



REVIEW

SGLT2 Inhibitors – The New Standard of Care for Cardiovascular, Renal and Metabolic Protection in Type 2 Diabetes: A Narrative Review

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ABSTRACT

A substantial evidence base supports the use of sodium-glucose cotransporter-2 inhibitors (SGLT2is) in the treatment of type 2 diabetes

mellitus (T2DM). This class of medicines has demonstrated important benefits that extend beyond glucose-lowering efficacy to protective mechanisms capable of slowing or preventing the onset of long-term cardiovascular, renal and metabolic (CVRM) complications, making their use highly applicable for organ protection and the maintenance of long-term health outcomes. SGLT2is have shown cost-effectiveness

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in T2DM management and economic savings over other glucose-lowering therapies due to reduced incidence of cardiovascular and renal events. National and international guidelines advocate SGLT2i use early in the T2DM management pathway, based upon a plethora of supporting data from large-scale cardiovascular outcome trials, renal outcomes trials and real-world studies. While most people with T2DM would benefit from CVRM protection through SGLT2i use, prescribing hesitancy remains, potentially due to confusion concerning their place in the complex therapeutic paradigm, variation in licensed indications or safety perceptions/misunderstandings associated with historical data that have since been superseded by robust clinical evidence and long-term pharmacovigilance reporting. This latest narrative review developed by the Improving Diabetes Steering Committee (IDSC) outlines the place of SGLT2is within current evidence-informed guidelines, examines their potential as the standard of care for the majority of newly diagnosed people with T2DM and sets into context the perceived risks and proven advantages of SGLT2is in terms of sustained health outcomes. The authors discuss the cost-effectiveness case for SGLT2is and provide user-friendly tools to support healthcare professionals in the correct application of these medicines in T2DM management. The previously published IDSC SGLT2i Prescribing Tool for T2DM Management has undergone updates and reformatting and is now available as a Decision Tool in an interactive pdf format as well as an abbreviated printable A4 poster/wall chart.

Keywords: Cardiovascular, renal and metabolic protection; Oral glucose-lowering medicines; SGLT2is; Sodium-glucose cotransporter-2 inhibitors; Standard of care; Type 2 diabetes mellitus

Key Summary Points

Evidence shows that early and sustained optimisation of type 2 diabetes mellitus (T2DM) management is critical to prevent microvascular and macrovascular complications associated with progressive disease and, therefore, support long-term health outcomes.

Current guidelines and expert opinion recommend the use of sodium-glucose cotransporter-2 inhibitors (SGLT2is) early in the T2DM treatment pathway based upon their clinical and economic value and proven beneficial effects in reducing and/or preventing diabetes-associated cardiovascular, renal and metabolic (CVRM) complications.

Considering the wealth of data supporting these medicines, the Improving Diabetes Steering Committee (IDSC) expects SGLT2i therapies to take a more prominent role in future guidelines, potentially as a key component of standard care for newly diagnosed individuals with T2DM.

The expansive evidence-base indicates that the proven advantages of SGLT2is in slowing or preventing the onset of serious CVRM complications and maintaining durable health outcomes should outweigh (or place into context) manageable issues (e.g. mycotic genital infections) and perceived potential risk of rare adverse events that may have previously delayed or deterred prescribing of these medicines for the right individuals.

Practical tools have been developed by the IDSC to support healthcare professionals (HCPs) in gaining greater confidence regarding the appropriate use of SGLT2is and key resources are signposted for HCPs and people living with T2DM to assist in addressing common questions or issues relating to SGLT2i use in clinical practice.

THE ROLE OF THE IMPROVING DIABETES STEERING COMMITTEE

The Improving Diabetes Steering Committee (IDSC) is a multi-disciplinary group of healthcare professionals (HCPs) convened to offer evidence-informed practical guidance for the appropriate use of the sodium-glucose cotransporter-2 inhibitor (SGLT2i) class of medicines in people with type 2 diabetes mellitus (T2DM). The Committee aims to produce materials that provide balanced review of the evidence and guidelines relating to use of SGLT2is in the management of T2DM, including their risk–benefit profile in reducing the risk of cardiovascular, renal and metabolic (CVRM) complications.

