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REVIEW

Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits

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Abstract

Sodium–glucose cotransporter 2 (SGLT2) inhibitors belong to a novel class of glucose-lowering medications that reduce plasma glucose concentrations by inhibiting glucose reabsorption by the kidney, inducing glucosuria. Their actions encompass reductions in HbA_{1c}, fasting and postprandial blood glucose levels, body weight and BP. To date, empagliflozin and canagliflozin have additionally been shown to improve cardiovascular outcomes in high-risk individuals and to slow the progression of diabetic kidney disease. Adverse effects associated with this class include urinary frequency, dehydration, genitourinary tract infections and, rarely, euglycaemic diabetic ketoacidosis. Of the SGLT2 inhibitors, only canagliflozin has been linked to a higher risk of lower-extremity amputations and bone fractures compared with placebo. Optimal prescribing of agents within this relatively new drug category requires a full understanding of their risks in addition to their benefits.

Keywords Benefits · Cardiovascular · Fractures · Ketoacidosis · Renal · Review · Risks · SGLT2 inhibitors · Type 2 diabetes

Abbreviations

AKI	Acute kidney injury
CANVAS	Canagliflozin Cardiovascular Assessment Study
CANVAS-R	CANVAS-Renal
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase-4
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
MACE	Major adverse cardiac events
PVD	Peripheral vascular disease
SGLT2	Sodium–glucose cotransporter 2
UTI	Urinary-tract infection

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Introduction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors belong to a novel class of medications that reduce plasma glucose concentrations by increasing urinary glucose excretion. Members of this class approved for use in the USA and Europe are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. Besides decreasing plasma glucose, they also induce some weight loss, lower BP and carry a low risk of hypoglycaemia. Some SGLT2 inhibitors also have cardiovascular and renal benefits. They are generally well tolerated but have several well-recognised adverse effects that should be considered to optimise their risk to benefit ratio. The benefits vs risks of SGLT2 inhibitors are shown in Fig. 1.

Beneficial effects of SGLT2 inhibitors

Glucose lowering SGLT2 inhibitors have been studied as monotherapy or in combination with other oral agents or insulin for the management of hyperglycaemia in type 2 diabetes. SGLT2 inhibitors achieve a reduction in HbA_{1c} of 4.4–12.1 mmol/mol (0.4–1.1%), depending on the baseline HbA_{1c} and the specific drug and dose used [1–4]. HbA_{1c} is reduced to a slightly greater extent by high-dose canagliflozin (vs other SGLT2 inhibitors), probably as a result of its additional action

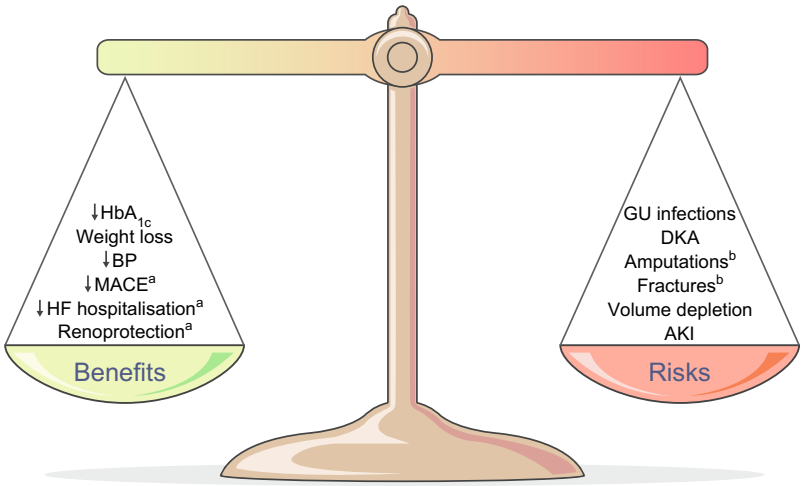

Fig. 1 Recognised major risks and benefits of SGLT2 inhibitors. To date, [a]only empagliflozin and canagliflozin have demonstrated cardiovascular and renal benefits, and [b]increased risk of amputations and fractures has only been observed with canagliflozin in large, randomised, controlled clinical trials. GU, genitourinary; HF, heart failure. This figure is available as part of a downloadable slideset

