



# Potential Safety Issues with Use of Sodium-Glucose Cotransporter 2 Inhibitors, Particularly in People with Type 2 Diabetes and Chronic Kidney Disease

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## Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a major advance in the fields of diabetology, nephrology, and cardiology. The cardiovascular and renal benefits of SGLT2 inhibitors are likely largely independent of their glycaemic effects, and this understanding is central to the use of these agents in the high-risk population of people with type 2 diabetes and chronic kidney disease. There are a number of potential safety issues associated with the use of SGLT2 inhibitors. These include the rare but serious risks of diabetic ketoacidosis and necrotising fasciitis of the perineum. The data regarding a possibly increased risk of lower limb amputation and fracture with SGLT2 inhibitor therapy are conflicting. This article aims to explore the potential safety issues associated with the use of SGLT2 inhibitors, with a particular focus on the safety of these drugs in people with type 2 diabetes and chronic kidney disease. We discuss strategies that clinicians can implement to minimise the risk of adverse effects including diabetic ketoacidosis and volume depletion. Risk mitigation strategies with respect to SGLT2 inhibitor-associated diabetic ketoacidosis are of particular importance during the current coronavirus disease 2019 (COVID-19) pandemic.

## 1 Introduction

Diabetes is the leading cause of chronic kidney disease (CKD) [1], and the coexistence of both conditions places an individual at high risk of cardiovascular disease and death [2]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors inhibit proximal tubular glucose reabsorption, leading to glycosuria [3]. These drugs have important cardiovascular and renal benefits [4–9], leading one expert to refer to SGLT2 inhibitors as “cardiorenal risk reducing agents that have glucose lowering as a side effect”

### Key Points

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have a number of adverse effects—the most serious of which are diabetic ketoacidosis and necrotising fasciitis of the perineum.

Clinicians should educate patients to temporarily stop taking their SGLT2 inhibitor when acutely unwell with reduced oral intake, to reduce their risk of diabetic ketoacidosis and acute kidney injury, and this education is especially important during the coronavirus disease 2019 (COVID-19) pandemic.

In very large randomised controlled trials, SGLT2 inhibitors have been associated with a lower risk of acute kidney injury. These drugs should not, however, be prescribed to a patient who is hypovolaemic or hypotensive, and a patient’s loop and/or thiazide diuretic dose may need to be reduced.

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[10]. Furthermore, the cardiovascular and renal benefits of SGLT2 inhibitors appear to be largely independent of their glycaemic effects [9, 11–13]. This point is pertinent to the use of these drugs in people with type 2 diabetes and CKD where glycosuria secondary to SGLT2 inhibition is reduced, resulting in potentially limited anti-hyperglycaemic efficacy [14–17]. Indeed, in two heart failure trials (DAPA-HF and EMPEROR-Reduced) and a CKD trial (DAPA-CKD) where the primary endpoint was met, the effect of the SGLT2 inhibitor on the primary outcome was consistent in participants irrespective of the presence or absence of diabetes [9, 18, 19]. There are a multitude of proposed mechanisms for the cardioprotective properties of SGLT2 inhibitors, including natriuresis and osmotic diuresis, inhibition of the sodium-hydrogen exchanger in the myocardium, potential use of ketone bodies for cardiac metabolism, and reduced cardiac fibrosis and inflammation [20]. These results suggest that the benefits may be independent of effects on glycaemia. Given the use of these drugs by not only endocrinologists and primary care physicians, but also nephrologists and cardiologists, clinicians need to become familiar with the physiology, efficacy, and safety of SGLT2 inhibitors [10, 21, 22]. Indeed, SGLT2 inhibitors are associated with a number of adverse effects, including diabetic ketoacidosis (DKA), which is potentially life-threatening. Furthermore, adverse effects can occur very quickly. There have been many reviews exploring the efficacy of these agents in different population groups. Hence, this article examines the potential safety issues associated with the use of SGLT2 inhibitors, with a particular focus on the safety of these drugs in people with type 2 diabetes and CKD. We highlight measures that clinicians can implement to minimise the risk of adverse effects, including DKA, which is of particular relevance during the current coronavirus disease 2019 (COVID-19) pandemic.