This narrative review summarises the key topics that were discussed during a Steering Committee meeting held in July 2023. The article is based upon previously conducted trials and does not involve any new studies of human or animal subjects. Some authors were involved in studies discussed within the paper that included human subjects, all of which complied with the tenets of the Declaration of Helsinki and used protocols that had received Institutional Review Board/Ethics Committee approval, with written informed consent provided by participants.

This paper aims to provide HCPs working in the field of T2DM with a practical understanding of the place, value and advantages of appropriate SGLT2i use in the T2DM treatment pathway. The main objectives for SGLT2i use are discussed alongside information on guideline-directed selection of suitable recipients and the cost–benefit case supporting these agents. As with the previous reviews published by the IDSC in *Diabetes Therapy*, the Committee has developed a range of pragmatic tools and materials to support HCPs [1–4]. These are provided within the body of the article as well as in the associated supplementary materials and include key practice points for HCPs prescribing SGLT2is, common frequently asked questions (FAQs) relating to SGLT2is (from the perspective of HCPs and people with T2DM) and a summary of helpful resources that are

available for HCPs, people living with T2DM and those who care for them. Finally, the IDSC SGLT2i Prescribing Tool for T2DM Management has undergone an update and format change. It is now available as an SGLT2i Decision Tool, provided in an interactive pdf format, which can be downloaded as a supplementary material associated with this review paper.

BRIDGING THE GAP BETWEEN GUIDELINES AND CLINICAL PRACTICE: IMPLEMENTING EVIDENCE-INFORMED, PERSON-CENTRED T2DM MANAGEMENT WITH SGLT2IS

T2DM management has become increasingly complex over the past decade, with new medicines gaining regulatory approval and treatment pathways continually evolving to incorporate the latest data, new therapeutic indications and guideline recommendations. HCPs face ongoing challenges in healthcare settings dealing with multiple competing priorities and pressures. Unsurprisingly, such an environment fosters unintentional therapeutic inertia and does not support the prompt action that people living with T2DM need to gain control of their diabetes, lower their risk of cardiovascular (CV) and renal complications and maintain their health in the long term [5–7]. The latest guidelines published by the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) and the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) support the use of SGLT2i therapies early in the T2DM treatment paradigm for appropriate individuals and prescribing of SGLT2is has increased in response to the recommendations [7–10]. However, data indicate that use of these medicines remains suboptimal in clinical practice [7, 10]. There is a need for greater clarity and connection between current guidelines, expert consensus and the wealth of data surrounding SGLT2is in T2DM so that they are

initiated at the right time to slow the onset and progression of CVRM complications and ensure the optimisation of overall health outcomes [5–9, 11, 12].

Data from the UK Prospective Diabetes Study (UKPDS) have emphasised the importance of achieving and maintaining intensive T2DM management, from diagnosis, to prevent long-term microvascular complications [13, 14]. Elsewhere, data suggest that HbA1c may be better sustained with combination therapy, compared with stepwise T2DM treatment, and the debate regarding the advantages of intensive blood-glucose management in reducing adverse CV outcomes continues [15, 16]. The beneficial properties of oral glucose-lowering drugs in avoiding or decelerating progression toward macrovascular complications have been demonstrated in many studies and are well recognised in the literature and in current NICE, ADA/EASD, Primary Care Diabetes Europe and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which advocate early combination therapy incorporating SGLT2is for appropriate individuals [3, 4, 8, 9, 11, 16–39]. Diabetes therapy should aim to provide the maximum protection in the minimum time with the relative risks and side effects considered alongside other chronic diseases/comorbidities. Yet, traditional approaches to disease management encourage steady, phased intensification of treatment for chronic conditions, which can hinder the timely initiation of important therapeutic interventions that prevent the onset of life-altering complications [5, 6, 40]. T2DM medicines that protect the kidney and the heart provide additional clinical advantages beyond glycaemic outcomes. Furthermore, robust economic models have demonstrated the overwhelming value of appropriate SGLT2i prescribing [4, 41–43]. In higher-risk groups that include people with long-term diabetes and pre-existing complications, SGLT2is deliver cost savings across health services in as little as 2 years due to reduced CV and renal events, compared with other oral diabetes therapies [41]. Further studies are required to fully understand the economic impact of using SGLT2is during earlier stages of T2DM [44]. HCPs face many

practical challenges when implementing guidelines in routine practice, including poor/fragmented attendance for regular T2DM reviews and lack of time and resources for adequate face-to-face consultations to allow opportunity for thorough clinical assessment. The guidelines place emphasis on individualised approaches to care, but better tools and resources are required to help simplify decision-making and address confusion/misconceptions relating to SGLT2i prescribing [8, 9, 32].

