JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
REVIEW

Safety of sodium–glucose cotransporter 2 inhibitors in Asian type 2 diabetes populations

Jaime A Davidson[1†], Norlela Sukor[2*†], Fen-Lee Hew[3], Mafauzy Mohamed[4], Zanariah Hussein[5]

[1]Touchstone Diabetes Center, The University of Texas Southwestern Medical Center, Dallas, Texas, USA, [2]Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [3]Subang Jaya Medical Centre, Subang Jaya, Selangor, Malaysia, [4]School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia, and [5]Putrajaya Hospital, Putrajaya, Malaysia

Keywords
Safety, Sodium–glucose cotransporter 2 inhibitors, Type 2 diabetes

***Correspondence**
Norlela Sukor
Tel.: +60-3-9145-6087
Fax: +60-3-9173-7829
E-mail address:
drlela2020@yahoo.com

J Diabetes Investig 2023; 14: 167–182

doi: 10.1111/jdi.13915

ABSTRACT

The prevalence of type 2 diabetes mellitus continues to increase in many Asian countries, with possible contributing factors, such as younger-onset disease, diabetes development at lower body mass index, higher visceral fat accumulation and poorer β-cell function, among Asian populations. Sodium–glucose cotransporter 2 inhibitors have been shown to confer favorable effects in type 2 diabetes mellitus patients, such as improved glycemic control, weight and blood pressure reduction, and importantly, cardiorenal benefits. Sodium–glucose cotransporter 2 inhibitors are generally well-tolerated, and have a well-defined safety profile based on evidence from numerous clinical trials and post-marketing pharmacovigilance reporting. To our knowledge, this review is the first to provide a comprehensive coverage of the adverse events of sodium–glucose cotransporter 2 inhibitors, as well as their management and counseling aspects for Asian type 2 diabetes mellitus populations.

INTRODUCTION

Diabetes in Asian populations

In 2019, the International Diabetes Federation estimated that 162.6 million (9.6%) and 87.6 million (8.8%) of the adult population (aged 20–79 years) in Western Pacific and South-East Asia regions have diabetes, respectively[1]. By 2045, a combined total of 365 million adults in both regions are expected to have diabetes, representing a staggering rise by 45.4% versus the year 2019[1]. China has the highest number of adults with diabetes in the world (116.4 million)[1]. Singapore, the United Arab Emirates, Malaysia and Saudi Arabia, meanwhile, are among Asian countries with high national prevalence of diabetes, with 14.2, 15.4, 16.8 and 18.3%, respectively[1]. In 2019, the number of diabetes-related deaths in Asia reached approximately 2.5 million, with a total of $US170.3 billion being spent for diabetes-related health expenditure[1].

The Asian diabetes phenotypes

The Asian type 2 diabetes mellitus population is characterized by several unique phenotypes that distinguish them from white patients[2]. These include having a higher predisposition to developing diabetes at a lower body mass index; higher central obesity and visceral adiposity leading to increased susceptibility to insulin resistance; and poorer beta β-cell function that further compounds impairment in insulin secretion[2–4]. Furthermore, Asian type 2 diabetes mellitus patients have a higher prevalence of young-onset diabetes[2,5]. As high as one in five Asians are diagnosed with diabetes before the age of 40 years[2,5]. With longer diabetes duration and prolonged exposure to glucolipotoxicity, these patients have a higher possibility of developing cardiovascular (CV), eye and renal complications, as well as worse glycemic control, as compared with late-onset diabetes patients[2,6]. These phenotypes place Asian patients at a much elevated risk of diabetes-related adverse outcomes, and at a younger age[2].

SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS IN TYPE 2 DIABETES MELLITUS MANAGEMENT

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) represent the newer class of oral glucose-lowering agents for type 2 diabetes mellitus[2,7]. SGLT2i work by reducing renal glucose reabsorption, thereby inducing glycosuria[2,4]. In a study on rodent models of diabetes, it was also found that SGLT2i acts on α-cells, and reduces blood glucose levels by suppressing hepatic glucagon signaling through downregulation of the hepatic glucagon receptor[8].

On SGLT2i treatment, durable blood glucose-lowering, as well as improvement in both β-cell function and peripheral insulin sensitivity, have been observed in type 2 diabetes

†These authors contributed equally to this work.
Received 19 May 2022; revised 2 September 2022; accepted 10 September 2022

mellitus patients. Furthermore, SGLT2i are associated with weight loss and a decrease in both systolic and diastolic blood pressure (BP)[2,4,7,9]. Large CV outcome trials in type 2 diabetes mellitus have also provided compelling evidence of SGLT2i in reducing the risks of adverse CV and kidney events in patients with multiple risk factors or with established CV disease or chronic kidney disease (CKD)[10–14]. Subsequent heart failure (HF) outcome trials showed that SGLT2i were effective in reducing CV death or HF hospitalization in patients with HF across a broad spectrum of ejection fractions, regardless of whether they have diabetes at baseline[15–19]. In addition, the renoprotective benefits of SGLT2i, which had been previously confirmed in diabetic nephropathy patients[20], are now extended to the non-diabetic CKD population[21].

The latest guidelines by the European Society of Cardiology, Kidney Disease: Improving Global Outcomes and American Diabetes Association on the management of type 2 diabetes mellitus have recommended that the choice of glucose-lowering medications should be prioritized based on the presence of atherosclerotic CV disease, HF or CKD, as well as the existence of risk factors that fuel the development of such diseases[22–25]. SGLT2i as a result are now placed high on the recommended treatment algorithm, along with glucagon-like peptide-1 receptor agonists[22,23]. Similarly, recent updated guidelines in several Asian countries have elevated the importance of assessing the presence of risk factors or established cardiorenal diseases in selecting appropriate anti-diabetes medications, with SGLT2i being elevated to at least second-line therapy after metformin[26–29].

After these developments, it is anticipated that SGLT2i use will continue to rise globally, including in Asia[9,30]. Concerns, nevertheless, remain on several adverse events associated with SGLT2i therapy[31]. It is therefore essential to constantly take the safety aspects of SGLT2i therapy into consideration. In most Asian countries, five SGLT2i, namely, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and luseogliflozin, have been approved for clinical use in type 2 diabetes mellitus patients[9]. Ipragliflozin has been approved to be used in Korea and Japan[32]. Another SGLT2i, tofogliflozin, thus far is only available in Japan[9]. The present review intends to provide contemporary discussions on the safety aspects of SGLT2i therapy from the Asian type 2 diabetes mellitus population perspective. Important counseling points to address common adverse events associated with SGLT2i will also be deliberated to provide guidance on how Asian patients might derive the best outcome from SGLT2i with minimal safety concerns.

ADVERSE EVENTS RELATED TO SGLT2I

In general, SGLT2i are well-tolerated, and the incidence of their adverse events was similar to that of other anti-diabetes agents, including metformin, sulfonylurea (SU) and insulin[33,34]. Adverse events that have been reported in the literature for SGLT2i treatment include genital infection (GI), urinary tract infection (UTI), volume depletion, bone fracture, renal impairment, lower limb amputation, hypoglycemia and diabetic ketoacidosis (DKA)[33,34]. SGLT2i adverse events and their relevant counseling points are summarized in Table 1.

Genital infection

Overview and risk factors

Diabetes itself is a predisposing factor for GI both in women and men. This is further aggravated by poor glycemic control and hyperglycemia-associated immune dysfunction[50,51]. Women and men with diabetes are two- and threefold more likely to develop vaginitis and balanitis, respectively, due to *Candida albicans* compared with those without diabetes[50,51]. Other forms of GI in uncontrolled diabetes patients might be manifested by bacteriuria associated with glycosuria and increased adherence of *Escherichia coli* to uroepithelial cells[50]. Risk factors that predispose to GIs include poor hygiene, immunosuppression, pregnancy and uncircumcised men, as well as antibiotic, corticosteroid or oral contraceptive use[51]. Prior history of chronic or recurrent GIs also predisposes to subsequent infection[50].

As SGLT2i induce sustained glycosuria, it is not unexpected that the most common adverse event is GI[4,52]. The increased glucose load in the urinary tract might promote fungal growth and interfere with the body's immune responses[51,53]. The overall GI incidence associated with SGLT2i was previously shown to be 4–6%, as compared with 1% with placebo[50]. Subsequently, large cardiovascular outcome trials (CVOTs) found that GI was more common in the SGLT2i group versus placebo[10,12,13,15], with a higher incidence in women than men[4,33,52].