## 2 Safety Issues in Patients With Versus Those Without CKD

The cardiovascular, renal and heart failure outcome trials to date have differed with respect to inclusion and exclusion criteria, including estimated glomerular filtration rate (eGFR) cut-offs [4, 6–9, 18, 23, 24]. Importantly, there is limited available data specifically about SGLT2 inhibitor use in patients with severe CKD. Subgroup analyses from the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 trials found similar adverse event profiles with respect to specific SGLT2 inhibitors among participants with different baseline eGFR levels (Table 1) [25–27]. In a subgroup analysis of the CREDENCE trial, severe adverse events were consistent among screening eGFR categories. There was a significant interaction test for volume depletion, with a higher risk with canagliflozin apparent in participants with screening eGFR 30 to <45, but not eGFRs 45 to <60 or 60 to <90 mL/min/1.73 m<sup>2</sup> (Table 1) [28]. Of note, empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin exposure increases with advancing renal impairment; however, the area under the concentration–time curve does not exceed by twofold that reported in subjects with normal renal function [14–17]. Canagliflozin is the only one of these four SGLT2 inhibitors for which use of the lower dose (100 mg once daily) is recommended for patients with renal impairment (specifically eGFR 30 to <60 mL/min/1.73 m<sup>2</sup>) [29]. However, in Australia, empagliflozin, dapagliflozin, and ertugliflozin are contraindicated in patients with eGFR persistently <45 mL/min/1.73 m<sup>2</sup>, largely due to limited anti-hyperglycaemic efficacy [30–32].

**Table 1** Subgroup analyses from major SGLT2 inhibitor trials with respect to adverse event profiles of SGLT2 inhibitors in participants with different baseline eGFRs [25–28]

Trial (SGLT2 inhibitor studied)	Adverse event profile of SGLT2 inhibitors in participants with different baseline eGFRs
EMPA-REG OUTCOME (empagliflozin)	Similar in participants with eGFR <45, 45 to <60, and ≥60 mL/min/1.73 m <sup>2</sup>
CANVAS Program (canagliflozin)	Consistent across eGFR subgroups (<45, 45 to <60, 60 to <90, and ≥90 mL/min/1.73 m <sup>2</sup> ); however, trend ( <i>P</i> heterogeneity = 0.06) for higher risk of hypoglycaemia in lower eGFR subgroup—noted that subgroups with lower eGFR had higher insulin use
DECLARE-TIMI 58 (dapagliflozin)	Consistent across eGFR subgroups (<60, 60 to <90, and ≥90 mL/min/1.73 m <sup>2</sup> )
CREDENCE (canagliflozin)	Consistent across eGFR subgroups (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m <sup>2</sup> at screening) with respect to serious adverse events, amputation, and fracture. However, significant interaction test for volume depletion ( <i>P</i> = 0.01), hazard ratio of volume depletion for participants with eGFR 30 to <45 mL/min/1.73 m <sup>2</sup> 1.99 (95% CI 1.33–2.98) (canagliflozin vs placebo), compared with hazard ratio for participants with eGFR 60 to <90 mL/min/1.73 m <sup>2</sup> 0.89 (0.58–1.38)

CI confidence interval, eGFR estimated glomerular filtration rate, SGLT2 sodium-glucose cotransporter 2