of inhibiting SGLT1 in the intestine. When compared head-to-head with dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors appear minimally more potent [5]. Interestingly, compared with sulfonylureas, the initial HbA_{1c} reduction is more prominent with sulfonylureas but there is partial loss of efficacy over time, resulting in a slight HbA_{1c} advantage for SGLT2 inhibitors at 2 years [6]. SGLT2 inhibitors are associated with a low incidence of hypoglycaemia [1–4] and can be added to any existing diabetes treatment to effect a reduction in HbA_{1c} regardless of background therapy.

Weight loss Glucosuria-induced energy loss caused by SGLT2 inhibitors leads to weight loss, which appears to be sustained over time. The degree of weight loss varies slightly according to the agent and the dose used. A meta-analysis of randomised controlled trials involving participants treated with canagliflozin 300 mg, empagliflozin 25 mg or dapagliflozin 10 mg daily showed a weight loss of 2.66 kg, 1.81 kg and 1.80 kg, respectively, compared with placebo [7].

BP reduction SGLT2 inhibitors lower BP by promoting osmotic diuresis and intravascular volume contraction. This effect does not appear to be linked to reduction in HbA_{1c}, as individuals with moderately reduced renal function display decreased BP despite minimal HbA_{1c} reduction. SGLT2 inhibitors decrease systolic BP by 3.4–5.4 mmHg and diastolic BP by 1.5–2.2 mmHg. Type 2 diabetic individuals with uncontrolled BP at baseline experience the largest reduction in systolic BP after SGLT2 inhibitor treatment [1–4].

Cardiovascular benefits Among the SGLT2 inhibitors, empagliflozin and canagliflozin have been shown to significantly reduce cardiovascular events in individuals with underlying cardiovascular disease (CVD).

In the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, involving individuals with diabetes and established CVD, participants randomised to receive empagliflozin displayed a lower rate of the primary major adverse cardiac events (MACE) outcomes compared with those who received placebo (HR 0.86 [95% CI 0.74, 0.99]; $p = 0.04$) [8]. This was predominantly driven by a 38% reduction in the risk of cardiovascular death; there was no significant between-group difference in the rates of myocardial infarction or stroke. Risk of death from any cause was reduced by 32% and risk of hospitalisation for heart failure was reduced by 35%. The difference in blood glucose control between the empagliflozin and placebo groups was small, suggesting that extra-glycaemic effects were responsible for the CVD outcome. In a post hoc analysis, the change in haematocrit (~3% absolute increase), corresponding to ~7% reduction in plasma volume, explained about 50% of the benefit of the drug on cardiovascular death [9]. Other mechanistic theories include a small increase in β-hydroxybutyrate, which may provide a more efficient energy source for the diabetic heart [10], and inhibition of the Na^+/H^+ exchanger in cardiac myocytes, which could improve energy dynamics within the heart [11].

The proportion of individuals experiencing stroke in the empagliflozin vs placebo group in the EMPA-REG OUTCOME study was 3.5% (164/4687) vs 3.0% (69/2333) (HR 1.18 [95% CI 0.89, 1.56]; $p = 0.26$) [8]. In a subsequent analysis, the investigators showed that this difference was driven by non-fatal ischaemic stroke, with no isolated increase in any specific subtype [12]. Importantly, the difference was due to events that occurred >90 days after the last intake of study drug, suggesting no direct effect of the drug. For stroke occurring during treatment or ≤90 days after the last dose of drug, the HR for empagliflozin vs placebo was 1.08 (95% CI 0.81, 1.45; $p = 0.60$).

