

Adverse Effects and Safety of SGLT2 Inhibitor Use among Patients with Type 2 Diabetes: Findings from RCT Evidence

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a novel class of glucose-lowering agents, act in an insulin-independent manner by increasing urinary glucose excretion. In addition to reduce hyperglycemia, SGLT2 inhibitor exerts beneficial effects on cardiovascular risk factors (e.g., lower blood pressure and enhance weight loss), which may confer additional health benefits for type 2 diabetes patients. The EMPA-REG OUTCOME trial showed that empagliflozin not only reduced the risk of major adverse cardiovascular events but also slowed down the progression of kidney disease compared with placebo. However, some evidence indicated an increased risk of composite renal events among patients using dapagliflozin. The beneficial cardiovascular and renal effects of EMPA-REG OUTCOME trial representing a class effect or a specific drug effect warrants to be further investigated. SGLT2 inhibitors were associated with increased risks of genital mycotic infections and urinary tract infections. Some mechanisms indicated that SGLT2 inhibitor might lead to diabetic ketoacidosis and bone fracture. These risks remain uncertain, though some evidence from the meta-analyses did not find any significantly increased risks of diabetic ketoacidosis and bone fracture. The findings of ongoing trials will provide more definitive evidence on safety of SGLT2 inhibitors.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolism disease, which is characterized by relative insulin deficiency caused by pancreatic β -cell dysfunction and insulin resistance.¹ It is estimated that about 6% of the world's adult population are diagnosed T2DM around the world, which accounts for approximately 90% of all diabetes cases.² T2DM is associated with increased risk of microvascular and macrovascular complications (e.g., cardiovascular disease, stroke, and nephropathy), leading to huge economic burden on both patients and health-care systems.³ Estimated evidences have been showed that intensive glucose management may reduce the diabetes related complications.⁴⁻⁷

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of glucose-lowering agents.⁸ Currently, three SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) have been approved for treating T2DM in the United States, European Union and in other parts of the world. Three additional SGLT2 inhibitors (ipragliflozin, luseogliflozin, and tofogliflozin) have been approved and

marketed in Japan, and further SGLT2 inhibitors are still under development (e.g., ertugliflozin, sotagliflozin, and remogliflozin etabonate).⁹ In contrast to other glucose lowering agents, SGLT2 inhibitors offer a novel insulin-independent hypoglycemia mechanism by selectively inhibiting renal glucose reabsorption to increase urinary glucose excretion.^{10,11} Because of the advantage of this novel mechanism, SGLT2 inhibitors, in addition to reduce hyperglycemia,¹² have also been demonstrated to improve cardiovascular risk factors (e.g., lower blood pressure and enhance weight loss).¹³ Moreover, SGLT2 inhibitors were shown to reduce major cardiovascular end points,¹⁴ and were associated with slower progression of kidney disease and lower risk of clinically relevant renal events in patients with T2DM at high cardiovascular risk as compared to placebo.¹⁵ However, other potential safety issues of SGLT2 inhibitors raise our concern. U.S. Food and Drug Administration (FDA) successively issued drug safety warnings about potential risks of diabetic ketoacidosis (DKA),^{16,17} bone fracture,¹⁸ urinary tract infections (UTIs),¹⁷ and acute kidney injury¹⁹ associated with SGLT2 inhibitors. In this article, we reviewed current evidence from randomized controlled trials (RCTs) and meta-analyses or systematic reviews of RCTs to summarize the adverse effects and safety issues of SGLT2 inhibitor use in patients with T2DM.

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METHODS

We searched PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 15 February 2017 to identify eligible articles using the following search terms: sodium-glucose co-transporter; SGLT2; SGLT-2; and the names of individual SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, sotagliflozin, luseogliflozin, ipragliflozin, remogliflozin etabonate, tofogliflozin and ertugliflozin). References lists of included articles were also screened for additional studies. We included RCTs and systematic reviews/meta-analyses of RCTs that evaluated the safety outcomes and adverse effects of SGLT2 inhibitors (e.g., cardiovascular outcomes, renal outcomes, bone fracture, ketoacidosis, genital mycotic infections and UTIs).