### 3 Infections of the Genitalia and Perineum

Diabetes, particularly with poor control and glycosuria, is a known risk factor for genital infection [33]. Diabetes may suppress the immune response to infection [34]. Glucose present on the genitalia due to SGLT2 inhibition is believed to aid growth and adherence of yeast and impair the local immune response [35]. A meta-analysis of randomised controlled trials (RCTs) and two large population-based studies have demonstrated an approximate threefold increase in risk of genital infection with SGLT2 inhibitor use compared with placebo or other diabetes drug classes [36–38]. In the CREDENCE trial, the event rate for genital mycotic infection in the canagliflozin versus placebo groups for females was 12.6 versus 6.1 per 1000 person-years, and for men, 8.4 versus 0.9 per 1000 person-years [8]. A study of two large cohorts of commercially insured patients in the United States found that the elevated risk of genital infections was apparent within the first month of SGLT2 inhibitor treatment and remained elevated during the course of treatment [37]. Furthermore, the risk of genital infections with SGLT2 inhibitor use was greater in the subgroup of patients aged 60 years and over. History of prior genital infection (especially recent history) is a clear risk factor for the development of genital infection during SGLT2 inhibitor treatment [39]. Toyama et al. conducted a meta-analysis of RCTs of SGLT2 inhibitors in patients with type 2 diabetes and CKD (defined as  $eGFR < 60 \text{ mL/min/1.73 m}^2$ ) and found an approximate threefold increase in the risk of genital infections [40]. This suggests that the increase in the risk of genital infections in patients with CKD is similar to that in the non-CKD population. Most genital infections are mild to moderate in severity and are responsive to topical antifungals or a single dose of fluconazole [41, 42]. These infections do not necessitate cessation of the agent [42]. Clinicians should recommend good perineal hygiene to patients [43].

In 2018, the Food and Drug Administration (FDA) issued a warning about the risk of necrotising fasciitis of the perineum (Fournier's gangrene) with SGLT2 inhibitor treatment [44]. There were 55 cases of Fournier's gangrene requiring surgical debridement associated with SGLT2 inhibitor use reported to the FDA Adverse Event Reporting System (FAERS) between March 2013 and January 2019 [45]. All patients were severely ill, at least 25 patients needed more than one surgery, and three patients died. A number of patients had complicating DKA, sepsis, and/or acute kidney injury (AKI). The time between initiation of SGLT2 inhibitor therapy and infection was variable—5 days to 49 months. Large RCTs have not demonstrated an increased risk of Fournier's gangrene with SGLT2 inhibitor treatment. In the DECLARE-TIMI 58 trial, one patient in the dapagliflozin group compared with five patients in the placebo group

experienced Fournier's gangrene [7]. However, RCTs are not designed or powered to demonstrate or refute an increased risk of extremely rare events such as Fournier's gangrene. The documented case reports submitted to regulatory and surveillance agencies need to be carefully considered.

### 4 Urinary Tract Infections

In 2015, the FDA issued a warning about the risk of serious urinary tract infections (UTIs) with SGLT2 inhibitor use due to 19 cases of urosepsis and pyelonephritis reported over an 18-month period [46]. In contrast, SGLT2 inhibitors have generally not been associated with an elevated risk of UTIs in large meta-analyses and population-based studies [36, 38, 47, 48]. One of the four cardiovascular outcome trials to date, however, has demonstrated a significant increase in risk of UTIs with SGLT2 inhibitor therapy; in the VERTIS CV trial approximately 12% versus 10% of participants randomised to ertugliflozin and placebo, respectively, experienced a UTI [49]. In the CREDENCE trial, there was no significant difference in the rate of UTIs between the canagliflozin and placebo groups [8]. The exact rate of pyelonephritis and urosepsis was not reported. Whether there are differences in the risk of UTI based on the type of SGLT2 inhibitor is yet to be established. With respect to why SGLT2 inhibition may not increase the risk of UTIs despite causing glycosuria, Fralick and MacFadden have hypothesised that diuresis and polyuria secondary to SGLT2 inhibition counters potential bacterial growth due to glycosuria and/or prevents bacterial ascension of the urinary tract [35]. Severe CKD may lead to reduced urine output, and glycosuria secondary to SGLT2 inhibition is reduced [14–17]. The influence of these factors on the risk of UTIs is uncertain as data regarding SGLT2 inhibitor treatment in patients with stage 4 and 5 CKD ( $eGFR 15\text{--}29 \text{ mL/min/1.73 m}^2$  and  $< 15 \text{ mL/min/1.73 m}^2$  or requiring dialysis, respectively) are limited. Also unclear is the risk of UTIs in higher-risk populations such as people with urinary tract structural or functional abnormalities or people who are immunosuppressed. With regard to post-transplant diabetes mellitus in renal transplant recipients, in one RCT ( $n = 49$  patients), which compared empagliflozin or placebo treatment for 24 weeks, three patients in both the empagliflozin and placebo groups experienced a UTI [50]. However, two patients in the empagliflozin group had to discontinue treatment—one because of urosepsis and one because of repeated UTIs. The patient who experienced urosepsis had a history of recurrent UTIs, and clinicians should be cautious when considering prescribing SGLT2 inhibitors to patients with a history of recurrent UTIs.