In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program involving individuals at high cardiovascular risk, the primary MACE outcome was significantly reduced in the canagliflozin arm vs placebo arm (HR 0.86 [95% CI 0.75, 0.97]; $p = 0.02$ for superiority) [13]. None of the individual components of MACE, nor all-cause mortality, were significantly reduced by canagliflozin, but the drug did exhibit a similar benefit to empagliflozin (vs placebo) in reducing hospitalisations due to heart failure (HR 0.67 [95% CI 0.52, 0.87]). CANVAS recruited individuals with and without CVD, which might initially suggest potential benefits of canagliflozin in primary prevention [14]. However, the point estimate for the primary outcome was only 0.98 in those without established CVD, implying that the benefit may be mostly in secondary prevention. In contrast, the point estimate for heart failure hospitalisation was similar in both cohorts, suggesting that this specific cardiac benefit may extend to diabetic individuals without overt CVD.

Several observational studies have confirmed that SGLT2 inhibitors are associated with decreased risks of cardiovascular mortality and MACE and lower rates of hospitalisation for heart failure [15, 16]. The decrease in cardiovascular mortality and MACE occurs in individuals with and without CVD at baseline, suggesting that the benefits obtained with empagliflozin and canagliflozin in randomised trials in individuals at high cardiovascular risk may be a class effect applicable to a broad population of individuals with type 2 diabetes.

Reduction in nephropathy The EMPA-REG OUTCOME trial studied the long-term renal effects of empagliflozin. The composite renal outcome included incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine level, initiation of renal-replacement therapy, death from renal disease). Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care. Incident or worsening nephropathy occurred in 12.7% of participants in the empagliflozin group vs 18.8% in the placebo group (HR 0.61 [95% CI 0.53, 0.70]; $p < 0.001$). There was no significant between-group difference in the rate of incident albuminuria. The renal benefit was seen irrespective of baseline eGFR, occurring in individuals with an eGFR down to 30 ml min^{-1} [1.73 m]$^{-2}$. The adverse-event profile of empagliflozin in individuals with impaired kidney function at baseline was similar to that reported in the overall trial population [17]. The mechanism behind the positive renal outcomes of empagliflozin probably includes a direct renovascular action. The short duration of the study and the modest decrease in HbA_{1c} make it unlikely that the improved renal outcomes of this medication can be explained by its glucose-lowering effect.

In the CANVAS Program (which included CANVAS and CANVAS-Renal [CANVAS-R] studies, the latter study assessing specifically the effects on albuminuria), canagliflozin was found to have a beneficial effect on the progression of albuminuria (HR 0.73 [95% CI 0.67, 0.79]) and the composite outcome of a sustained 40% reduction in the eGFR, the need for renal-replacement therapy or death from renal causes (HR 0.60 [95% CI 0.47, 0.77]) [13]. Whether other SGLT2 inhibitors have similar beneficial renal effects is unknown but this would be expected based on their known mechanism of action.

Adverse effects of SGLT2 inhibitors

Genitourinary infections The most common side effect of SGLT2 inhibitors is an increased incidence of genital mycotic infections (mainly balanitis and vulvovaginitis). Some, but not all, studies showed that these drugs are also associated with a small increase in the risk of urinary tract infections (UTIs) [8, 13, 18]. These effects are attributed to the increased glucosuria induced by these agents. Generally, the events are mild to moderate in severity and do not necessitate discontinuation of the drug. Infections of the upper urinary tract, such as pyelonephritis, and urosepsis are extremely rare complications.

A meta-analysis of randomised trials comparing SGLT2 inhibitors with placebo or other medication for type 2 diabetes showed that SGLT2 inhibitors were significantly associated with a fivefold increase in the risk of genital mycotic infections (OR 5.06 [95% CI 3.44, 7.45]) and a more modest increase in UTIs (OR 1.42 [95% CI 1.06, 1.90]) [18]. Genital mycotic infections can be treated with a single dose of an oral antifungal drug (e.g. fluconazole) or several days' application of an antifungal cream (e.g. miconazole, clotrimazole). Uncomplicated UTIs can usually be managed with routine therapy. There are no data to support surveillance urinalyses or urine cultures in diabetic individuals taking SGLT2 inhibitors.

Diabetic ketoacidosis Diabetic ketoacidosis (DKA) is a complication of treatment with SGLT2 inhibitors. It has sometimes been associated with serum glucose levels <13.9 mmol/l and has arguably been referred to as 'euglycaemic DKA'. This occurs more frequently in individuals with type 1 diabetes treated off-label with SGLT2 inhibitors but can also occur in individuals with type 2 diabetes [19–21].