BACK TO BASICS IN T2DM MANAGEMENT: IMPROVING QUANTITY AND QUALITY OF LIFE

HCPs working in primary care have the greatest impact on the health and well-being of individuals living with T2DM during the early years, after diagnosis [12, 45]. With progressive disease, the burden on primary care rises as CVRM complications and associated comorbidities require greater resource and time to manage, and patient quality of life (QoL) diminishes [12, 45–47]. Treatment must aim to improve and maintain enduring health while maximising the durability of any medicines prescribed [8, 9]. With swift and effective intervention following T2DM diagnosis, the course of disease can be altered to impede or prevent gradual progression toward chronic kidney disease (CKD)/diabetic kidney disease (DKD) and cardiovascular disease (CVD) [8, 9, 12, 37]. While the UKPDS trial was focused on intervention with metformin, sulphonylureas (SUs)/insulin or conventional diet approaches, the results from the 44-year follow-up revealed the important legacy effect of early intensive blood-glucose management in the reduction of microvascular complications and the improvement in clinical outcomes [13, 14]. Recently published registry data from Italy examining the associated risk of CVD in 251,339 people with T2DM and no CVD at baseline showed poor glycaemic outcomes (>64 mmol/mol or HbA1c>8%) during the first 3 years after diabetes diagnosis to be predictive of increased subsequent CVD risk, compared with having

HbA1c < 53 mmol/mol (< 7%) [48]. Introduction of SGLT2i therapy during the initial 2 years appeared to remove the association between glycaemic management and CVD risk and early intervention seemed to be critical in achieving those outcomes [48]. The CVD-REAL study also demonstrated improvements in CV outcomes with SGLT2is, compared with other oral glucose-lowering treatments, in a real-world setting (in the United States, Norway, Denmark, Sweden, and the UK) [49, 50]. In the initial CVD-REAL analysis, the majority of participants (87%) did not have CVD at baseline and significant relative risk reductions regarding hospitalisation for heart failure (HHF; $p < 0.001$) and all-cause mortality ($p < 0.001$) were reported across the study population [49]. The CVD-REAL 3 study provided further real-world evidence concerning the impact of SGLT2is in decelerating kidney function decline ($p < 0.0001$) and the risk of major kidney events ($p < 0.0001$), compared with other oral glucose-lowering therapies [51]. Moreover, recent real-world data showed that increasing canagliflozin dosage to the highest approved level in individuals with T2DM and less-than-optimal metabolic results led to notable enhancements in key factors including fasting plasma glucose, HbA1c, body weight and blood pressure, complementing the existing cardiorenal protection offered by lower-dose therapy [52]. Real-world studies reaffirmed well-established data from large randomised controlled cardiovascular outcomes trials (CVOTs; EMPA-REG Outcome, CANVAS, DECLARE-TIMI 58), which have provided an ever-expanding body of evidence regarding SGLT2i-related reductions in CV events, including composite endpoints that encompass major adverse cardiovascular events (MACE), heart failure (HF) and CV death, HHF and worsening HF events [17, 18, 53]. Renal outcomes trials, post hoc analysis from CVOTs and real-world studies have provided unequivocal evidence of the effectiveness of SGLT2is in reducing kidney disease and associated adverse outcomes [3, 21–23, 26, 28, 31, 36, 51, 54–56]. The CREDENCE trial focused on kidney outcomes in individuals with T2DM and albuminuric CKD [21]. It found that treatment with canagliflozin reduced the risk of

the primary outcome, which comprised of end-stage kidney disease (ESKD), doubling of serum creatinine, or death from renal or cardiovascular causes, by 30% in this high-risk population [21]. The EMPA-KIDNEY (empagliflozin) and DAPA-CKD (dapagliflozin) trials showed similar results in individuals with CKD, whether or not they had T2DM [21, 28, 31]. SGLT2i use has also been typically associated with the lowering of other CV risk factors, such as blood pressure, and recipients often experience weight loss [2, 12, 17, 18, 34, 35, 49, 52, 53, 57–60]. Organ protection remains the cornerstone objective for long-term management of T2DM and the wider implementation of SGLT2is early in the therapeutic pathway would support better outcomes through the lowering of both macrovascular risk and complication severity [1–4, 12, 17–23, 28, 31, 35, 52, 53, 56, 61].