## 5 Hypoglycaemia

Given the insulin-independent mechanism of action of SGLT2 inhibitors, these agents are not associated with an increased risk of hypoglycaemia [4, 6, 7, 51]. These drugs lower plasma glucose by inducing glycosuria, resulting in a reduction in plasma insulin concentration and an increase in plasma glucagon concentration, leading to an increase in endogenous glucose production [51, 52]. The absence of hypoglycaemia risk was clearly seen in the DAPA-HF trial, where 55% of patients did not have diabetes [9]. However, if a patient is prescribed insulin and/or a sulfonylurea, the doses of these medications may need to be reduced, as SGLT2 inhibitors reduce glycated haemoglobin (HbA1c) by 0.6–0.9% (Table 2) [53]. With regard to adjusting concomitant diabetes medications in patients with moderate to severe CKD, clinicians should note that SGLT2 inhibitors have limited anti-hyperglycaemic efficacy, due to reduced glycosuria [54].

## 6 Volume Depletion

In 2015/2016, the FDA issued a warning about the risk of AKI with canagliflozin and dapagliflozin based on 101 cases over an approximate 2.5-year period, some requiring hospitalisation and dialysis [55]. In approximately half of the cases, AKI occurred within 1 month of SGLT2 inhibitor initiation. CREDENCE and the cardiovascular outcome trials have clearly demonstrated the important renoprotective effects of SGLT2 inhibitors [8, 56, 57]. In CREDENCE and the cardiovascular outcome trials (EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58), there was a 25% lower risk of AKI with SGLT2 inhibitor treatment compared with placebo [57]. There is often a mild acute decrease in eGFR with SGLT2 inhibitor initiation that is

reversible on treatment cessation—the reduction in the CREDENCE trial at 3 weeks was  $-3.7 \text{ mL/min/1.73 m}^2$  [8, 58]. In the trial, the mean change in eGFR slope was lower in the canagliflozin group compared with the placebo group ( $-3.19$  vs  $-4.71 \text{ mL/min/1.73 m}^2$  per year) [8]. The mild reduction in eGFR with SGLT2 inhibitor initiation does not represent AKI. This effect is thought to be due to increased tubular sodium delivery to the macula densa activating tubuloglomerular feedback, resulting in afferent arteriolar vasoconstriction, which is protective in the long-term because of the reduction in intraglomerular pressure [58]. This theory is partly based on data in young adults with type 1 diabetes and hyperfiltration [59]. However, the recent Renoprotective Effects of Dapagliflozin in Type 2 Diabetes trial questioned this theory [60]. In patients with type 2 diabetes without overt nephropathy, 12 weeks of dapagliflozin reduced GFR, filtration fraction, and intraglomerular pressure without increasing renal vascular resistance—suggesting that the acute eGFR decline is due to efferent arteriolar vasodilation rather than afferent arteriolar vasoconstriction [60, 61]. In the EMPA-REG OUTCOME trial, the acute dip in eGFR with empagliflozin treatment was greater in users of an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), or any diuretic compared with non-users [62]. However, in users of these medications, adding empagliflozin did not increase the risk of AKI compared with adding placebo [62].