A recent analysis, using a large database of commercially insured individuals in the USA, compared a cohort of diabetic individuals who had newly started treatment with an SGLT2 inhibitor vs a DPP-4 inhibitor [21]. The unadjusted rate of DKA within 180 days after the initiation of an SGLT2 inhibitor was about twice the rate after the initiation of a DPP-4 inhibitor before propensity-score matching to adjust for differences in

individuals' characteristics (4.9 vs 2.3 events per 1000 person-years; HR 2.1 [95% CI 1.5, 2.9]). The same was true after propensity matching (HR 2.2 [95% CI 1.4, 3.6]).

In the EMPA-REG OUTCOME study the proportion of individuals with DKA was very low in both the empagliflozin and placebo groups (4/4687 [0.09%] vs 1/2333 [0.04%], respectively) and not statistically significantly different [8]. In the CANVAS Program, a small number of DKA events were observed in the canagliflozin and placebo groups (0.6 vs 0.3 events per 1000 patient-years, respectively; HR 2.33 [95% CI 0.76, 7.17]) [13].

Individuals presenting with euglycaemic DKA complain of nausea, vomiting and malaise. Biochemical evaluation reveals an anion-gap metabolic acidosis and positive serum and urine ketones. As mentioned, serum glucose is often lower than in diabetic individuals with traditional DKA because of increased renal clearance of glucose mediated by the drug. The absence of markedly elevated serum glucose levels can, however, delay recognition by both the affected individual and the clinician. Treatment of DKA includes administration of intravenous fluids, insulin, and monitoring and replacing the electrolytes. If a diabetic individual develops DKA during SGLT2 inhibitor therapy, the inhibitor should not be restarted, at least not immediately, as there have been several reports of individuals who have had recurrences of DKA with continuous SGLT2 inhibitor therapy [19]. It is reasonable in such cases to avoid use of the class going forward. SGLT2 inhibitor therapy should be also stopped during acute illness and at least 48 h before any planned surgical procedure, so that a catabolic state is not aggravated and the risk of DKA is minimised.

The mechanism of euglycaemic DKA has not been fully elucidated. Illness, surgical stress or ethanol binge, with a reduction in food intake and/or insulin doses, preceded the development of DKA in some cases. The significant improvement in hyperglycaemia following initiation of SGLT2 inhibitor treatment can lead to a decrease in insulin requirements in some individuals. The reduced insulin doses and increased insulin resistance caused by an acute illness may tip the balance towards ketosis [19]. In addition, SGLT2 inhibitors are associated with an increase in plasma glucagon levels through uncertain mechanisms [22, 23]. Hyperglucagonaemia increases the tendency towards ketone production at the level of the liver [24]. By promoting osmotic diuresis, SGLT2 inhibitors also predispose to dehydration and urinary loss of sodium. This may worsen the already hypovolaemic state of DKA, particularly where there is nausea and decreased oral intake. Hypovolaemia activates the adrenergic nervous system, further increasing insulin resistance, lipolysis and ketogenesis [19]. SGLT2 inhibitors may also decrease urinary excretion of ketones, thus increasing ketone levels in the blood [25]. Partly because of these safety concerns, SGLT2 inhibitors are not currently approved by regulatory authorities for use in type 1 diabetes.

Amputation In the CANVAS Program, participants treated with canagliflozin were at higher risk of lower-extremity amputation than those receiving placebo (6.3 vs 3.4 participants affected per 1000 person-years; HR 1.97 [95% CI 1.41, 2.75]), with 71% of the affected participants having their highest amputation at the level of the toe or metatarsal [13]. The highest absolute risk of amputation occurred among individuals who had a history of amputation or peripheral vascular disease (PVD) but the relative risk of amputation with canagliflozin vs placebo was similar across these subgroups. The reason for the increased risk of amputation with this agent remains unclear. Additional analyses are needed to understand the potential mechanism underlying amputations with canagliflozin.