CURRENT GUIDELINES FOR SGLT2I USE IN T2DM

While the NICE NG28 recommendations are used by the majority of UK HCPs to guide T2DM treatment decisions, there are some gaps in the current NICE guidelines that are considered in the ADA/EASD and KDIGO guidance [8, 9, 32]. The NG28 guideline recommends initiation of SGLT2i therapy in combination with metformin (once metformin tolerability has been confirmed) for individuals with high CV risk, established atherosclerotic cardiovascular disease (ASCVD), comorbid HF and comorbid CKD [8]. SGLT2i monotherapy is also advocated for use in high-risk individuals with T2DM who are unable to tolerate metformin [8]. NICE recommends the use of the QRISK2[®] tool (QRISK[®]3 is also available as an updated version to use online but is currently less widely integrated in primary care systems) to assess a person's risk of CVD [8]. People with T2DM who are under the age of 40 years and therefore unsuitable for QRISK assessment should be considered at high risk if they have one or more CV risk factor, defined as hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature CVD [8]. According to

ADA/EASD guidelines, SGLT2is may be used as a first-line treatment in combination with other glucose-lowering therapies (or alone) where the treatment goal is to achieve and maintain glycaemic and weight management targets, with early combination therapy endorsed to optimise outcomes and extend the time to therapeutic failure [9]. Under the same guidelines, SGLT2is are the recommended first-line therapy (in addition to comprehensive CV risk-management strategies) when the goal of treatment is cardiorenal risk reduction in high-risk people with T2DM, comprising those with known cardiorenal disease (established CVD/HF/CKD) or indicators of high ASCVD risk [9]. The Primary Care Diabetes Europe position statement recommends combining SGLT2i therapy with metformin for individuals with T2DM and HF or CKD, ensuring both glycaemic control and cardiorenal protection [33]. The KDIGO 2022 recommendations include SGLT2is within their comprehensive care strategy to reduce the risk of kidney disease progression and CVD in people with diabetes [32]. KDIGO supports combination therapy with metformin and an SGLT2i and advises that SGLT2is may be initiated when estimated glomerular filtration rate (eGFR) is ≥ 20 ml/min/1.73 m² and continued (as tolerated), until dialysis or transplantation is initiated [32]. Likewise, the UK Kidney Association (UKKA) recommends SGLT2is for people with T2DM and eGFR ≥ 25 ml/min/1.73 m² attributed to diabetic nephropathy and in people with T2DM and coronary disease or stable symptomatic HF (irrespective of ejection fraction) [62–66].

An update to the NG28 recommendations is due to be published toward the end of 2024, but it remains unclear whether NICE will take a similar approach to that of the ADA/EASD or KDIGO in supporting the upfront use of SGLT2is following diagnosis and CVRM risk assessment [8]. The European Society for Cardiology (ESC) currently supports the use of SGLT2i in people with HF and T2DM at risk of CV events to reduce HHF, major CV events, end-stage renal dysfunction and CV death and these guidelines are also due to be updated in 2024 [67, 68]. Current guidelines do not specifically mention fixed-dose SGLT2i-metformin combinations,

but there may be scope for such treatments in people with T2DM, once they are stable on individual treatments.

Future direction for guidelines should account for the additional value offered by SGLT2is in relation to weight management, blood pressure lowering, CVRM risk reduction and economic benefit. The IDSC would expect more prominent positioning of SGLT2i therapy among first-line treatment options for a wider range of people with T2DM in upcoming guidelines, due to their protective properties. Key caveats regarding the prescribing of SGLT2i agents in a wider population would include people living with frailty and women of childbearing age. Any recommendations regarding SGLT2i use in older people should include frailty assessments and the potential for postural hypotension, which may be more common in this group due to factors including comorbidities, concomitant medications and changes in water/sodium balance with SGLT2is [63–66, 69]. Rising prevalence of T2DM in younger people has major implications regarding long-term management of disease and risk. Evidence from the TODAY study suggests that younger people with T2DM have high lifetime CVD risk and rapidly progressing complications tend to appear early in this group making the need for prompt intensive treatment all the more important [8, 70, 71]. SGLT2is are not licensed for use during pregnancy and data are lacking regarding potential fertility implications [63–66]. Although women under 40 years of age with T2DM can benefit from SGLT2is, it is important to prescribe these medications only when they are using reliable contraception. The QRISK[®]3-Lifetime tool may be more appropriate for assessment of people aged 18–40 years since QRISK[®]2 estimates a 10-year risk and may underestimate lifetime CV risk, resulting in eligible people with young onset T2DM being overlooked for SGLT2i treatment [8, 72, 73]. People aged <40 years with at least one CV risk factor are considered appropriate to begin SGLT2i treatment, which should not then be stopped when they reach 40 years of age (even if their QRISK score is <10%) as individuals will continue to gain protection against CV, renal and metabolic complications of T2DM [8, 71].