SGLT2 inhibitors should not be initiated in patients who are hypovolaemic and/or hypotensive, because this could contribute to AKI. Further, patients prescribed loop and/or thiazide diuretics may need dose reduction of these medications to prevent volume depletion (Table 2) [63, 64]. Patients should be instructed when acutely unwell (for example, vomiting, diarrhoea, and reduced oral intake) to withhold their SGLT2 inhibitor (part of a sick day management plan) [43].

There has been a recent reported case of AKI secondary to osmotic nephrosis attributed to recent prescription

**Table 2** Suggested adjustment of concomitant diabetic and non-diabetic medication when initiating an SGLT2 inhibitor [43, 93]

Medication	Suggested adjustment
<i>Diabetes</i>	
Insulin	Consider reducing dose if HbA1c < 8.0%. However, do not excessively reduce insulin dose (for example, > 20%) as this increases the risk of DKA
Sulfonylurea	Consider reducing dose or stopping if HbA1c < 8.0% In patients with advanced CKD, SGLT2 inhibitors have limited anti-hyperglycaemic efficacy due to reduced glycosuria, which should factor into decisions about potentially changing other diabetes medications. Insulin doses need to be reduced in advanced CKD due to an increased half-life of the drug irrespective of concomitant SGLT2 inhibitor use
<i>Non-diabetes</i>	
Loop and/or thiazide diuretics	Consider reducing dose of diuretic if systolic blood pressure < 120 mmHg. If evidence of dehydration based on fluid balance assessment, recommend reducing dose or stopping diuretic and only starting SGLT2 inhibitor when dehydration resolved

DKA diabetic ketoacidosis, CKD chronic kidney disease, HbA1c glycated haemoglobin, SGLT2 sodium-glucose cotransporter 2

of canagliflozin, postulated to be due to increased tubular osmotic pressure secondary to glucose reabsorption inhibition [65]. The authors of this report recommend consideration of a kidney biopsy in cases of prolonged AKI despite SGLT2 inhibitor discontinuation. Furthermore, the issue of possible hypoxic medullary injury secondary to SGLT2 inhibition, due to increased distal natriuresis augmenting transport workload in the medulla and oxygen consumption, has been raised by Heyman et al. [66]. These authors caution against concomitant administration of agents that could worsen medullary hypoxia, and recommend cessation of SGLT2 inhibitors prior to radiocontrast studies.

## 7 Diabetic Ketoacidosis

DKA is a rare but potentially life-threatening adverse effect of SGLT2 inhibitor therapy [67, 68], estimated to occur in approximately one in 1000 SGLT2 users who have type 2 diabetes (although the precise incidence is unknown) [69]. The event rate of SGLT2 inhibitor-associated DKA in the CREDENCE trial was higher compared with the cardiovascular outcome trials (2.2 vs < 1 event per 1000 patient-years) [8, 56]. This may be, at least in part, related to the higher use of insulin at baseline in CREDENCE; all except one of the 12 patients in CREDENCE who developed DKA had concomitant insulin treatment [4, 6–8]. In contrast, there were no reported DKA events in patients randomised to dapagliflozin in the DAPA-CKD trial; however, this trial included patients with and without diabetes [19]. The higher risk of DKA in insulin-treated patients is pertinent to nephrologists as patients with advanced CKD have relatively limited therapeutic options for the management of type 2 diabetes. SGLT2 inhibitor-associated DKA is commonly referred to as “euglycaemic” DKA as the degree of hyperglycaemia is often lower than expected due to glycosuria [70]. However, in a review of 105 cases of SGLT2 inhibitor-associated DKA, 35% of cases had an admission plasma glucose concentration < 200 mg/dL (11.1 mmol/L) [71].