This adverse effect has not been reported with other SGLT2 inhibitors. A post hoc analysis of the EMPA-REG OUTCOME data showed that lower-limb amputation occurred in 1.9% of participants treated with empagliflozin and 1.8% of individuals treated with placebo, with an incidence rate of 6.5 per 1000 person-years in both groups [26]. When time to first event was analysed, the risk of lower-limb amputation was similar between the empagliflozin pooled group and placebo (HR 1.00 [95% CI 0.70, 1.44]). The finding was consistent across subgroups by established risk factors for amputation. Data pooled from randomised controlled trials of dapagliflozin vs placebo or vs another glucose-lowering agent showed that the risk of lower-limb amputation was similar after dapagliflozin treatment (0.1%) and control treatment (0.2%) [27].

Skeletal fractures Canagliflozin may also increase the risk of bone fractures. In the CANVAS Program the rate of all fractures was higher with canagliflozin vs placebo (15.4 vs 11.9 participants with fracture per 1000 person-years; HR 1.26 [95% CI 1.04, 1.52]). Findings were similar with respect to low-trauma fracture events (11.6 vs 9.2 participants with fracture per 1000 person-years; HR 1.23 [95% CI 0.99, 1.52]). There was, however, evidence of heterogeneity in the findings between the two trials comprising the CANVAS Program (CANVAS and CANVAS-R), with both low-trauma fractures and all fractures occurring at greater frequency in the canagliflozin vs placebo groups in CANVAS but not in CANVAS-R [13]. This is surprising since in CANVAS-R participants might be considered at higher fracture risk owing to their greater degree of renal function impairment. The increase in fracture risk with canagliflozin was observed within the first few weeks of initiation, with a continued rate of increase thereafter [28].

An analysis of data on canagliflozin use from nine randomised controlled studies, including CANVAS, showed a higher incidence of fractures with canagliflozin (2.7%) vs comparators (1.9%) in the overall population, but this was driven by the CANVAS data [28].

The cause of the increased fracture risk with canagliflozin is unknown. Canagliflozin is not likely to have a direct effect on the skeleton via SGLT2 as the transporter is not found in bone. A possible explanation, particularly for fractures occurring after only a few months of drug exposure, is orthostatic hypotension resulting in postural dizziness and falls (CANVAS found an increased risk of volume depletion in the canagliflozin-treated group, see below for more information). Additionally, canagliflozin could potentially negatively affect bone density and bone metabolism. A randomised study showed that administration of canagliflozin doses of 100 and 300 mg were associated with a decrease in total hip bone mineral density over 104 weeks, (placebo-subtracted changes: −0.9% and −1.2%, respectively); bone mineral density was not affected at other sites measured. No meaningful changes in bone strength assessed by quantitative computed tomography finite element analysis were observed. Canagliflozin was associated with an increase in bone resorption (as suggested by an increase in collagen type 1 β-carboxy-telopeptide), an increase in bone formation (as suggested by an increase in osteocalcin) and, in women, a decrease in oestradiol levels [29]. An indirect effect of canagliflozin on bone through alterations in calcium homeostasis is also unlikely as in phase 2 clinical studies in individuals with type 2 diabetes and overweight/obese non-diabetic individuals canagliflozin treatment was not associated with meaningful changes in serum calcium, phosphorus, parathyroid hormone or 25- or 1,25-dihydroxyvitamin D [30, 31].

In the EMPA-REG OUTCOME study the proportion of participants who developed fractures was low in both the pooled empagliflozin group and the placebo group (3.8% and 3.9%, respectively) [8].

A meta-analysis of trials evaluating combined safety outcomes of canagliflozin, dapagliflozin and empagliflozin did not support a harmful effect of SGLT2 inhibitors on bone [32]. The fracture event rate was 1.59% in the SGLT2 inhibitor group and 1.56% in the control group. Moreover, the incidence of fracture events was similar among the three SGLT2 inhibitors.

Volume depletion SGLT2 inhibitors lower BP by inducing osmotic diuresis. This effect is beneficial in individuals with uncontrolled hypertension but can lead to postural dizziness, orthostatic hypotension and dehydration, especially in elderly individuals with kidney disease or those taking loop diuretics.