Rates in Asian type 2 diabetes mellitus populations

A similar trend was observed in Asian type 2 diabetes mellitus populations. In a study involving 1,326 Asian patients, GI was more common in patients taking empagliflozin 10 mg (3.4%) or 25 mg (2.3%), as compared with placebo (0.9%)[36]. In another phase III study of an Asian population where the majority of the population was Chinese (n = 393), GI was reported in 0.8%, 3.1% and 4.5% of patients receiving placebo, and dapagliflozin 5 and 10 mg, respectively[35]. GI was also reported in 2.1% of studied Japanese patients taking luseogliflozin in combination with other oral anti-diabetes medications[54]. Most cases resolved spontaneously or with antibiotic treatment, with no patient discontinuation reported as a result of GI[54]. A post-marketing surveillance study evaluating the safety of ipragliflozin in elderly Japanese patients (STELLA-ELDER; n = 7,170) reported that 1.45% of patients complained of non-serious GI[55]. Bashier *et al.*[56] meanwhile reported three GI cases out of 371 Emirati patients receiving dapagliflozin, all of which were resolved with a single dose of topical anti-mycotic agents and none required discontinuation of dapagliflozin.

Management and counseling point

Despite being common among SGLT2i users, including those who are Asian, GI tends to occur early in patients recently initiated on SGLT2i, particularly in those with high baseline

Table 1 | Safety profile of sodium–glucose cotransporter 2 inhibitors in Asian type 2 diabetes mellitus populations

Adverse event	Potential risk factors among SGLT2i users	Rates in Asian type 2 diabetes mellitus populations†	Management and counseling points for patients
Genital infection (GI)	• Poorly controlled diabetes • Poor hygiene • Immunosuppressed • History of chronic or recurrent GI • Uncircumcised men • Pregnancy	Dapagliflozin[35]: • 5 mg: 3.1% • 10 mg: 4.5% • Placebo: 0.8% Empagliflozin[36]: • 10 mg: 3.4% • 25 mg: 2.3% • Placebo: 0.9%	• Maintaining good personal hygiene • SGLT2i discontinuation is not required in mild-to-moderate cases • Use of antifungal therapy to treat GI • Avoid SGLT2i if patients have recurrent GIs (>4×/year)
Urinary tract infection (UTI)	• Poorly controlled diabetes • Elderly • Women • History of chronic or recurrent UTI • KUB structural defects	SGLT2i vs Placebo[37]: HR of 1.01 (95% CI 0.67–1.54) SGLT2i vs control[38]: HR of 0.93 (95% CI, 0.68–1.27)	• Maintaining good personal hygiene • Maintaining good glycemic control • SGLT2i discontinuation is not required • Standard UTI treatment is sufficient
Fournier gangrene	• Poorly controlled diabetes • Obesity • Smoking history • Liver or renal failure • Alcohol abuse • Immunocompromised	Not available	• Ensuring good glycemic control • Maintaining good personal hygiene
Volume depletion	• Elderly • Use of loop diuretics, ACEis/ARBs • Moderate renal impairment	Canagliflozin[39]: • 100 mg: 0.4% • 300 mg: 0% • Placebo: 0% Dapagliflozin[35,40]: None reported in 5 mg, 10 mg and placebo Empagliflozin[41]: • 10 mg: 4.0% • 25 mg: 5.4% • Placebo: 3.3% Luseogliflozin[42]: None reported in 2.5 mg and placebo	• Adequate fluid intake during exercise, fasting period or hot weather • Monitoring volume status and BP • Use SGLT2i with appropriate diuretic doses
AKI or renal impairment	• Elderly • Hypovolemic • Pre-existing renal impairment • Use of loop diuretics or nephrotoxic drugs such as NSAIDs, amphotericin and radiocontrast agent	Dapagliflozin[40]: • 5 mg: 1.0% • 10 mg: 2.4% • Placebo: 1.6% Empagliflozin[41]: • 10 mg: 5.7% • 25 mg: 5.8% • Placebo: 5.7% Luseogliflozin[42]: • 2.5 mg: 7.6% • Placebo: 7.6%	• Renal function assessment before SGLT2i initiation • Close monitoring among those with high risks of adverse renal events • Adjust loop diuretic dose and avoid nephrotoxic drugs • Withhold SGLT2i temporarily during acute illness

Table 1. (*Continued*)

Adverse event	Potential risk factors among SGLT2i users	Rates in Asian type 2 diabetes mellitus populations†	Management and counseling points for patients
Bone fracture	• Poorly controlled diabetes • Use of thiazolidinediones and SSRIs • Elderly • Post-menopausal women • Volume-depleted • Renal impairment • Peripheral or autonomic neuropathy	SGLT2i vs control[38]: HR of 1.60 (95% CI, 0.48–5.29) Empagliflozin[41]: • 10 mg: 4.6% • 25 mg: 2.4% • Placebo: 3.1%	• Cautious use of SGLT2i in patients with high fracture risk
Lower limb amputation	• History of amputation • Peripheral vascular disease • Neuropathy • Diabetic foot ulcer	Canagliflozin[43]: None reported in Japanese patients Dapagliflozin[40]: None reported in 5 mg, 10 mg and placebo Empagliflozin[44]: • 10 mg: 0.1 per 100 patient-year • 25 mg: 0 per 100 patient-year • Placebo: 0 per 100 patient-year	• Consider all risk factors before SGLT2i initiation • Routine foot and wound care • Adequate hydration
Hypoglycemia	• Concomitant use of insulin or SU • Irregular meals • Alcohol intake • Elderly • Strenuous exercise • Renal impairment	Dapagliflozin[35]: • 5 mg: 0.8% • 10 mg: 0.8% • Placebo: 1.5% Dapagliflozin vs SU in fasting Muslims during Ramadan[45]: HR 0.24 (95% CI 0.09–0.68) Ipragliflozin[46,47]: None reported in 50 mg, 100 mg and placebo	• Lower insulin or SU dose when used together with SGLT2i • Continuously monitor blood glucose and risk factors • Muslim patients should take SGLT2i post-sunset meal during Ramadan
Diabetic ketoacidosis	• LADA, type 1 diabetes and long-standing type 2 diabetes mellitus • Presence of precipitating factors e.g., intensive exercise, prolonged fasting, acute illness, infection, CV events and surgery • Inappropriate insulin withdrawal or dose reduction during SGLT2i initiation	SGLT2i vs DPP-4 inhibitor[48]: HR 0.96 (95% CI 0.58–1.57) SGLT2i[49]: 0.72 cases per 1,000 person-years in Singapore	• Address and treat appropriately the precipitating factors during SGLT2i therapy • Discontinue SGLT2i 72 h before metabolically stressful events • Avoid inappropriate withdrawal or dose reduction of insulin • Avoid SGLT2i in type 1 diabetes

†Presented data should not be treated as a direct head-to-head comparison, as study design and population might differ between trials. ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GI, genital infection; HR, hazard ratio; KUB, kidney, ureter, bladder; LADA, latent autoimmune diabetes in adult; NSAIDs, non-steroidal anti-inflammatory drugs; SGLT2i, SGLT2-inhibitors; SSRI, selective serotonin reuptake inhibitor; SU, sulfonylurea; UTI, urinary tract infection.

hemoglobin A1c (HbA1c) levels[50]. Most patients only had one GI event in which it is usually self-limiting and resolves over time[2,33]. GI is typically mild-to-moderate in intensity, and very rarely leads to the need for SGLT2i discontinuation[4,50,57]. Furthermore, GIs can be managed with standard therapy and good personal hygiene[4,9].

To prevent GI, patients should be advised to maintain good perineal hygiene, in which the genital area should be washed

after each toilet visit with water and mild soap if required[4]. For uncircumcised men, the prepuce should be retracted before washing, and the use of alcohol or acidic-based cleansing agents are highly discouraged[4]. For GI treatment, patients should be made aware of available over-the-counter anti-fungal oral treatment or cream that can be locally applied intravaginally by women and directly to the penis by men[51,58]. The South Asian Federation of Endocrine Societies recommended that SGLT2i should be avoided if patients have a history of recurrent GIs (>4 times a year)[4].

Urinary tract infection

Overview and risk factors

Similar to GI, people with type 2 diabetes mellitus are already at a higher risk of developing UTI[50]. Various studies showed an almost twofold higher incidence of UTIs in patients with diabetes than in patients without diabetes[59,60]. Increased risk of UTI in type 2 diabetes mellitus patients could be attributed to several reasons. Higher urinary glucose level might promote the growth and uroepithelial adherence of UTI-causing bacteria[31,61]. Furthermore, hyperglycemia could lead to immune system impairment and incomplete bladder clearance due to autonomic neuropathy, all of which would enhance the risk of UTI in people with diabetes[61]. Among type 2 diabetes mellitus patients, the prevalence of UTI is higher in women, the elderly, those with poor glycemic control or those who have long-term complications, such as nephropathy and cystopathy[61].

The association between the incidence of UTI in patients with diabetes and the use of SGLT2i has also been evaluated. Pooled safety analyses from placebo-controlled studies suggested that UTIs were more common in patients receiving SGLT2i[62-64]. Among SGLT2i users, there seems to be a higher incidence of UTI in women, elderly patients and those with poor glucose control or with a prior history of chronic or recurrent UTIs[62,63]. The increased risk of UTI associated with SGLT2i was postulated to be secondary to glycosuria, which might facilitate bacterial growth in the lower urinary tract[50]. UTI cases reported among SGLT2i users were mainly mild-to-moderate in intensity, and rarely lead to discontinuation of the drug[50]. Several reports of serious cases, including urosepsis and pyelonephritis, requiring hospitalization among patients receiving SGLT2i, have also been described, however any causality has not been established[62-64]. It is important to keep in mind, however, that the incidence of such severe infections is no lesser in people without diabetes than in those with diabetes[65].