A more precise term for this adverse effect is “DKA with lower-than-anticipated glucose levels”, as recommended by the American Association of Clinical Endocrinologists and American College of Endocrinology [70]. The duration of SGLT2 inhibitor treatment prior to the onset of DKA is highly variable (0.3–420 days) [69, 71].

With regard to the pathophysiology of DKA, SGLT2 inhibitor use leads to a reduction in plasma insulin concentration and an increase in plasma glucagon concentration [52]. Additionally, free fatty acid suppression post-meal is impaired [52]. This decrease in the insulin-to-glucagon ratio and increase in free fatty acids promotes ketogenesis [52, 72]. SGLT2 inhibitor treatment increases plasma ketone levels, and an elevated ketone level does not necessarily indicate DKA [72–75]. SGLT2 inhibitor-associated DKA most frequently occurs in patients with one or more additional risk factor(s) for insulin deficiency and/or ketogenesis (Table 3) [67–71]. In a recent Australian retrospective cohort study of SGLT2 inhibitor-associated DKA cases, 22% of patients with presumed type 2 diabetes were subsequently diagnosed as having type 1 diabetes [69]. Fourteen of 37 cases of DKA related to SGLT2 inhibition occurred during hospital admission. Eleven of the 14 patients were fasting due to surgery, and SGLT2 inhibitor therapy was continued during admission in six of these cases. Eleven of the 14 inpatients were on insulin treatment prior to hospitalisation, and insulin was generally ceased prior to the onset of DKA. These findings highlight the need to employ specific strategies to reduce the risk of DKA, including educating patients to temporarily withhold their SGLT2 inhibitor when acutely unwell with reduced oral intake (Table 4) [67, 70, 71].

Treatment of SGLT2 inhibitor-associated DKA involves rehydration and an insulin-dextrose infusion [70]. A higher rate of intravenous dextrose (10–20%) is often needed to enable sufficient dosage of insulin for resolution of ketoacidosis [67]. An endocrinologist should be involved in the management of DKA and decisions regarding subsequent diabetes pharmacotherapy.

**Table 3** Risk factors for SGLT2 inhibitor-associated DKA

Type 1 diabetes including latent autoimmune diabetes in adults (patients with presumed type 2 diabetes where there is clinical suspicion of type 1 diabetes should have autoantibodies tested)
Type 2 diabetes with insulin deficiency
Excessive reduction in exogenous insulin dose or insulin cessation
Diabetes due to pancreatic disease
Fasting, including during the perioperative state
Very low carbohydrate diet
Hypovolaemia
Excessive alcohol consumption (daily consumption and/or binge drinking)
Metabolic stress including acute infection, surgery, myocardial infarction, pancreatitis, and intensive exercise

DKA diabetic ketoacidosis, SGLT2 sodium-glucose cotransporter 2

**Table 4** Strategies to reduce the risk of SGLT2 inhibitor-associated DKA

Careful prescription of an SGLT2 inhibitor in light of a patient's risk factors for DKA (see Table 1)
Reducing a patient's insulin dose cautiously when commencing an SGLT2 inhibitor, as excessive insulin dose reduction or cessation of insulin therapy can contribute to the risk of DKA
Informing patients about the risk of SGLT2 inhibitor-associated DKA, including when to withhold an SGLT2 inhibitor, including acute illness with reduced oral intake (part of a sick day management plan), symptoms of DKA (nausea, vomiting, abdominal pain, tiredness, rapid breathing), and the need to seek medical attention if symptoms occur (provision of written information is recommended)
Cessation of an SGLT2 inhibitor $\geq 3$ days prior to an operation and only recommencing therapy when a patient is eating and drinking normally

