should be taken given the associated risk of DKA.

With regard to SGLT inhibition in type 1 diabetes, there have been a number of clinical trials assessing the efficacy and safety of an SGLT2 inhibitor and dual SGLT1/SGLT2 inhibitor in adults with type 1 diabetes [72–76]. These studies have shown that the use of an SGLT2 inhibitor or dual SGLT1/SGLT2 inhibitor is efficacious with regard to reducing HbA1c, insulin doses and body weight. However, as expected, use of these agents is associated with a higher rate of DKA compared with placebo. For this reason, prescription of an SGLT2 inhibitor to a patient with type 1 diabetes is not recommended.

Table 3 Contraindications and precautions for SGLT2 inhibitor use and conditions where SGLT2 inhibitor should be temporarily discontinued [67–71]

Contraindications to SGLT2 inhibitor use:

- Renal impairment—empagliflozin, canagliflozin and ertugliflozin if eGFR persistently < 45 mL/min/1.73 m^2, dapagliflozin if eGFR persistently < 60 mL/min/1.73 m^2
- Type 1 diabetes
- Pregnancy and breastfeeding
- Hypersensitivity to SGLT2 inhibitor or any of the excipients in tablet
- Dapagliflozin, canagliflozin and ertugliflozin not recommended in patients with severe hepatic impairment due to lack of studies in this population

Conditions where caution should be taken in SGLT2 inhibitor prescription:

- Factors predisposing to ketoacidosis including: insulin deficiency from any cause (including history of pancreatitis or pancreatic surgery), low carbohydrate diet, malnourishment, alcohol abuse
- Factors predisposing to volume depletion including: use of diuretics, age ≥ 75 years
- History of recurrent urogenital infections
- Factors increasing the risk of lower limb amputation (canagliflozin)

Conditions where SGLT2 inhibitor should be temporarily discontinued:

- Conditions predisposing to ketoacidosis including:
  - Surgery: starting at least 3 days preoperatively and restarted once patient's condition has stabilised and oral intake is normal
  - Acute illness, dehydration, reduced caloric intake
  - Very low carbohydrate diet
- Conditions predisposing to volume depletion, e.g. gastrointestinal illness, heat stress

Conclusion

SGLT2 inhibitors are potentially emerging as important drugs to improve cardiovascular and renal outcomes in patients with type 2 diabetes and CKD. Greater research is needed particularly with regard to efficacy and safety outcomes in patients with stage 4 CKD and patients with non-diabetic CKD. The evidence to date suggests that the glycaemic and cardiovascular effects of this class of agents are independent.

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Compliance with ethical standards

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