In contrast, large CVOTs did not show significant imbalance in UTI between SGLT2i and placebo groups[10,12,13]. The observed discrepancy could be attributed to the fact that data from pooled safety analyses were largely based on identified symptoms in the phase III development programs for SGLT2i rather than results of laboratory tests for infection[31]. A meta-analysis by Dave *et al.*[66] involving a large USA insurance-based dataset of ≥200,000 type 2 diabetes mellitus patients followed for up to 15 months showed no significant difference in the risk for either severe or outpatient-treated UTI between SGLT2i and two other glucose-lowering agent (dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists) users[66].

Rates in Asian type 2 diabetes mellitus populations

Data from Asian studies seem to be consistent with findings by Dave *et al.*[66] A meta-analysis on 17 randomized controlled trials (RCTs) with Asian type 2 diabetes mellitus patients (n = 2,660) showed no significant increase in the risk of UTI in SGLT2i users as compared with placebo (hazard ratio [HR] of 1.01, 95% confidence interval [CI] 0.67–1.54)[37]. Another meta-analysis focusing on 33 RCTs involving almost 8,500 East Asian patients also showed similar findings (HR 0.93 vs control; 95% CI 0.68–1.27)[38]. Together with favorable safety in terms of UTI shown in three CVOTs that enrolled 5,104 Asian patients[10,12,13], all available data from RCTs thus far offer important reassurance for patients and physicians in Asia when it comes to UTI.

Management and counseling point

Type 2 diabetes mellitus patients who are taking SGLT2i should be made aware and reassured by physicians that the UTI risk might be increased by diabetes itself[31]. At worst, the earlier data showed that the increase in risk from SGLT2i is small[62-64]. If symptoms occur, they should consult their physicians. In the event of confirmed UTI diagnosis, they usually respond to standard treatment, and SGLT2i discontinuation is not required[50]. Although UTI is deemed as a non-serious adverse effect, it might still potentially affect patients' quality of life and their adherence to SGLT2i treatment[67].

Fournier gangrene

Overview and risk factors of adverse events

Fournier gangrene (FG) is an extremely rare, but progressive, bacterial necrotizing fasciitis of the perineum that can be potentially fatal[30]. Preceding events for FG include perianal or scrotal abscesses or pressure ulcers. Uncontrolled diabetes, along with obesity, smoking, liver or renal failure, alcohol abuse and immunocompromised state, are well-known risk factors for FG[30,68]. It is thought that FG-causing pathogens spread from the skin or intestine rather than from the urogenital tract[69].

Rates in Asian type 2 diabetes mellitus populations

In 2018, the US Food and Drug Administration (FDA) issued a warning of reports of 12 FG cases in patients taking SGLT2i[70]. These cases are rare in the context of 1.7 million SGLT2i users in the USA[70]. The number increased to 55 in 2019 (data from US FDA Adverse Event Reporting System)[71]. At the time of writing, there were very limited reports on the occurrence of FG among Asian type 2 diabetes mellitus patients taking SGLT2i, suggesting that FG is rare and uncommon in Asian populations.

In view of the FDA warning, the incidence of FG was evaluated in the large Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial (n = 17,160), whereby no significant imbalance was

observed between dapagliflozin (one case) and placebo (five cases) groups[12]. In the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS-CV) trial, FG was neither observed in the ertugliflozin group nor in the placebo group[15]. A recent meta-analysis carried out by Silverii *et al.*[72] on 84 RCTs (n = 69,573) also did not detect an increase in the risk of FG in the SGLT2i group versus the comparator group (HR 0.41, 95% CI 0.09–1.82).

Management and counseling point

It remains important to continuously recognize that diabetes itself is a risk factor for developing FG; however, this condition is still rare among patients with diabetes[73]. Nevertheless, the nature of this infection warrants vigilant surveillance among SGLT2i users. Similar to GI and UTI management, physicians must emphasize the importance of good personal hygiene among SGLT2i users, especially those with poorly controlled diabetes and with concurrent presence of other aforementioned risk factors[30]. A high index of suspicion is critical to detect FG early to minimize potential morbidity and mortality among SGLT2i users[71]. In the event where it is diagnosed early, FG can be treated with fluid resuscitation, immediate broad-spectrum antibiotics and urgent surgical debridement, while SGLT2i should be withdrawn[30].

Volume depletion

Overview and risk factors

Volume depletion-related effects with the use of SGLT2i do not cause serious adverse outcomes. Even if present, they are usually mild-to-moderate in severity and are dose-related[74,75]. It is thought that osmotic diuresis induced by the glycosuric effect of SGLT2i might lead to intravascular volume contraction and adverse reactions, such as ambulatory or systolic BP reduction, dehydration, hypovolemia, orthostatic hypotension and syncope[4,62–64,76]. Patients who are elderly (aged >65 years), receiving loop diuretics, taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or having moderate renal impairment tend to have a higher incidence of volume depletion-related adverse reactions while taking SGLT2i.[62–64,77]

Despite these, the large outcome trials that enrolled patients across a broad kidney function spectrum, having mild-to-severe renal impairment at baseline (lowest estimated glomerular filtration rate [eGFR] was 30 mL/min/1.73 m^2), showed no significant difference in symptoms related to volume depletion in the SGLT2i groups versus placebo[11–13,15]. Reassuringly, heart failure with reduced ejection fraction and advanced CKD patients who are at much higher risk of mortality and hospitalization did not showed a significant imbalance in serious adverse events related to volume depletion in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trials regardless of their baseline glycemic status[18,20,21].

Further analysis in the DECLARE-TIMI 58 trial showed that volume depletion events increased with increasing age, with incidence rates of 5.6, 7.8 and 14.9 cases per 1,000 person-years in age-groups <65, ≥65 to <75 and ≥75 years respectively ($P < 0.0001$)[78]. However, these volume depletion events were balanced between dapagliflozin and placebo regardless of age, suggesting minimal concern of volume-related adverse reactions in elderly patients receiving dapagliflozin[78]. Similar analysis in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients- Removing Excess Glucose (EMPA-REG OUTCOME) trial showed that the frequency of volume depletion events was similar between empagliflozin and placebo in the age groups of <65 and ≥65 to <75 years[79]. A greater proportion of these events occurred in patients aged ≥75 years taking empagliflozin (6.8% vs 5.7% in placebo), although, understandably, by virtue of its inclusion criteria, patients in this age group would have a much lower eGFR[79].

Rates in Asian type 2 diabetes mellitus populations

Detailed examination of Asian populations suggests that the incidence of volume depletion with SGLT2i use was relatively low. A pooled analysis of phase I–III clinical trials showed comparable rates of volume depletion events among East Asian patients receiving empagliflozin 10 mg, 25 mg and placebo (0.8–1.4/100 patient-years)[44]. The subanalysis of Asian populations (n = 1,517) in the EMPA-REG OUTCOME trial, however, showed a slight imbalance in volume depletion, with reported incidence rates of 4.0%, 5.4% and 3.3% in the empagliflozin 10 mg, 25 mg and placebo groups, respectively. However, the percentage of such events was still considerably low, and did not culminate in an increase of study drug discontinuation[41]. Consistent with the above, early studies of other SGLT2i in Asian populations did not find any increase or a very slight increase in adverse events related to volume depletion in the SGLT2i groups, with an overall incidence rate that did not exceed 3% of the studied patients[35,39,40,42,55,80,81].

Management and counseling point

To prevent volume depletion, SGLT2i users are recommended to maintain adequate fluid intake, especially during exercise, and particularly for Asian patients, during fasting periods or hot weather[4]. Assessment of volume status and BP, adjustment of diuretic dose and monitoring for hypotension are advisable when patients are initiated on SGLT2i[4,82]. This is particularly important among Asian patients living in the hot weather climate and, hence, exposed to the risk of dehydration[4]. The use of diuretics together with SGLT2i in frail elderly patients should be treated with caution[4]. No dose adjustment for SGLT2i thus far has been recommended for elderly patients[9]. In hypovolemic or hypotensive patients, SGLT2i use should be delayed until volume status and BP are corrected[82]. Thiazide can be continued in euvolemic and normotensive patients, but for patients who are taking the more potent loop diuretics, they are recommended to half the loop diuretic dose with close follow up[82].

Acute kidney injury and renal impairment

Overview and risk factors

Evidence from the large outcome trials have shown that SGLT2i reduced the risk of worsening renal outcomes in type 2 diabetes mellitus patients[83]. Remarkably, renoprotective benefits of SGLT2i appear to be consistent across the renal continuum, encompassing a population for whom the majority have preserved kidney function, as seen in DECLARE-TIMI 58, to those with a relatively higher proportion of renal impairment, as observed in the EMPA-REG OUTCOME, Canagliflozin Cardiovascular Assessment Study (CANVAS Program) and VERTIS-CV trials, as well as to patients who have established nephropathy, such as that shown in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and DAPA-CKD trials[10–12,14,15,21].