*DKA* diabetic ketoacidosis, *SGLT2* sodium-glucose cotransporter 2

## 8 Lower Limb Amputation

The CANVAS Program is the only cardiovascular outcome trial that has shown an increased risk of lower limb amputation with SGLT2 inhibitor therapy compared with placebo [6, 7, 76]. Approximately six versus three participants per 1000 person-years in the canagliflozin versus placebo groups experienced lower limb amputation; 71% of amputations occurred at the level of the toe or metatarsal [6]. Multivariate modelling revealed a number of baseline characteristics that were significantly associated with amputation during follow-up, including male sex, prior amputation, peripheral vascular disease, neuropathy, albuminuria, and higher HbA1c [77]. However, the effect of canagliflozin on amputation risk did not vary according to any baseline characteristic or dose of canagliflozin (100 or 300 mg daily) [77]. Interestingly, there was no difference in the risk of amputation between the canagliflozin and placebo groups in the CREDENCE trial [8]. During the CREDENCE trial, there was a protocol amendment asking investigators to examine patients' feet and temporarily withhold the study drug if there was any active condition present that might lead to amputation [8].

A cohort study using nationwide health and administrative registers in Sweden and Denmark found that compared with new users of glucagon-like peptide 1 (GLP-1) receptor agonists, new users of SGLT2 inhibitors had an increased risk of lower limb amputation (incidence rate 2.7 vs 1.1 events per 1000 person-years, hazard ratio 2.3) [48]. Ninety-nine per cent of SGLT2 inhibitor users were taking dapagliflozin (61%) or empagliflozin (38%). These results contrast with safety results of the EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF trials [7, 9, 76].

In summary, whether there is a definite increase in risk of lower limb amputation with canagliflozin treatment is unclear. Furthermore, the mechanisms underlying such a potential adverse effect are unknown. Postulated mechanisms include volume depletion secondary to diuresis, and an effect on calcium, magnesium, and vitamin D metabolism that may impair foot ulcer healing [78, 79]. Based on available evidence to date, we recommend that clinicians provide education to patients about preventive foot care and perform regular foot screening, as well as avoiding canagliflozin in

patients with an acute heightened risk of amputation (as per the CREDENCE protocol—history of amputation within past 12 months, active ulcer, osteomyelitis, gangrene, or critical leg ischaemia within 6 months) [8].

## 9 Mineral Metabolism and Fracture

Blau et al. examined the acute effect of canagliflozin on mineral metabolism in healthy adults [80]. Subjects received canagliflozin 300 mg daily or placebo for 5 days, and later crossed over to the other treatment. Canagliflozin administration rapidly increased serum phosphorus, corresponding to an increase in urinary phosphorus reabsorption. Additionally, canagliflozin treatment increased plasma fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) and reduced 1,25-dihydroxyvitamin D. The differences in mean serum phosphorus and plasma FGF23 between the canagliflozin and placebo groups were no longer significant by day 5. In contrast, differences in 1,25-dihydroxyvitamin D and PTH were still significant at this time point. There was no significant difference in serum calcium, but there was a significant decrease in urinary calcium excretion on day 4. de Jong et al. performed a post hoc analysis of the IMPROVE trial, a randomised, placebo-controlled, crossover trial involving dapagliflozin in patients with type 2 diabetes and albuminuric CKD (eGFR  $\geq 45$  mL/min/1.73 m<sup>2</sup>) [81]. Compared with the start of treatment, 6 weeks of dapagliflozin increased serum phosphorus (+ 11%), PTH (+ 15%), and FGF23 (+ 20%) and decreased 1,25-dihydroxyvitamin D (− 19%). Importantly, these changes did not correlate with change in eGFR. The increase in serum phosphorus with SGLT2 inhibition is believed to be due to increased sodium in the proximal tubule driving sodium-dependent phosphate reabsorption [82]. This is postulated to increase FGF23, which decreases 1,25-dihydroxyvitamin D, leading to an increase in PTH [80, 83]. In the study by Blau et al., the increase in serum phosphorus correlated with urinary sodium excretion, but not urinary glucose excretion [80]. In severe CKD, the effects of SGLT2 inhibition on urinary glucose and presumably also urinary sodium excretion are attenuated, perhaps resulting in a less marked effect

on serum phosphorus. However, more data are needed with regard to patients with stage 4 CKD, where control of hyperphosphataemia can be difficult.