RESULTS

Beneficial Effects on Cardiovascular Outcomes

Cardiovascular disease is one of the leading causes of death in patients with T2DM, accounting for more than 60% of deaths.²⁰ Although SGLT2 inhibitors have demonstrated their ability to improve cardiovascular risk factors, their effect on preventing and/or reducing cardiovascular outcomes is unclear until the publication of the EMPA-REG OUTCOME trial in September 2015.¹⁴ In the EMPA-REG OUTCOME trial, a total of 7,020 patients with T2DM at high risk of cardiovascular disease were randomized to receive empagliflozin 10 mg or 25 mg or placebo per day in addition to standard care and followed up for a median of 3.1 years. Empagliflozin could significantly decreased major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, by 14%, the hazard ratio [HR] was 0.86 (95% confidence interval [CI], 0.74 - 0.99). In addition, we noted a 38% reduction in risk of cardiovascular deaths ($P = 0.001$) and a 35% reduction in hospitalization for heart failure ($P = 0.002$).¹⁴ However, the underlying mechanisms for these findings remain unclear, especially since the non-fatal myocardial infarction (HR, 0.87; $P = 0.22$) and non-fatal stroke (HR, 1.24; $P = 0.23$) were not significantly reduced. All these evidence suggested that the beneficial effect of empagliflozin on cardiovascular outcomes might be not related to slowing atherosclerotic process.²¹ Several meta-analyses were performed to address the cardiovascular outcomes of SGLT2 inhibitors.²²⁻²⁴ According to one meta-analysis of 38 RCTs, Tang and colleagues concluded that the three common SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) were not associated with increased risk of cardiovascular outcomes, and that empagliflozin may have a protective effect, which was largely driven by EMPA-REG OUTCOME trial.²² SGLT2 inhibitors are effective in improving HbA1c, blood pressure, body weight, and other metabolic parameters.²⁵ Thus, the observed reductions in cardiovascular events and cardiovascular mortality could not be fully explained by an improvement in cardiometabolic markers. The mechanism of cardiovascular benefit, as well as the benefit effects of cardiovascular outcomes representing a specific drug effect or a class effect warrants further investigation. The ongoing cardiovascular outcome trials for canagliflozin (CANVAS;

NCT01032629), dapagliflozin (DECLARE-TIMI58; NCT01730534), and ertugliflozin (VERTIS CV; NCT01986881) will in further clarify whether SGLT2 inhibitors have a cardiovascular protective effect.

Renal Safety

SGLT2 raises our concern about their renal safety, because their hypoglycemic mechanisms of action are depending on kidney. The osmotic diuresis associated with SGLT2 inhibitors may lead to intravascular volume depletion.²⁶ Subsequently, transient hypotensive episodes secondary to volume reduction are likely to result in acute kidney injury.²⁷ On June 14th, 2016, the U.S. FDA strengthened an existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin based on the fact that 101 confirmable cases of acute kidney injury were reported associated with these two drugs.¹⁹ Some evidence also indicated that the risk of adverse renal events was increased with the use of dapagliflozin or canagliflozin as compared to placebo.^{12,28} Some trials found an early dose-dependent increase in serum creatinine or blood urea nitrogen levels and a decrease in estimated glomerular filtration rate during the initial weeks of therapy, especially in patients with chronic kidney disease.^{29,30} However, the early observed abnormal renal parameters returned toward baseline in patients receiving SGLT2 inhibitors over time.³¹ Inversely, SGLT2 inhibitors are associated with an renal benefit.³² Recently, the EMPA-REG OUTCOME trial with a median follow-up of 3.1 years showed that patients taking empagliflozin were less likely to experience incident or worsening nephropathy than those taking placebo (HR, 0.61; 95% CI, 0.53-0.70; $P < 0.01$). In addition, use of empagliflozin was associated with decreased risk of doubling of the serum creatinine level (HR, 0.56; $P < 0.001$) and initiation of renal-therapy therapy (HR, 0.45; $P = 0.04$) as compared to placebo. No significant difference in rate of incident albuminuria was observed (HR, 0.95; $P = 0.25$).¹⁵ In agree with the findings from EMPA-REG OUTCOME trial, one network meta-analysis included 1,334 composite renal events among 39,741 patients from 58 RCTs and 511 acute renal impairment/failure events among 36,716 patients from 53 RCTs. The meta-analysis found that empagliflozin seemed to confer a lower risk of composite renal events than placebo (OR, 0.63, 95% CI, 0.54 to 0.72), canagliflozin (OR, 0.48; 95% CI, 0.29 to 0.82), and dapagliflozin (OR 0.38, 95% CI, 0.28 to 0.51).³³ Furthermore, only empagliflozin was significantly associated with a lower risk of acute renal impairment/failure than placebo (OR, 0.72, 95% CI, 0.60 to 0.86). However, an increased risk of composite renal events was observed among the patients taking dapagliflozin compared to placebo (OR, 1.64; 95% CI, 1.26 to 2.13).³³