The risk of acute kidney injury was also shown to be significantly lower in the SGLT2i group versus placebo based on the pooled analysis of large outcome trials (HR 0.75, 95% CI 0.66–0.85; $P < 0.0001$), hence allaying earlier concern that SGLT2i might cause deterioration in renal function secondary to diuresis through development of volume depletion and initial acute eGFR reduction[83,84]. The acute eGFR drop by 4–6 mL/min/1.73 m^2 on SGLT2i initiation is usually transient, followed by a progressive recovery with renal function stabilization, all of which are due to the hemodynamic effect of SGLT2i[84,85]. In studies of patients with moderate-to-severe renal impairment receiving SGLT2i, transient eGFR reduction and subsequent stabilization were not followed by an increased risk of renal-related adverse events and acute kidney injury[11,86,87]. This suggests that renal safety of SGLT2i does not differ substantially according to the CKD stages.

Rates in Asian type 2 diabetes mellitus populations

In the Asian subanalysis of the EMPA-REG OUTCOME trial, a comparable incidence rate of acute kidney injury was observed across all treatment groups (5.7–5.8%), consistent with the overall results[41]. Further analysis showed that Asian patients with CKD (eGFR <60 mL/min/1.73 m^2) had a higher frequency of renal-related adverse events consistent with acute renal failure, volume depletion and hyperkalemia than the non-CKD patients[88]. Nevertheless, the frequency of these events was well balanced between the empagliflozin and placebo groups[88]. Meanwhile, a 24-week pooled analysis of eight phase IIb/III trials comparing dapagliflozin 5 mg, 10 mg and placebo in Asian populations (n = 1,453) did not show an increase in adverse renal events, such as renal impairment, eGFR decline, increased creatinine levels and renal failure (1.0%, 2.4% and 1.6% respectively)[40]. Similarly, luseogliflozin 2.5 mg showed no increase in adverse events affecting renal functions in Japanese population (7.6% vs 7.6% in placebo)[42].

Management and counseling point

Notwithstanding the renal safety and benefits of SGLT2i, it is advisable to assess patients' renal functions before initiation of these agents[84]. Although trials evaluating SGLT2i in patients with eGFR >20 mL/min/1.73 m^2 are currently ongoing, SGLT2i should not be started in patients with eGFR levels below the recommended threshold stated in the local product monographs that might vary across different Asian countries[84]. Close monitoring among elderly, hypovolemic or renal-impaired patients is essential, as they might be more susceptible to developing renal-related adverse reactions[62–64]. They should seek medical advice immediately if they have reduced food intake (e.g., due to acute illness or fasting) or increased fluid losses (e.g., due to vomiting, diarrhea or excessive heat exposure)[63,64]. In these instances, temporary discontinuation of SGLT2i might be required[63,64]. Caution should be exercised if a patient is already taking loop diuretics or other nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs, amphotericin and radiocontrast agents[89].

Bone fracture

Overview and risk factors

Despite having normal or elevated bone mineral density, type 2 diabetes mellitus patients have an increased risk of bone fracture[90–92]. Type 2 diabetes mellitus complications (e.g., retinopathy, autonomic dysfunction and nephropathy), hypoglycemia and the use of certain medications (e.g., thiazolidinediones and selective serotonin reuptake inhibitors) might contribute to bone fracture by increasing the fall risk and impairing the bone remodeling process[90–92]. Previous meta-analyses showed a significant positive association between type 2 diabetes mellitus and hip, vertebral or foot fractures[91,93].

Previously, increased risk of fracture was shown in those taking canagliflozin based on the CANVAS Program trial, with a HR of 1.55 (95% CI 1.21–1.97)[10]. The reasons underpinning such finding were still unknown, but it was thought that SGLT2i might increase proximal tubular reabsorption of phosphate into the bloodstream, thereby leading to increased levels of parathyroid hormone and fibroblast growth factor-23[94]. Increased parathyroid hormone level might enhance bone resorption, thus augmenting the risk of fracture, while increased fibroblast growth factor-23 has been associated with bone diseases, such as rickets and osteomalacia[94].

In contrast, no significant imbalance in fracture risk was observed in the EMPA-REG OUTCOME (HR 0.98, 95% CI 0.76–1.25) and DECLARE-TIMI 58 trials (HR 1.04, 95% CI 0.91–1.18)[12,13]. The dedicated renal outcome trial of canagliflozin, CREDENCE, showed differing data from the CANVAS Program, whereby no significant difference was found in the rate of fracture (HR 0.98, 95% CI 0.70–1.37)[11]. At this juncture, there is no clear explanation underlying this discrepancy, but CREDENCE data, nevertheless, was reassuring and consistent with other SGLT2i trials. In congruence with findings from EMPA-REG OUTCOME, CREDENCE and DECLARE-TIMI 58, a large meta-analysis by Tang *et al.*[95] evaluating 38 RCTs involving >30,000 patients showed that SGLT2i were not significantly associated with an increased risk of fracture in type 2 diabetes mellitus patients.

Rates in Asian type 2 diabetes mellitus populations

No bone fracture cases were reported in the Survey of Ipragliflozin Treatment in Elderly Type 2 Diabetes Patients (STELLA-ELDER) study evaluating long-term safety of ipragliflozin in elderly Japanese patients[55]. An Asian-specific subanalysis in the EMPA-REG OUTCOME trial reported that the rate of fracture was similar in the empagliflozin 10 mg, 25 mg and placebo groups (4.6, 2.4 and 3.1%, respectively)[41]. A meta-analysis by Yang *et al.*[38] also provided a reassuring finding, as increased fracture risk was not observed among SGLT2i users in the East Asian populations (HR 1.60, 95% CI 0.48–5.29).

Management and counseling point

An expert consensus statement from India opined that there was insufficient evidence to suggest causality between SGLT2i therapy and increased risks of bone fracture and osteoporosis in patients with type 2 diabetes mellitus[96]. It was nevertheless recommended that SGLT2i should be used with caution in patients with high fracture risk, such as those who were elderly, post-menopausal women, having prior history of CV disease, impaired renal function or volume depleted[96]. These patients must be counseled appropriately on the potential factors that might increase bone fracture risk before SGLT2i initiation. With or without SGLT2i, it remains important to recognize that type 2 diabetes mellitus patients, especially those with peripheral or autonomous neuropathy showing orthostatic hypotension, have a high risk of fracture[90,91].

Lower limb amputation

Overview and risk factors

Diabetes is inherently a risk factor of amputation, particularly in patients who have previous ulceration, prior amputation, vascular insufficiency, infection, peripheral neuropathy, CV disease or on renal replacement therapy[97,98]. According to the World Health Organization, amputation in individuals with diabetes is 10-fold more common than those without diabetes[99]. Adler *et al.*[100] reported that for each percentage increase in HbA1c, the risk of amputation increases by 44% and 18% in type 2 diabetes mellitus and type 1 diabetes patients, respectively. Lower limb infections, diabetic foot ulcers, peripheral arterial disease and gangrene were the most common medical events associated with the need for amputation[101].

In the CANVAS Program, a small proportion of the total 10,142 studied patients, 1.8% (n = 187) were reported to have atraumatic lower extremity amputations, whereby the majority of the reported cases (71%) were of minor amputations affecting the toe and transmetatarsal[102]. Among these cases, the risk of amputation was approximately twofold higher in the canagliflozin group (HR 1.97, 95% CI 1.41–2.75), especially in those who had a history of amputation, peripheral vascular disease and neuropathy[10,102]. The reason behind the increased risk of lower limb amputation with canagliflozin is yet to be established, although volume depletion and reduced tissue perfusion might have contributed to the risk[98,103,104].

In contrast, the CREDENCE trial did not detect a significant difference in the rate of amputation between the canagliflozin and placebo groups[11]. It was unknown if the differing finding on lower limb amputation between the CANVAS Program and CREDENCE was attributed to different study populations and protocol or due to chance[11]. Yet, the result from CREDENCE offers reassurance, and is consistent with those of the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials, which reported no increased risk of amputation with empagliflozin and dapagliflozin, respectively[12,105].

Rates in Asian type 2 diabetes mellitus populations

Available data on Asian type 2 diabetes mellitus patients thus far seem to suggest that the incidence of amputation associated with SGLT2i is rare. A pooled analysis of phase I–III studies in East Asian patients found that the rates of lower limb amputations between those treated with empagliflozin 10 mg, 25 mg and placebo were 0.1, 0 and 0 per 100 patient-years, respectively[44]. Similar pooled analyses for dapagliflozin and ipragliflozin carried out on patients whose majority were of Asian origin (≥80%) did not observe any lower limb amputation events[40,106]. There were also no reports of amputations in clinical trials of canagliflozin involving Japanese patients[43]. Matthews *et al.*[102] pointed out in their detailed examination of the CANVAS Program that Asian ethnicity was associated with a far lower risk of amputations versus their non-Asian counterparts (HR 0.32, 95% CI 0.17–0.61), which in part, helps to explain the rare occurrence of SGLT2i-associated amputation among Asian populations.