Changes to mineral metabolism secondary to SGLT2 inhibition may be relevant to the heightened risk of fracture evident in the CANVAS Program (15.4 vs 11.9 participants with fracture randomised to canagliflozin vs placebo per 1000 patient-years) [6], although this is the only very large RCT to date with a fracture safety signal. Meta-analyses of RCTs of SGLT2 inhibitors have not demonstrated an increased risk of fractures compared with placebo [84, 85]. The increased risk of fracture with canagliflozin was only seen in one of the two trials that compose the CANVAS Program (CANVAS, not CANVAS-R). Furthermore, there was no difference in risk of fracture between the canagliflozin and placebo groups in CREDENCE [8]. The mean follow-up was longer in CANVAS compared with CANVAS-R (5.7 vs 2.1 years). The median follow-up of CREDENCE was 2.6 years. Interestingly, in a fracture analysis of CANVAS, there was no difference between canagliflozin-treated patients with or without fractures with respect to post-randomisation per cent changes from baseline in serum phosphate [86]. There was a similar fracture incidence in the canagliflozin 100 mg and 300 mg groups. A possible relationship between falls (potentially caused by volume depletion) and fractures cannot be excluded. An RCT of dapagliflozin in patients with stage 3 CKD demonstrated a higher risk of fracture with the SGLT2 inhibitor compared with placebo; seven of the 13 participants randomised to dapagliflozin who sustained a fracture exhibited orthostatic hypotension or had a history of diabetic neuropathy [87].

In summary, meta-analyses and population-based studies of SGLT2 inhibitor therapy have largely not demonstrated an increased risk of fracture [40, 47, 84, 85, 88]. However, given the changes in mineral metabolism and the results of the CANVAS Program described, longer-term data are needed with respect to risk of fracture. This issue is of relevance to the population of patients with CKD, who have or are at risk of CKD–mineral and bone disorder (CKD-MBD).

## 10 Safety Considerations of SGLT2 Inhibitor Use During the COVID-19 Pandemic

Patients with comorbidities including diabetes, older age and hypertension are at risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [89]. Therefore, it is important that clinicians inform patients taking SGLT2 inhibitors that they should temporarily stop their SGLT2 inhibitor when acutely unwell with reduced oral intake (as part of a sick day management plan), and that patients understand this advice, to try to reduce the risk of DKA and dehydration potentially leading to AKI [90, 91].

Patients admitted to hospital with SARS-CoV-2 infection should have their SGLT2 inhibitor discontinued [90, 91]. In a systematic literature review of cases involving patients with COVID-19 and DKA or combined DKA and hyperglycaemic hyperosmolar syndrome, at least seven of the 110 patients were taking SGLT2 inhibitors. Self-monitoring of plasma ketone levels when DKA is suspected has been recommended [92], although there are cost and possibly test kit availability issues. Additionally, patients must understand how to correctly use a meter that measures plasma ketone levels and be able to seek advice, preferably from a diabetes educator or endocrinologist, as to what actions to take based on their symptoms, plasma glucose, and ketone level.

## 11 Conclusion

SGLT2 inhibitors have clinically important cardio-renal benefits, especially for people with type 2 diabetes and CKD, who are at high risk of cardiovascular disease and end-stage kidney disease. Clinicians need to be aware of the potential safety issues with SGLT2 inhibitor therapy in order to try to minimise the occurrence of adverse events, as well as to detect and intervene early if these events occur. Our understanding regarding the safety of these agents is evolving, and longer-term data will provide greater knowledge. Additionally, there is a need for greater specific data with respect to people with severe CKD.

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