THE COST–BENEFIT CASE FOR SGLT2IS

Understanding value in healthcare is important in the context of rapidly expanding populations, widespread ill health and greater use of health technologies. However, increasingly, prospective cost analyses do not represent the true value and economic impact of treatments/technologies from a holistic, multisystem, multistakeholder perspective. Stakeholders in the healthcare setting include not only people living with diabetes, but also payers, healthcare systems, carers, social care and the wider society. While evaluating healthcare value through cost-effectiveness analyses, it is crucial to recognise that medical interventions yield social returns on investments beyond utility. Integrated Care Boards in England often review prescriptions as spending exceeds a threshold, prompting healthcare providers to assess whether drug treatments align with clinical and economic rationale. This is particularly relevant for SGLT2is, which may (by conservative estimates) be appropriate for the treatment of approximately 1.7 million people with T2DM in England alone, if prescribed according to the current NICE NG28 guideline [74].

SGLT2is can offer value across the natural history and continuum of T2DM. Early in the treatment pathway, value is offered through health gain associated with better metabolic outcomes, weight loss, reduced blood pressure and low risk of hypoglycaemia [1, 35, 37, 57–60]. Progressing through the course of T2DM, SGLT2is are associated with reduced CVD, renal disease and HF, delivering health gain as well as cost savings via reduced resource utilisation and effective management of complications and releasing capacity within the system [3, 4, 17–22, 28, 29, 31, 41, 44, 53, 55, 56, 75–77]. Systematic review data examining the results of 24 studies revealed SGLT2i therapy to be cost-effective in T2DM management when compared against treatment with dipeptidyl-peptidase-4 inhibitors (DPP-4is), SUs, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and other glucose-lowering therapies that included thiazolidinediones, alpha-glucosidase inhibitors and insulin [43]. A

recent study by McEwan et al. (2023) demonstrated cost-effectiveness and cost-savings with SGLT2is alongside improvements in health outcomes (e.g. HHF, CKD) when implemented in eligible populations (high CV risk, established ASCVD, comorbid HF and comorbid CKD), according to NICE NG28 guidelines [41]. Analyses examined relative spending, treatment effects (changes in HbA1c, weight, and rates of hypoglycaemia) and cardiorenal complications in terms of predicted lifetime costs, quality-adjusted life-years (QALYs) and total life-years, comparing outcomes for SGLT2is with those of SU treatment and DPP-4is [41]. An overall cost-saving was associated with SGLT2i use, versus SU or DPP-4i treatment, for each of the populations specified as appropriate for SGLT2i therapy in the NG28 guidelines [41]. All spending increases associated with additional prescribing were substantially offset by the lowering of management costs for expected complications of T2DM [41]. The time to cost saving status is a critical consideration when establishing the value of a medicine or healthcare technology. Compared with SUs or DPP-4is, the analysis by McEwan et al. [41] showed SGLT2is to be cost-effective from initiation (over a 25-year projection) and costs savings were predicted against DPP-4is within 2 years for comorbid HF and CKD populations, and within 9–11 years for ASCVD and high CVD risk groups [41]. In comparison with SUs, the time to cost savings with SGLT2i treatment ranged between 5 years for the comorbid CKD population and 16 years for people with high CVD risk [41]. Published studies examining the cost-effectiveness of first-line SGLT2i use in people living with T2DM are limited and do not evaluate the value of SGLT2is within the whole healthcare system, beyond simple cost-effectiveness analyses, in view of their multiple indications and reported outcomes (e.g. delaying the onset and progression of DKD) [21, 28, 31, 44, 55, 78]. However, in the UK, NICE approved SGLT2is as first-line treatment in cases where metformin is not indicated or tolerated (when SU or pioglitazone is not appropriate) in 2016, before many of the CVOT and renal outcomes trials were published [79]. This recommendation was based on a detailed network meta-analysis

and systematic review of cost-effectiveness data [79].