Management and counseling point

It remains important, nevertheless, that physicians should take careful medical history of patients to minimize the risk of lower limb amputation. Certain intrinsic risk factors, such as prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers, could increase the risk of amputations with or without SGLT2i[34,97,98,107]. Guidance from the US FDA and European Medicines Agency include advising physicians to remind patients of routine foot and wound care, adequate hydration, and to always monitor for any infection, new pain, tenderness, sores or ulcers on their legs[107,108]. It is imperative to consider the overall net clinical benefits with SGLT2i in patients having high risk of amputation as lower limb artery disease could increase the risk of developing severe coronary artery disease and premature mortality[34].

Hypoglycemia

Overview and risk factors

Hypoglycemia remains a common major concern in type 2 diabetes mellitus patients receiving glucose-lowering therapy, as it could place patients at risk of injury and death[109]. Given their insulin-independent mechanism of action, SGLT2i on its own should not induce nor increase the risk of hypoglycemia, as compared with other conventional anti-diabetes agents[57,77]. The

sustained blood glucose-lowering by SGLT2i might eventually result in reduced renal glucose filtration and diminished glycosuria, hence explaining the low hypoglycemia risk associated with this agent[4,110]. Large CVOTs further backed this notion, whereby the risk of hypoglycemia was found to be similar between patients treated with SGLT2i and placebo, plus hypoglycemia is uncommon in patients without diabetes[10,12,13,15].

Rates in Asian type 2 diabetes mellitus populations

In general, the occurrence of hypoglycemia with SGLT2i among Asian type 2 diabetes mellitus patients is relatively low and well-tolerated[2]. In 24-week studies involving Asian patients inadequately controlled with metformin, no hypoglycemic event was shown in both the ipragliflozin and placebo groups[46,47]. Hypoglycemia was also uncommon among Asian drug-naïve patients treated with placebo, and dapagliflozin 5 and 10 mg (1.5, 0.8 and 0.8%, respectively), with no study discontinuation reported due to hypoglycemic event[35]. Seino *et al.*[54] showed that luseogliflozin addition to other oral agents, such as SUs, biguanides and dipeptidyl peptidase-4 inhibitors, for 24 weeks among a Japanese population did not cause any severe hypoglycemic events. Hypoglycemic events, if present, were mild and patients recovered rapidly on food or oral glucose intake[54].

The low hypoglycemia risk of SGLT2i confers several notable advantages to Asian type 2 diabetes mellitus patients. Working adults with early-onset diabetes might benefit from SGLT2i therapy, as the concern of hypoglycemia impacting their working capacity is minimal[2]. Furthermore, as fasting is a common practice in Asia, particularly among Muslims during the Ramadan month, SGLT2i safety is essential in view of the potential risk of hypoglycemia and dehydration due to fasting[4]. In a study carried out in Malaysia during Ramadan (n = 110), dapagliflozin 10 mg was found to be safe among fasting Muslim type 2 diabetes mellitus patients with significantly lower hypoglycemic events versus those taking SUs (HR 0.24, 95% CI 0.09–0.68; P = 0.002)[45].

Management and counseling point

Although the risk of hypoglycemia is low as monotherapy, such risk is higher if SGLT2i are to be taken together with insulin or insulin secretagogues, such as SU[34]. Hence, a lower dose of insulin or SU might be required to reduce the risk of hypoglycemia when used in combination with SGLT2i[34]. For patients with HbA1c ≤8.5% initiating SGLT2i, it is recommended that their daily insulin doses are reduced by 20%, whereas SU dose should be halved or stopped[111]. In contrast, patients having HbA1c >8.5% should maintain their insulin or SU dose[111]. Regardless of their baseline HbA1c, patients taking SGLT2i are recommended to self-monitor their blood glucose and adjust their insulin/SU dose according to their glycemic control[111]. During Ramadan, the Malaysian clinical practice guideline has recommended that SGLT2i should be taken post-sunset (evening) meal with no dose adjustment to reduce the hypoglycemia and hypovolemia risks among fasting Muslim patients[29]. Physicians should pay attention if their patients are elderly, having irregular meals, consuming alcohol and engaging in strenuous exercise, as well as comorbidities, such as renal impairment and loss of insulin secretion, all of which could increase the risk of hypoglycemia[112].

Diabetic ketoacidosis

Overview and risk factors

SGLT2i CVOTs have shown that the incidence of DKA was low in patients either receiving SGLT2i or placebo, although DKA appears to be more common in the former[113]. The concern regarding SGLT2i-associated DKA was initially raised by the US FDA communication in 2015, which highlighted 20 euglycemic DKA cases among SGLT2i users, requiring emergency room visits or hospitalization while showing slightly increased blood glucose level <11.1 mmoL/L (<200 mg/dL)[114].

It is thought that SGLT2i-associated euglycemic DKA might occur through several mechanisms. The insulin-independent glucose-lowering action of SGLT2i might reduce dependency on pancreatic β-cell insulin secretion, thereby reducing the circulating insulin level[115]. As such, anti-lipolytic activity of insulin decreases, which stimulates production of free fatty acids that are in turn converted to ketone bodies in the liver[115]. In addition, it was postulated that potential stimulation of glucagon secretion by SGLT2i in response to reduced insulin secretion might also contribute to the overproduction of ketone bodies[115].

In an analysis of 17,596 patients taking canagliflozin, DKA and its related events occurred at a low frequency, and were only reported in 12 patients, whereby six of them were found to have latent autoimmune diabetes of adulthood, GAD65 antibody positivity or type 1 diabetes[116]. Indeed, the FDA acknowledged that some of the DKA cases were reported in type 1 diabetes patients[117]. There had been an increase in off-label use of SGLT2i among these patients, possibly due to its favorable insulin-independent action and weight loss benefits[117]. However, SGLT2i use was not approved in type 1 diabetes patients by the FDA, as their safety and efficacy have not been fully established at that time[114]. Nevertheless, it is noteworthy that the use of dapagliflozin as an oral adjunct treatment to insulin in type 1 diabetes adults has been approved in Japan in light of newer evidence of its safety and efficacy[118-121]. Ipragliflozin has also been approved to be used in type 1 diabetes and no reported cases of DKA were noted[122].

In response to the FDA communication, the American Association of Clinical Endocrinologists and American College of Endocrinology released a position statement on the association of SGLT2i and DKA[123]. It was concluded that DKA occurs infrequently in patients taking SGLT2i, and the risk–benefit ratio favors continued use of these agents[123]. American Association of Clinical Endocrinologists/American College of Endocrinology experts also agreed that most SGLT2i-associated DKA occurred in patients with diabetes who are insulin deficient, such as those with latent autoimmune diabetes of

adulthood, type 1 diabetes and long standing type 2 diabetes mellitus[123]. These DKA events can be precipitated by stressful physical, metabolic and medical conditions, such as intensive exercise, prolonged fasting, serious infection, myocardial infarction, stroke and surgery[123]. Inappropriate withdrawal of insulin or insulin secretagogues during SGLT2i initiation is also a risk factor for the development of euglycemic DKA[115,123].

Rates in Asian type 2 diabetes mellitus populations

The risk of SGLT2i-associated DKA remains a considerable concern among Asian type 2 diabetes mellitus patients owing to their high association with β-cell dysfunction[124,125]. Nevertheless, available evidence suggests that DKA is infrequent in Asian populations. In the EMPA-REG OUTCOME trial, DKA was not reported in Asian patients treated with empagliflozin 10 mg and 25 mg, as opposed to one placebo patient[41]. There were also no confirmed DKA cases among those treated with placebo, ertugliflozin 5 and 15 mg in the 26-week VERTIS Asia study[126]. Insulin-treated Japanese patients who had gradual reduction of the mean daily insulin dose by −2.14 U/day (95% CI −3.74, −0.54) did not experience DKA while taking dapagliflozin for 36 weeks[127]. Hence, these data suggest that DKA risk in type 2 diabetes mellitus patients can be mitigated should SGLT2i be properly used as indicated.

Real-world data on Asian patients receiving SGLT2i offer further insight on the occurrence of DKA in this region. Based on the Korean Health Insurance claim database, the risk of hospitalization for DKA was not increased in SGLT2i users versus dipeptidyl peptidase-4 inhibitor users (HR 0.956, 95% CI 0.581–1.572; $P = 0.996$)[48]. Meanwhile, the Health Sciences Authority of Singapore recorded a cumulative reporting rate of 0.72 SGLT2i-associated DKA cases per 1,000 person-years[49]. None of these cases were fatal, suggesting that DKA incidence among SGLT2i users was infrequent[49]. The majority of reported DKA cases (>71%) occurred within 180 days of SGLT2i initiation, in women or in long-standing type 2 diabetes mellitus patients, all of whom with known precipitating factors, such as acute illnesses and infections, as well as insulin dose reduction or cessation[49].