In the EMPA-REG OUTCOME trial, adverse events consistent with volume depletion were rare and occurred at similar frequency in the empagliflozin and placebo groups (5.1% vs 4.9%, respectively) [8]. In contrast, in CANVAS, volume depletion was more common in the canagliflozin vs placebo group (26 vs 18.5 events per 1000 person-years; $p = 0.009$) [13].

Acute kidney injury Reports suggesting a possible association between SGLT2 inhibitors and acute renal failure led the US Food and Drug Administration to issue an alert regarding the increased risk of acute kidney injury (AKI) with canagliflozin and dapagliflozin. Most reported incidences occurred within 1 month of starting therapy and improved following discontinuation, although some individuals required hospitalisation and dialysis. Volume depletion, hypotension or concomitant use of other nephrotoxic medications could have contributed to the kidney injury. An analysis of SGLT2 users and non-users in two different cohorts showed that the risk of AKI was not increased with SGLT2 inhibitor therapy [33]. Indeed, some studies support the beneficial effect of empagliflozin and canagliflozin on the progression of nephropathy and a renal protective effect after an initial small reduction in eGFR [13, 17].

Risk of cancer Bladder and breast cancer concerns were raised with dapagliflozin due to the data from early trials included in the drug application submitted to the US Food and Drug Administration in 2011. Subsequent data submitted in 2013, which included additional trials, showed no overall imbalance of malignancies, however [34].

A recent meta-analysis of randomised controlled trials reporting cancer events in individuals treated with SGLT2 inhibitors for at least 24 weeks showed that, compared with placebo or other glucose-lowering treatments, SGLT2 inhibitors were not significantly associated with an increased risk of overall cancer (OR 1.14 [95% CI 0.96, 1.36]), although an increased risk of bladder cancer was found (OR 3.87 [95% CI 1.48, 10.08]), especially with empagliflozin (OR 4.49 [95% CI 1.21, 16.73]) [35]. However, the EMPA-REG OUTCOME investigators commented that the authors did not include all bladder cancer events from this, the largest and longest empagliflozin trial to date [36]. Herein, bladder cancer with an onset after 6 months of cumulative exposure to study drug was reported in 0.2% of participants in both the placebo and the pooled empagliflozin groups. The EMPA-REG OUTCOME data thus did not support any association between bladder cancer and empagliflozin. It should also be noted that a detection bias may occur with pharmaceuticals that are associated with urinary symptoms. Importantly, the potential carcinogenic effects of any drug cannot be easily assessed in short-term trials or even in those of a few years duration. Interestingly, in the aforementioned meta-analysis [35], canagliflozin appeared to protect against gastrointestinal cancers (OR 0.15 [95% CI 0.04, 0.60]) but this finding is likely spurious, based on the known biology of cancer.

The place of SGLT2 inhibitors in diabetes management

In a 2015 update to the 2012 ADA–EASD position statement on the management of hyperglycaemia in individuals with

type 2 diabetes, SGLT2 inhibitors are suggested as second- or third-line agents after metformin in individuals needing additional glucose control [37]. In the 2018 ADA diabetes care guidelines they are recommended as second-line agents after metformin, as they are proven to reduce MACE and/or cardiovascular mortality in individuals with type 2 diabetes and established CVD (Fig. 2) [38]. Based on available data, two members of the SGLT2 inhibitor class, empagliflozin and canagliflozin are now proven to have an overall cardiovascular benefit (with only empagliflozin reducing mortality), while cardiovascular protection with other SGLT2 inhibitors is not yet established. The proposed benefits of these drugs on renal outcomes has not yet been acknowledged in treatment algorithms, to our knowledge.