The precise mechanisms of the renal benefit of empagliflozin remain unclear. Some studies showed that SGLT2 inhibitors might reduce proximal tubular hypertrophy, inflammation, and fibrosis, and ameliorate the hyperfiltration associated with increased intraglomerular pressure.^{34,35} In addition, they might also reduce albuminuria, a marker of glomerular damage in patients with chronic kidney disease.^{29,36,37} A key issue is whether the renal benefit from empagliflozin applies to other

drugs in class of SGLT2 inhibitors, though some evidence suggests that dapagliflozin and canagliflozin may have a harm effect on renal function.³³ Nevertheless, additional data are required to explore different renal effects by these SGLT2 inhibitors. Several prospective large RCTs are still ongoing, including Canagliflozin and Renal Events in Diabetes with Estimated Nephropathy Clinical Evaluation (CREDENCE; NCT02065791), CANagliflozin cardiovascular Assessment Study-renal outcomes (CANVAS-R; NCT01989754), and DECLARE-TIMI58 (NCT01730534).

Genital Mycotic Infections and Urinary Tract Infections

The major adverse effect of SGLT2 inhibitors on urinary system is genital mycotic infections with an incidence ranging from 2.3% to 13.4%, especially in women.³⁸ Numbers of RCTs and meta-analyses have demonstrated that SGLT2 inhibitors are associated with an increase in risk of genital mycotic infections, and to a lesser extent UTIs, as compared to placebo.^{23,25,39} A network meta-analysis of RCTs found that SGLT2 inhibitors were associated with risk of genital mycotic infections, with odds ratios ranging from 3.21 for dapagliflozin 2.5 mg to 5.23 for canagliflozin 300 mg, and only dapagliflozin 10 mg lead to higher risk of UTIs than placebo (OR, 1.28; 95% CI, 1.06 to 1.54).³⁹ Furthermore, dapagliflozin seemed to increase the risk of genital mycotic infections and UTIs in a dose-response relationship.³⁹ In December 2015, the U.S. FDA added a warning for SGLT2 inhibitors about the potential serious side effect of UTIs.¹⁷ However, the mechanism underlying the increased risk of genital mycotic infections and UTIs remains unclear. The glycosuria caused by SGLT2 inhibitors was considered as a factor leading to increase these infections.³⁸ However, this association is not observed in patients with familial renal glucosuria, a rare inherited disease with glucose excretion in the urine despite normal blood glucose levels.³⁸ Furthermore, the meta-analysis by Li et al, indicated that some other proposed high risk factors (e.g., hyperglycemia and women) might not significantly affect the risk of genital mycotic infections and UTIs.³⁹ Although most patients who developed these infections are mild to moderate, further studies are required to better understand the mechanisms, as well as identify the high-risk people to avoid these risks.

Diabetic Ketoacidosis

DKA is one of the most serious and potentially life-threatening complication of diabetes. Cumulative post-marketing reports have documented a small number of patients suffering from DKA when taking SGLT2 inhibitors.^{40,41} Most of cases were reported in patients with T1DM (e.g., off-label use).^{40,41} Some of these cases were diagnosed as “euglycemic diabetic ketoacidosis”, characterized by without marked hyperglycemia.⁴¹ The U.S. Food and Drug Administration issued a drug safety communication warning about SGLT2 inhibitors potentially increasing the risk of DKA.^{16,17} A meta-analysis of 10 eligible RCTs involving 13,134 patients and 14 DKA events found that SGLT2 inhibitors were not significantly associated with increased risk of DKA (OR, 1.71; 95% CI 0.56 to 5.20), with the event rate of 0.1% in the group of SGLT2 inhibitor users versus 0.06% in the control group.⁴²

The underlining pathophysiology related to DKA associated with SGLT2 inhibitors is limited. However, the risk of DKA related to SGLT2 inhibitors may be increased among patients with insulin-deficient diabetes (including those with long term T2DM, or insulin dose reduction), severe acute illness, dehydration, extensive exercise, surgery, low-carbohydrate diets, or excessive alcohol intake.⁴³ Further researches are required to understand the high risk factors, which may help clinicians to better identify high risk patients and prevent future incident.⁴⁴