To date, there are no head-to-head studies comparing the adverse events of SGLT2i in Asian versus Western populations. However, in a recent publication on the DAPA-HF trial investigating the efficacy and safety of dapagliflozin compared with placebo in heart failure with reduced ejection fraction patients in Asia compared with the non-Asia region, it was shown that, in general, the proportions of adverse events were similar. However, not all adverse events were collected in that trial[128]. In other clinical trials that did gather all adverse events, the rate of genital fungal infection was reported to be lower in Asian patients than in studies carried out in other geographic regions[4,37,38,40,129,130].

Management and counseling point

Although DKA appeared to be low and infrequent, physicians should still maintain clinical vigilance in regard to Asian SGLT2i users, especially those who are at risk of developing DKA, and to monitor for symptoms, such as nausea, vomiting, tachycardia, dyspnea and abdominal pain[49,123]. Addressing the underlying precipitating factors are crucial in mitigating the risk of DKA during SGLT2i therapy[49]. Patients taking SGLT2i should be advised to seek medical advice promptly during stress periods, such as fever, trauma, infection or surgery, as medication requirements might change[123]. The latest FDA approval for SGLT2i label update recommends stopping SGLT2i at least 72 h before a planned surgery to lessen the risk of DKA post-surgery[131]. In the case of sudden severe external stress or emergency surgery, SGLT2i should be stopped immediately[123,132]. It is also pertinent to avoid inappropriate withdrawal or excessive dose reduction of insulin[111,123]. Additionally, patients should avoid alcohol intake, very low-carbohydrate or ketogenic diets while using SGLT2i[123]. Physicians in Asia should also be mindful that SGLT2i are not approved for type 1 diabetes patients, with the exception for dapagliflozin in Japan, which was approved as an adjunct to insulin therapy[119].

If a type 2 diabetes mellitus patient develops DKA while taking SGLT2i, intravenous insulin and glucose should be administered, along with assessment on anion gap, serum β-hydroxybutyrate and arterial pH[123]. SGLT2i should not be restarted immediately, as there could be a risk of recurrence of DKA with continuous SGLT2i therapy[133]. Should recurrent DKA arise, it is reasonable to avoid the use of SGLT2i[133].

Other counseling points

Regardless of their multiple benefits, type 2 diabetes mellitus patients should be continuously reminded of the importance of adherence to dietary instructions, regular physical activity and periodic blood glucose monitoring while on SGLT2i therapy[4,134]. In addition, patients should be educated on holistic management of both hypo- and hyperglycemia, and diabetes complications[4,134].

Although there were rare reports on serious hypersensitivity reactions, such as urticaria and angioedema with SGLT2i, patients should be advised to immediately alert their physicians of any signs or symptoms suggesting allergic reaction, and to discontinue SGLT2i until they have consulted their physicians[62–64].

As there are no adequate and well-controlled studies, SGLT2i are not recommended during pregnancy and breast-feeding[62-64]. Therefore, female patients should immediately inform their physicians if they are pregnant or planning to get pregnant or are breast-feeding. It is not known if SGLT2i are safe and effective in children aged <18 years, although clinical trials on the efficacy and safety of SGLT2i in type 2 diabetes mellitus patients aged between 10 and <18 years are ongoing[134]. Until further data are available, SGLT2i use in children should be avoided.

CONCLUSION

Cumulative evidence has shown that SGLT2i are well-tolerated. The rate of adverse events is still reasonably low among Asian

type 2 diabetes mellitus patients. Appropriate patient counseling and proper selection of patients are necessary to ensure a successful type 2 diabetes mellitus management with SGLT2i. Together with compelling cardiorenal benefits of SGLT2i, the overall beneficial effects of these agents outweigh the risks related to common adverse events of SGLT2i.

ACKNOWLEDGMENTS

The authors thank AstraZeneca Malaysia for the educational grant and Mediconnexions Consulting Sdn. Bhd. for their medical writing/editorial support.

DISCLOSURE

Jaime A Davidson disclosures: Consultant/Advisory Board for AstraZeneca, Janssen, Merck and Novo Nordisk. Fen-Lee Hew disclosures: Advisory Board for AstraZeneca, Merck-Sharp Dohme and Novo Nordisk. The other authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels: International Diabetes Federation, 2019.
2. Lim LL, Tan AT, Moses K, *et al*. Place of sodium-glucose cotransporter-2 inhibitors in east Asian subjects with type 2 diabetes mellitus: insights into the management of Asian phenotype. *J Diabetes Complications* 2017; 31: 494–503.
3. Kodama K, Tojjar D, Yamada S, *et al*. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care* 2013; 36: 1789–1796.
4. Kalra S, Ghosh S, Aamir AH, *et al*. Safe and pragmatic use of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes mellitus: South Asian Federation of Endocrine Societies consensus statement. *Indian J Endocrinol Metab* 2017; 21: 210–230.
5. Yeung RO, Zhang Y, Luk A, *et al*. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. *Lancet Diabetes Endocrinol* 2014; 2: 935–943.
6. Ma RC, Chan JC. Type 2 diabetes in east Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci* 2013; 1281: 64–91.
7. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *BMJ Open* 2016; 6: e009417.
8. Wang MY, Yu X, Lee Y, *et al*. Dapagliflozin suppresses glucagon signaling in rodent models of diabetes. *Proc Natl Acad Sci USA* 2017; 114: 6611–6616.
9. Deerochanawong C, Chan SP, Matawaran BJ, *et al*. Use of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes mellitus and multiple cardiovascular risk factors: an Asian perspective and expert recommendations. *Diabetes Obes Metab* 2019; 21: 2354–2367.
10. Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.
11. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
12. Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
13. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
14. Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334.
15. Cannon CP, Pratley R, Dagogo-Jack S, *et al*. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020; 383: 1425–1435.
16. Bhatt DL, Szarek M, Steg PG, *et al*. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021; 384: 117–128.
17. Bhatt DL, Szarek M, Pitt B, *et al*. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021; 384: 129–139.
18. McMurray JJV, Solomon SD, Inzucchi SE, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381: 1995–2008.
19. Anker SD, Butler J, Filippatos G, *et al*. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; 385: 1451–1461.
20. Packer M, Anker SD, Butler J, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383: 1413–1424.
21. Heerspink HJ, Stefánsson BV, Correa-Rotter R, *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383: 1436–1446.
22. Buse JB, Wexler DJ, Tsapas A, *et al*. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care* 2020; 43: 487–493.
23. Cosentino F, Grant PJ, Aboyans V, *et al*. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; 41: 255–323.
24. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;98: S1–S115.

25. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44(Suppl 1): S111–S124.
26. Kim MK, Ko SH, Kim BY, *et al*. 2019 clinical practice guidelines for type 2 diabetes mellitus in Korea. *Diabetes Metab J* 2019; 43: 398–406.
27. Chawla R, Madhu SV, Makkar BM, *et al*. RSSDI-ESI clinical practice recommendations for the management of type 2 diabetes mellitus 2020. *Indian J Endocr Metab* 2020; 24: 1–122.
28. Diabetes Association of The Republic of China Taiwan. Executive summary of the DAROC clinical practice guidelines for diabetes care-2018. *J Formos Med Assoc* 2020; 119: 577–586.
29. Malaysian Clinical Practice Guidelines. Management of Type 2 Diabetes Mellitus, 6th edn. [Internet]. Malaysia: Ministry of Health, 2020 [updated 2020 December] . http://www.acadmed.org.my/view_file_captcha.cfm?fileid=763 Accessed May 6, 2021.Available from:
30. Lim LL, Chan JC. Sodium-glucose co-transporter-2 inhibitors: know the patient and the drugs. *Hong Kong Med J* 2019; 25: 268–270.
31. Wilding J. SGLT2 inhibitors and urinary tract infections. *Nat Rev Endocrinol* 2019; 15: 687–688.
32. Alkabbani W, Gamble JM. Profile of ipragliflozin, an oral SGLT-2 inhibitor for the treatment of type 2 diabetes: the evidence to date. *Drug Des Devel Ther* 2021; 15: 3057–3069.
33. Rossenwasser RF, Sultan S, Sutton D, *et al*. SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes Metab Syndr Obes* 2013; 6: 453–467.
34. Scheen AJ. An update on the safety of SGLT2 inhibitors. *Expert Opin Drug Saf* 2019; 18: 295–311.
35. Ji L, Ma J, Li H, *et al*. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther* 2014; 36: 84–100.e9.
36. Yoon KH, Nishimura R, Lee J, *et al*. Efficacy and safety of empagliflozin in patients with type 2 diabetes from Asian countries: pooled data from four phase III trials. *Diabetes Obes Metab* 2016; 18: 1045–1049.
37. Cai X, Gao X, Yang W, *et al*. No disparity of the efficacy and all-cause mortality between Asian and non-Asian type 2 diabetes patients with sodium-glucose cotransporter 2 inhibitors treatment: a meta-analysis. *J Diabetes Investig* 2018; 9: 850–861.
38. Yang L, Zhang L, He H, *et al*. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in east Asians with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Ther* 2019; 10: 1921–1934.
39. Ji L, Han P, Liu Y, *et al*. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. *Diabetes Obes Metab* 2015; 17: 23–31.
40. Yang W, Ji L, Zhou Z, *et al*. Efficacy and safety of dapagliflozin in Asian patients: a pooled analysis. *J Diabetes* 2017; 9: 787–799.
41. Kaku K, Lee J, Mattheus M, *et al*. Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease – results from EMPA-REG OUTCOME®. *Circ J* 2017; 81: 227–234.
42. Seino Y, Sasaki T, Fukatsu A, *et al*. Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. *Curr Med Res Opin* 2014; 30: 1245–1255.
43. Inagaki N, Harashima SI, Iijima H. Canagliflozin for the treatment of type 2 diabetes: a comparison between Japanese and non-Japanese patients. *Expert Opin Pharmacother* 2018; 19: 895–908.
44. Yabe D, Yasui A, Ji L, *et al*. Safety and tolerability of empagliflozin in east Asian patients with type 2 diabetes: pooled analysis of phase I–III clinical trials. *J Diabetes Investig* 2019; 10: 418–428.
45. Wan Seman WJ, Kori N, Rajoo S, *et al*. Switching from sulphonylurea to a sodium-glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia. *Diabetes Obes Metab* 2016; 18: 628–632.
46. Kashiwagi A, Kazuta K, Goto K, *et al*. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* 2015; 17: 304–308.
47. Lu CH, Min KW, Chuang LM, *et al*. Efficacy, safety, and tolerability of ipragliflozin in Asian patients with type 2 diabetes mellitus and inadequate glycemic control with metformin: results of a phase 3 randomized, placebo-controlled, double-blind, multicenter trial. *J Diabetes Investig* 2016; 7: 366–373.
48. Kim YG, Jeon JY, Han SJ, *et al*. Sodium-glucose co-transporter-2 inhibitors and the risk of ketoacidosis in patients with type 2 diabetes mellitus: a nationwide population-based cohort study. *Diabetes Obes Metab* 2018; 20: 1852–1858.
49. Limenta M, Ho CSC, Poh JWW, *et al*. Adverse drug reaction profile of SGLT2 inhibitor-associated diabetic ketosis/ketoacidosis in Singapore and their precipitating factors. *Clin Drug Investig* 2019; 39: 683–690.
50. Chaplin S. SGLT2 inhibitors and risk of genitourinary infections. *Prescriber* 2016; 27: 26–30.
51. Nyirjesy P, Sobel JD. Genital mycotic infections in patients with diabetes. *Postgrad Med* 2013; 125: 33–46.
52. Zaccardi F, Webb DR, Htike ZZ, *et al*. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab* 2016; 18: 783–794.

53. Kalra S. Sodium glucose co-transporter-2 (SGLT2) inhibitors: a review of their basic and clinical pharmacology. *Diabetes Ther* 2014; 5: 355–366.
54. Seino Y, Inagaki N, Haneda M, *et al*. Efficacy and safety of luseogliflozin added to various oral antidiabetic drugs in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig* 2015; 6: 443–453.
55. Terauchi Y, Yokote K, Nakamura I, *et al*. Safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): interim results of a post-marketing surveillance study. *Expert Opin Pharmacother* 2016; 17: 463–471.
56. Bashier A, Khalifa AA, Rashid F, *et al*. Efficacy and safety of SGLT2 inhibitors in reducing glycated hemoglobin and weight in Emirati patients with type 2 diabetes. *J Clin Med Res* 2017; 9: 499–507.
57. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug Des Devel Ther* 2014; 8: 1335–1380.
58. Nyirjesy P, Zhao Y, Ways K, *et al*. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Curr Med Res Opin* 2012; 28: 1173–1178.
59. Hirji I, Guo Z, Andersson SW, *et al*. Incidence of urinary tract infection among patients with type 2 diabetes in the UK general practice research database (GPRD). *J Diabetes Complications* 2012; 26: 513–516.
60. Fu AZ, Iglay K, Qiu Y, *et al*. Risk characterization for urinary tract infections in subjects with newly diagnosed type 2 diabetes. *J Diabetes Complications* 2014; 28: 805–810.
61. Nitzan O, Elias M, Chazan B, *et al*. Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. *Diabetes Metab Syndr Obes* 2015; 8: 129–136.
62. AstraZeneca. Farxiga prescribing information [Internet]. United States, 2021 [updated 2021 April]. Available from: https://www.azpicentral.com/farxiga/farxiga.pdf#page=1 Accessed September 20, 2021.
63. Boehringer Ingelheim Pharmaceuticals. Jardiance prescribing information [Internet]. United States, 2021 [updated 2021 August]. Available from: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf Accessed September 20, 2021.
64. Janssen Pharmaceuticals, Inc. Invokana prescribing information [Internet]. United States, 2020 [updated 2020 August]. Available from: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf Accessed September 20, 2021.
65. Schneeberger C, Holleman F, Geerlings SE. Febrile urinary tract infections: pyelonephritis and urosepsis. *Curr Opin Infect Dis* 2016; 29: 80–85.
66. Dave CV, Schneeweiss S, Kim D, *et al*. Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: a population-based cohort study. *Ann Intern Med* 2019; 171: 248–256.
67. Health Sciences Authority of Singapore. Risk of genitourinary infections with SGLT2 inhibitors [Internet]. Singapore: Health Sciences Authority, 2018 [updated 2018 May 11]. Available from: https://www.hsa.gov.sg/announcements/safety-alert/risk-of-genitourinary-infections-with-sglt2-inhibitors Accessed June 22, 2018.
68. Sorensen MD, Krieger JN. Fournier's gangrene: epidemiology and outcomes in the general US population. *Urol Int* 2016; 97: 249–259.
69. Kaufmann JA, Ramponi D. Recognition of risk factors and prognostic indicators in Fournier's gangrene. *Crit Care Nurs Q* 2015; 38: 143–153.
70. Food and Drug Administration. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes [Internet]. United States: Food and Drug Administration, 2018 [updated 2018 July 9]. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm Accessed February 8, 2019.
71. Bersoff-Matcha SJ, Chamberlain C, Cao C, *et al*. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. *Ann Intern Med* 2019; 170: 764–769.
72. Silverii GA, Dicembrini I, Monami M, *et al*. Fournier's gangrene and sodium-glucose co-transporter-2 inhibitors: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020; 22: 272–275.
73. Voelzke BB, Hagedorn JC. Presentation and diagnosis of Fournier gangrene. *Urology* 2018; 114: 8–13.
74. Neal B, Perkovic V, de Zeeuw D, *et al*. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care* 2015; 38: 403–411.
75. Lavalle-González FJ, Januszewicz A, Davidson J, *et al*. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013; 56: 2582–2592.
76. John M, Gopinath D, Jagesh R. Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: clinical perspectives. *Indian J Endocr Metab* 2016; 20: 22–31.
77. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. *Cardiovasc Diabetol* 2015; 14: 142.
78. Cahn A, Mosenzon O, Wiviott SD, *et al*. Efficacy and safety of dapagliflozin in the elderly: analysis from the DECLARE-TIMI 58 study. *Diabetes Care* 2020; 43: 468–475.
79. Monteiro P, Bergenstal RM, Toural E, *et al*. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial. *Age Ageing* 2019; 48: 859–866.
80. Inagaki N, Kondo K, Yoshinari T, *et al*. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a