In addition to considering expert recommendations and national guidelines, prescribers and their patients should carefully weigh the now-recognised benefits of SGLT2 inhibitors against their safety concerns. Based on available evidence, it is reasonable to consider empagliflozin or canagliflozin as a second-line treatment for type 2 diabetes in individuals unable to achieve optimal glycaemic control with metformin, especially in those who may benefit from weight loss and/or BP reduction. These drugs appear to be particularly advantageous in those with established CVD and/or underlying prevalent kidney disease, so long as the eGFR is adequate. Despite the EMPA-REG OUTCOME trial demonstrating that mortality and chronic kidney disease benefits were observed down to an eGFR of 30 ml min^{-1} [1.73 $m]^{-2}$, current labelling states that empagliflozin and canagliflozin should be discontinued when the eGFR is <45 ml min^{-1} [1.73 $m]^{-2}$ and that dapagliflozin should be stopped when the GFR is <60 ml min^{-1} [1.73 $m]^{-2}$. Use below these cut-points would be considered experimental until more information is garnered from ongoing trials. Further, it is not yet known whether these drugs might provide similar benefits if used in individuals not requiring additional glucose lowering on their current therapy.

The post hoc analyses from CANVAS suggesting a heart failure and renal benefit even in those without prevalent CVD should also be considered hypothesis-generating at this point and need to be substantiated by additional studies. It is difficult to know whether other SGLT2 inhibitors, namely dapagliflozin and ertugliflozin, will have the same benefits, as cardiovascular outcome trials involving these drugs are still pending. Their risk profile also needs further elucidation.

Canagliflozin should be avoided in individuals at risk for amputations, such as those with advanced PVD, severe peripheral neuropathy or prior history of lower-limb amputation or foot ulceration. Even though amputations were not seen in the EMPA-REG OUTCOME trial, it is not unreasonable to avoid the entire class in those at the highest amputation risk until more safety data are accumulated. Canagliflozin should probably also be used cautiously in those with prior fragility fractures or at high fracture risk, such as women with osteoporosis.

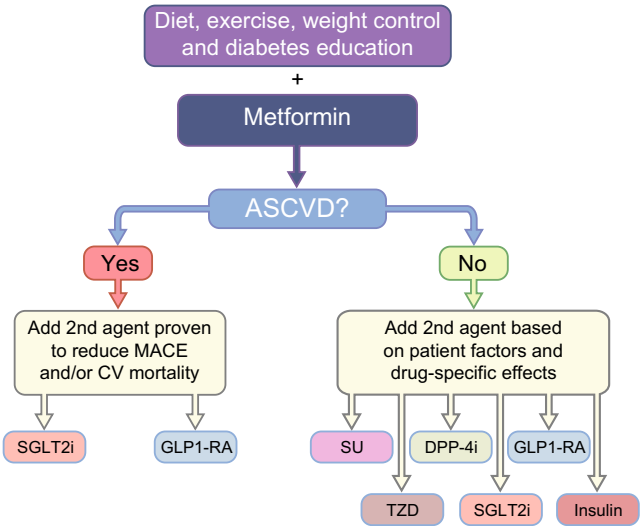

Fig. 2 Summary of latest ADA guidelines for the use of glucose-lowering drugs in individuals with type 2 diabetes in monotherapy and dual combination therapy. These are an adaptation of the most recent ADA–EASD position statement on this topic from 2015, now taking new cardiovascular data into account [38]. If HbA_{1c} is not adequately controlled by lifestyle interventions and metformin, add a second agent. The decision on which drug to add should be based on the presence or absence of known atherosclerotic CVD. If present, choose an agent that has been demonstrated to reduce MACE and/or cardiovascular mortality in a large, randomised outcomes trial. At the time of writing this manuscript, these drugs include the SGLT2 inhibitors empagliflozin (MACE and cardiovascular mortality) and canagliflozin (MACE) and the glucagon-like peptide-1 receptor agonists liraglutide (MACE and cardiovascular mortality) and semaglutide (MACE). Guidelines currently do not incorporate other secondary outcomes from these trials, such as reductions in heart failure hospitalisation and the progression of chronic kidney disease (both of which favour the SGLT2 inhibitors). If atherosclerotic CVD is not present, any of six drug classes may be used, with the choice based on a variety of individual factors and drug-specific effects, including potency, non-glycaemic benefits, prevailing contraindications, likelihood and potential impact of adverse events and cost. ASCVD, atherosclerotic CVD; DPP-4i, DPP-4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. This figure is available as part of a downloadable slideset

Although the trend in stroke in the EMPA-REG OUTCOME trial might suggest the drug be avoided in those with cerebrovascular disease, further analysis revealed that the imbalance in stroke events was largely due to occurrences in participants already off the study drug for at least 90 days. Accordingly, it is difficult to conclude that the drug specifically increases stroke risk. In addition, the trend for cardiovascular mortality was similar in individuals with and without a history of stroke at baseline [8].