When implemented appropriately, SGLT2is could offer cost savings in those high-risk populations defined by the NICE NG28 recommendations and they should be highly cost-effective in the rest of the T2DM population [41, 43, 74]. A clear whole system value gain would be seen with outcomes set in the context of reduced expenditure and resource usage due to slower progression of disease, fewer complications and CVD or ESKD events. Reduced bed day occupancy for CVD and ESKD events would release greater capacity within the healthcare system and result in less waste and enhanced efficiency. Maintaining health and well-being for longer would enable people living with T2DM to continue working and actively contributing to society. The greatest value should be obtained from initiating SGLT2i treatment before complications have begun as incident HF, ESKD events and other events should be reduced. Based on the clinical and health economic gains associated with SGLT2is, the IDSC would support earlier and increased use of these medicines in appropriate individuals with T2DM.

A STEP-CHANGE IN T2DM MANAGEMENT: BRIDGING THE GAP BETWEEN GUIDELINES AND ROUTINE CLINICAL PRACTICE

The NICE resource impact report for T2DM in adults suggested that around 1.7 million people with T2DM in England (approximately 50% of the T2DM population) should be eligible for SGLT2i treatment and the cost savings relating to their implementation have been recognized by NICE [74]. However, current data indicate that prescribing practices are in the region of 27% for this population [10]. This raises the question as to why there might be such disparity between current guidelines and clinical practice. Given the existing weight

of evidence and growing expert opinion/support in this area, the IDSC estimates that the proportion of people with T2DM who would benefit from SGLT2i treatment could be closer to 80%. Guideline fatigue, confusion and misconceptions regarding safety risks have represented a barrier to SGLT2i uptake in primary care since these agents first became available [7, 12, 80]. These aspects must be addressed to help colleagues understand how optimised use of SGLT2is may assist in releasing capacity and avoiding the occurrence of future complications that will only increase pressure on already over-stretched systems.

The wide-ranging advantages associated with SGLT2is in maintaining overall health and enduring CVRM outcomes far outweigh the observed incidence of potential adverse events (AEs). Figure 1 is adapted from the results reported by a meta-analysis of randomised data on kidney outcomes conducted by the Nuffield Department of Population Health Renal Studies Group (2022) [36]. The figure shows that, in people with T2DM and ASCVD, stable HF or CKD, the incidence of CVRM events (per 1000 patient-years) was substantially reduced with SGLT2i use while the incidence of AEs (e.g. ketoacidosis) was slightly raised in these high-risk T2DM subgroups [36]. The overwhelming weight of evidence indicates that SGLT2i treatment provides an overall advantage in improving long-term T2DM outcomes and avoiding CVRM events when compared against the risk of drug-related AEs (Fig. 2) [2–4, 8, 9, 11, 17–31, 41, 49, 51, 56, 81, 82].

Variation and changes in individual licence indications in people with reduced eGFR have fuelled misunderstandings about the appropriate circumstances for initiation and continuation of these agents when kidney function is impaired [63–66]. Each of the currently available SGLT2i agents are licensed for initiation in people with $eGFR < 45 \text{ ml/min/1.73 m}^2$, with product-specific caveats concerning initiation and continuation of treatment at $eGFR < 30 \text{ ml/min/1.73 m}^2$ and dosing (although dapagliflozin may be used in people with $eGFR 15 \text{ ml/min/1.73 m}^2$) [63–66, 83]. SGLT2i mechanism of action results in significantly reduced glucose-lowering effect when $eGFR$ is $< 45 \text{ ml/min/1.73 m}^2$ and