randomized, double-blind, placebo-controlled, 12-week study. *Diabetes Obes Metab* 2013; 15: 1136–1145.
81. Prasanna Kumar KM, Mohan V, Sethi B, *et al*. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus from India. *Indian J Endocrinol Metab* 2016; 20: 372–380.
82. Cherney DZ, Udell JA. Use of sodium glucose cotransporter 2 inhibitors in the hands of cardiologists: with great power comes great responsibility. *Circulation* 2016; 134: 1915–1917.
83. Neuen BL, Young T, Heerspink HJL, *et al*. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019; 7: 845–854.
84. Davidson JA. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence. *Postgrad Med* 2019; 131: 251–260.
85. Fioretto P, Zambon A, Rossato M, *et al*. SGLT2 inhibitors and the diabetic kidney. *Diabetes Care* 2016; 39(Suppl 2): S165–S171.
86. Fioretto P, Del Prato S, Buse JB, *et al*. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE study. *Diabetes Obes Metab* 2018; 20: 2532–2540.
87. Pollock C, Stefánsson B, Reyner D, *et al*. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; 7: 429–441.
88. Kadowaki T, Nangaku M, Hantel S, *et al*. Empagliflozin and kidney outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: results from the EMPA-REG OUTCOME® trial. *J Diabetes Investig* 2019; 10: 760–770.
89. Szalat A, Perlman A, Muszkat M, *et al*. Can SGLT2 inhibitors cause acute renal failure? Plausible role for altered glomerular hemodynamics and medullary hypoxia. *Drug Saf* 2018; 41: 239–252.
90. Moseley KF. Type 2 diabetes and bone fractures. *Curr Opin Endocrinol Diabetes Obes* 2012; 19: 128–135.
91. Moayeri A, Mohamadpour M, Mousavi SF, *et al*. Fracture risk in patients with type 2 diabetes mellitus and possible risk factors: a systematic review and meta-analysis. *Ther Clin Risk Manag* 2017; 13: 455–468.
92. Schneider AL, Williams EK, Brancati FL, *et al*. Diabetes and risk of fracture-related hospitalization: the atherosclerosis risk in communities study. *Diabetes Care* 2013; 36: 1153–1158.
93. Dytfeld J, Michalak M. Type 2 diabetes and risk of low-energy fractures in postmenopausal women: meta-analysis of observational studies. *Aging Clin Exp Res* 2017; 29: 301–309.
94. Taylor SI, Blau JE, Rother KI. SGLT2-inhibitors trigger downstream mechanisms that may exert adverse effects upon bone. *Lancet Diabetes Endocrinol* 2015; 3: 8–10.
95. Tang HL, Li DD, Zhang JJ, *et al*. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2016; 18: 1199–1206.
96. Singh AK, Unnikrishnan AG, Zargar AH, *et al*. Evidence-based consensus on positioning of SGLT2i in type 2 diabetes mellitus in Indians. *Diabetes Ther* 2019; 10: 393–428.
97. National Institute for Health and Care Excellence. Diabetic foot problems: prevention and management [Internet]. United Kingdom: National Institute for Health and Care Excellence, 2015 [updated 2015 August 26]. Available from: https://www.nice.org.uk/guidance/ng19/resources/diabetic-foot-problems-prevention-and-management-pdf-1837279828933 Accessed September 26, 2017.
98. Yuan Z, DeFalco FJ, Ryan PB, *et al*. Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: a retrospective cohort study. *Diabetes Obes Metab* 2018; 20: 582–589.
99. Hoffstad O, Mitra N, Walsh J, *et al*. Diabetes, lower-extremity amputation, and death. *Diabetes Care* 2015; 38: 1852–1857.
100. Adler AI, Erqou S, Lima TA, *et al*. Association between glycated haemoglobin and the risk of lower extremity amputation in patients with diabetes mellitus-review and meta-analysis. *Diabetologia* 2010; 53: 840–849.
101. Health Sciences Authority of Singapore. Update on canagliflozin and risk of lower limb amputation [Internet]. Singapore: Health Sciences Authority, 2018 [updated 2018 May 11]. Available from: https://www.hsa.gov.sg/announcements/safety-alert/update-on-canagliflozin-and-risk-of-lower-limb-amputation Accessed June 27, 2018.
102. Matthews DR, Li Q, Perkovic V, *et al*. Effects of canagliflozin on amputation risk in type 2 diabetes: the CANVAS program. *Diabetologia* 2019; 62: 926–938.
103. Health Products Regulatory Authority. SGLT2 inhibitors and risk of lower limb amputation (mainly toe) [Internet]. Ireland: Health Products Regulatory Authority, 2017 [updated April 2017]. Available from: https://www.hpra.ie/docs/default-source/default-document-library/hpra_mims_sglt2-inhibitors_april-2017.pdf?sfvrsn=0 Accessed September 27, 2017.
104. Tanaka A, Node K. Increased amputation risk with canagliflozin treatment: behind the large cardiovascular benefit? *Cardiovasc Diabetol* 2017; 16: 129.
105. Inzucchi SE, Iliev H, Pfarr E, *et al*. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. *Diabetes Care* 2018; 41: e4–e5.
106. Kashiwagi A, Shestakova MV, Ito Y, *et al*. Safety of ipragliflozin in patients with type 2 diabetes mellitus:

pooled analysis of phase II/III/IV clinical trials. *Diabetes Ther* 2019; 10: 2201–2217.
107. Food and Drug Administration. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) [Internet]. Food and Drug Administration, 2017 [updated 2017 May 16]. Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf Accessed August 17, 2017.
108. European Medicines Agency. EMA reviews diabetes medicine canagliflozin: review follows data on toe amputations in ongoing study [Internet]. London: European Medicines Agency, 2016 [updated 2016 July 8]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20/Procedure_started/WC500204901.pdf Accessed August 17, 2017.
109. Seaquist ER, Anderson J, Childs B, *et al*. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab* 2013; 98: 1845–1859.
110. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. *Kidney Int Suppl* 2011; 79(Suppl 120): S20–S27.
111. Gomez-Peralta F, Abreu C, Lecube A, *et al*. Practical approach to initiating SGLT2 inhibitors in type 2 diabetes. *Diabetes Ther* 2017; 8: 953–962.
112. Amiel SA, Dixon T, Mann R, *et al*. Hypoglycaemia in type 2 diabetes. *Diabet Med* 2008; 25: 245–254.
113. Zelniker TA, Wiviott SD, Raz I, *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; 393: 31–39.
114. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood [Internet]. Food and Drug Administration, 2015 [updated 2015 May 15]. Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM446954.pdf Accessed June 27, 2018.
115. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Investig* 2016; 7: 135–138.
116. Erondu N, Desai M, Ways K, *et al*. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care* 2015; 38: 1680–1686.
117. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care* 2015; 38: 1638–1642.
118. AstraZeneca. Forxiga approved in Europe for type-1 diabetes [Internet]. AstraZeneca, 2019 [updated 2019 March 25]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2019/forxiga-approved-in-europe-for-type-1-diabetes22032019.html Accessed May 29, 2019.
119. AstraZeneca. Forxiga approved in Japan for type-1 diabetes [Internet]. AstraZeneca, 2019 [updated 2019 March 27]. Available from: https://www.astrazeneca.com/media-centre/press-releases/2019/forxiga-approved-in-japan-for-type-1-diabetes-27032019.html Accessed May 29, 2019.
120. Dandona P, Mathieu C, Phillip M, *et al*. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. *Diabetes Care* 2018; 41: 2552–2559.
121. Mathieu C, Dandona P, Gillard P, *et al*. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care* 2018; 41: 1938–1946.
122. Kaku K, Isaka H, Sakatani T, *et al*. Efficacy and safety of ipragliflozin add-on therapy to insulin in Japanese patients with type 1 diabetes mellitus: a randomized, double-blind, phase 3 trial. *Diabetes Obes Metab* 2019; 21: 2284–2293.
123. Handelsman Y, Henry RR, Bloomgarden ZT, *et al*. American Association of Clinical Endocrinologists and American College of endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocr Pract* 2016; 22: 753–762.
124. Yabe D, Iwasaki M, Kuwata H, *et al*. Sodium-glucose co-transporter-2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: a randomized, open-label, 3-arm parallel comparative, exploratory study. *Diabetes Obes Metab* 2017; 19: 739–743.
125. Lin YH. Sodium-glucose cotransporter-2 inhibitors induced eu-glycemic diabetic ketoacidosis: the first report in a type 2 diabetic (T2D) Taiwanese and literature review of possible pathophysiology and contributing factors. *J Formos Med Assoc* 2018; 117: 849–854.
126. Ji L, Liu Y, Miao H, *et al*. Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. *Diabetes Obes Metab* 2019; 21: 1474–1482.
127. Araki E, Onishi Y, Asano M, *et al*. Efficacy and safety of dapagliflozin over 1 year as add-on to insulin therapy in Japanese patients with type 2 diabetes: the DAISY (dapagliflozin added to patients under InSulin therapY) trial. *Diabetes Obes Metab* 2017; 19: 562–570.
128. Docherty K, Anand I, Chiang C, *et al*. Effects of dapagliflozin in Asian patients with heart failure and reduced ejection fraction in DAPA-HF. *JACC: Asia* 2022; 2: 139–153.
129. Fujita Y, Inagaki N. Update on the efficacy and safety of sodium-glucose cotransporter 2 inhibitors in Asians and non-Asians. *J Diabetes Investig* 2019; 10: 1408–1410.

130. Khoo CM, Deerochanawong C, Chan SP, *et al*. Use of sodium-glucose co-transporter-2 inhibitors in Asian patients with type 2 diabetes and kidney disease: an Asian perspective and expert recommendations. *Diabetes Obes Metab* 2021; 23: 299–317.
131. Food and Drug Administration. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections [Internet]. Food and Drug Administration, 2020 [updated 2020 March 3]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious Accessed August 6, 2020.
132. Khunti K, Aroda VR, Bhatt DL, *et al*. Re-examining the widespread policy of stopping sodium-glucose cotransporter-2 inhibitors during acute illness: a perspective based on the updated evidence. *Diabetes Obes Metab* 2022; 24: 2071–2080.
133. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. *Diabetologia* 2018; 61: 2118–2125.
134. Davies MJ, D'Alessio DA, Fradkin J, *et al*. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41: 2669–2701.