SGLT2 inhibitors are to be avoided in individuals with prior history of complicated UTIs such as pyelonephritis or urosepsis, those with an indwelling urinary catheter and those with recurrent genital mycotic infections. Men with prostatic hypertrophy and women with urinary incontinence will find this drug class challenging to use, and this is likely to have a negative impact on quality of life. Caution should be taken

before initiating SGLT2 inhibitor therapy in individuals with a predisposition to hypovolaemia, those who have borderline kidney function or those taking concomitant potent diuretics or nephrotoxic medications such as non-steroidal anti-inflammatory drugs.

The diuretic effect exerted by SGLT2 inhibitors means it is important to assess volume status and BP before initiating treatment. In hypovolaemic or hypotensive individuals, the SGLT2 inhibitor should be delayed until the fluid status and BP are corrected. If an individual is euvolaemic but verging towards hypotension, SGLT2 inhibitors should be initiated cautiously and close monitoring is advised. Euvolaemic, normotensive individuals on thiazide therapy can continue with the thiazide as this diuretic does not further reduce BP beyond the reduction achieved with SGLT2 inhibitors. In contrast, in individuals receiving more potent loop diuretics, reducing the dose by 50% should be considered, with close follow-up. In individuals with heart failure, any such changes would ideally be made after consultation with a cardiologist. Individuals on concurrent SGLT2 inhibitor and any diuretic should have their BP, weight, creatinine and electrolytes measured periodically. Finally, SGLT2 inhibitors should not be started in individuals with labile volume status [39].

Despite possible glycaemic benefits, SGLT2 inhibitors should not be used in type 1 diabetes because of concerns regarding euglycaemic DKA; individuals with latent autoimmune diabetes of adults (LADA) may also be at higher risk of developing ketoacidosis. Avoidance of SGLT2 inhibitors is advisable in individuals with type 2 diabetes who have evidence of very low insulin secretory capacity, as suggested by labile diabetes control, lean body build and, of course, prior episodes of ketosis.

Finally, since SGLT2 inhibitors are relatively new and are thus far only available as proprietary brand formulations, cost should also be considered. In the USA, for example, retail costs are more than 100-fold higher than for generic metformin or sulfonylureas. Justifying such expenses, using the information from clinical trials available to date, may be difficult for the more typical newly diagnosed individuals with type 2 diabetes who do not have prevalent CVD or nephropathy. Benefit in this group will need to be proven.

Conclusions

SGLT2 inhibitors, constituting the most recently available oral glucose-lowering drug category, exert their effect by increasing urinary glucose excretion. Optimal prescribing of agents within this category requires a full understanding of their risks in addition to their benefits. Besides improving glycaemic control, weight and BP, some members of this class provide beneficial cardiovascular and renoprotective effects. SGLT2 inhibitors should be considered reasonable second-line treatment options for individuals at risk of cardiovascular events or those with underlying nephropathy, if good glycaemic control has not been achieved with metformin monotherapy. Possible side effects include urinary frequency and orthostasis. Additional potential adverse effects include genitourinary tract infections, euglycaemic DKA, AKI, lower-extremity amputations and fractures—the latter two to date being associated solely with canagliflozin. Individuals at risk for such complications should be monitored closely and treatment should be discontinued or at least reconsidered if they occur.

Duality of interest SI has consulted for Janssen and vTv Pharmaceuticals and served on Research Steering Committees for AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Novo Nordisk and Sanofi/Lexicon, Eisai (TIMI) and on a Data Monitoring Committee for Intarcia. BL declares that there is no duality of interest associated with her contribution to this manuscript.

Contribution statement Both authors were responsible for drafting and revising the article and approved this version for publishing.

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