Adverse Effects on Bone

SGLT2 inhibitors reduce hyperglycemia and lower blood pressure, at least in part through osmotic diuresis effect.⁴⁵ However, SGLT2 inhibitor-induced diuresis may lead to volume depletion, and finally electrolytes imbalance.⁴⁶ The changes of serum calcium and phosphate may show a harm effect on bone health.⁴⁷ One multiple centers RCT including 716 older patients (aged 55 to 80 years) with T2DM showed that either canagliflozin 100 mg or 300 mg were associated with a decrease in total hip bone mineral density over 104 weeks and might increase the bone turnover markers at week 52.⁴⁸ In September 2015, the U.S. FDA strengthened the fracture warning for canagliflozin by adding the bone fracture risk and decreased bone mineral density to the label.¹⁸ A pooled analysis of 10 RCTs suggested that the increased risk of fractures associated with canagliflozin was driven by a single trial involving patients with a prior history/risk of cardiovascular disease (fracture rate in CANVAS patients: 4.0% in canagliflozin group vs 2.6% in placebo group).⁴⁹ In one RCT that including 252 patients with T2DM and moderate renal impairment, Kohan et al. observed that 13 patients receiving dapagliflozin and no patients receiving placebo experienced bone fracture over 104 weeks.²⁹ In contrast, fewer fracture events of empagliflozin were reported as compared with placebo in patients with chronic kidney disease (5 cases among 419 patients in empagliflozin group versus 12 cases among 319 patients in placebo group).³⁶ One network meta-analysis of 38 eligible RCTs (10 canagliflozin, 15 dapagliflozin, and 13 empagliflozin) involving 30,384 patients with periods of follow-up ranged from 24 to 160 weeks found none of these three common SGLT2 inhibitors was associated with an increased risk of fracture, with an rate of 1.59% in the SGLT2 inhibitor groups and 1.56% in the control groups.⁵⁰ In addition, the incidence of fracture event was similar among these three SGLT2 inhibitor groups.⁵⁰

The underlying mechanisms of bone safety of SGLT2 inhibitors are unknown, although some potential mechanisms underlying the bone fracture associated with SGLT2 inhibitors are proposed.⁴⁷ SGLT2 inhibitors are associated with small increases in serum inorganic phosphate and magnesium,⁴⁶ but clinical relevance of these changes is unclear.⁵¹ It is proposed that SGLT2 inhibitors have a harm on bone turnover by increasing serum phosphate, and subsequently provoking secretion of parathyroid hormone, which enhances bone resorption and increase the risk of bone fractures.⁴⁷ Furthermore, serum parathyroid hormone has the potential to increase the concentrations of fibroblast growth factor 23,

leading to bone disease.⁵² In addition, the hyponatremia caused by SGLT2 inhibitors might increase the osteoporosis and fracture risk. Bone represents a substantial reservoir of sodium and mobilization of bone sodium requires arginine vasopressin-dependent and independent mechanisms, while arginine vasopressin shows a negative effect on regulation of osteoblasts and stimulates osteoclasts.^{53,54}

CONCLUSIONS

SGLT2 inhibitors are novel glucose-lowering agents that effectively lower glucose by increasing urinary glucose excretion, while simultaneously improving multiple risk factors (e.g., lower blood pressure and weight loss). Among the patients with T2DM at high cardiovascular risk, the EMPA-REG OUTCOME trial showed that empagliflozin showed a significant reduction in the risk of worsening or incident nephropathy and a composite of cardiovascular events. However, the beneficial cardiovascular and renal effects of EMPA-REG OUTCOME trial representing a class effect or a specific drug effect warrants to be investigated. Similarly, the mechanisms underlying cardiovascular and renal prevention remain to be elucidated. However, SGLT2 inhibitors might increase risk of genital mycotic infections and UTIs. The risks of DKA and bone fracture are uncertain, though the meta-analysis of RCTs did not find a significantly increased risk. The clinicians should carefully balance the potential benefits and/or risks for each patient when prescribing SGLT2 inhibitors. The findings of ongoing trials will provide more evidence to determine the role of SGLT2 inhibitors in patients with T2DM.

CONFLICT OF INTEREST

None.

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