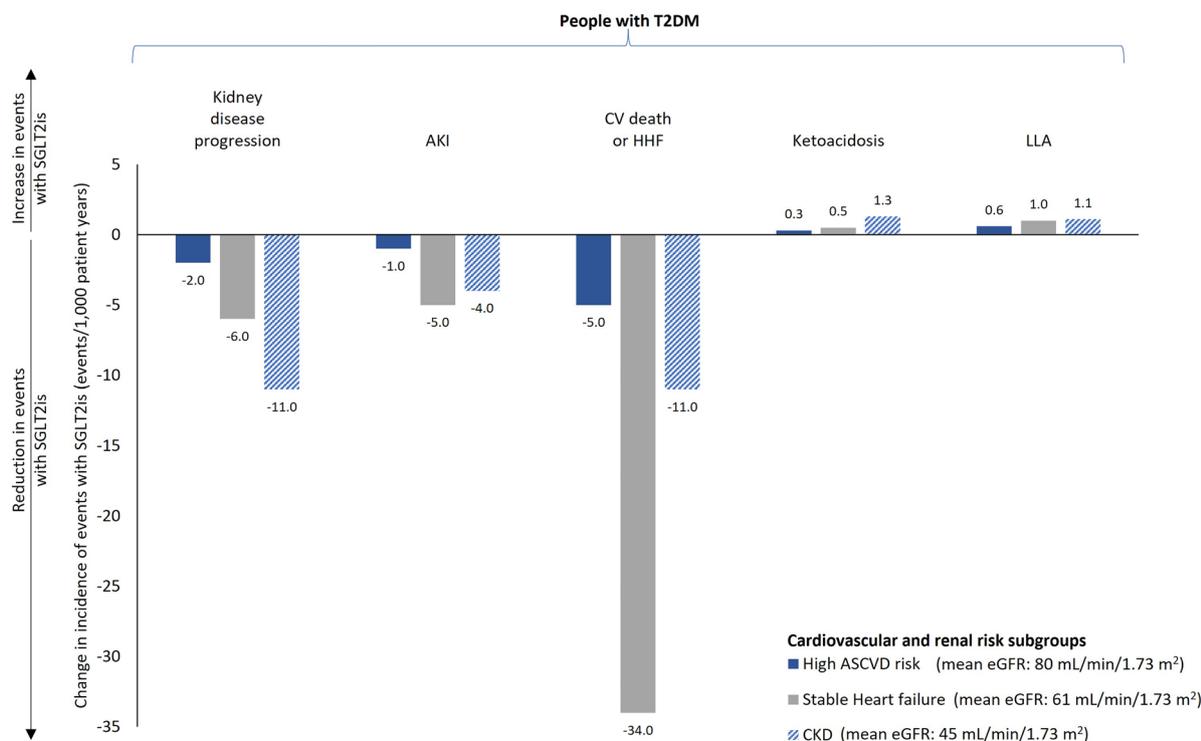


Fig. 1 Change in risk of adverse events with SGLT2is for people with T2DM [36]. Adapted from Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists’ Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400:1788–801 [36]. The figure shows the specific absolute effects on adverse events associated with SGLT2i use in people with T2DM, based on large-scale randomised trials. The absolute effects were estimated by

applying the specific relative risk of an event in the active treatment arm to the average event rate in the placebo arms (first event only). Negative numbers indicate events avoided by SGLT2 inhibition per 1000 patient-years. Mean eGFR values are given for combined trial populations. *ASCVD* atherosclerotic cardiovascular disease, *CKD* chronic kidney disease, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *LLA* lower limb amputation, *SGLT2i* sodium glucose co-transporter-2 inhibitor, *T2DM* type 2 diabetes mellitus

additional T2DM therapy will be needed if HbA1c is above target, although individuals will still benefit from the CVRM protection and slowing of further decline in kidney function offered by SGLT2is [8, 9, 32, 62, 83].

Fear of increased diabetic ketoacidosis (DKA) risk represents a significant barrier to SGLT2i use. Risk factors for this rare but serious condition include pronounced insulin resistance, low beta-cell function including those with T2DM and low C-peptide levels (particularly in people with latent autoimmune diabetes in adults [LADA]/slowly evolving immune-related diabetes or a history of pancreatitis), restricted food

intake (very low calorie or carbohydrate diets) or severe dehydration, sudden reduction in insulin or increased insulin requirements due to rising counter-regulatory hormones (e.g. during acute illness), major surgery and alcohol abuse [84, 85]. Two recently reported cases of severe ketoacidosis triggered by reduced oral nutrition intake in people taking SGLT2i therapy for HF show that ketoacidosis can occur in people without T2DM and risk factors, such as dietary intake, should be considered for all indications [86]. As highlighted in the ADA/EASD guidelines, incidence of DKA is low in general and SGLT2is are associated with a small incremental

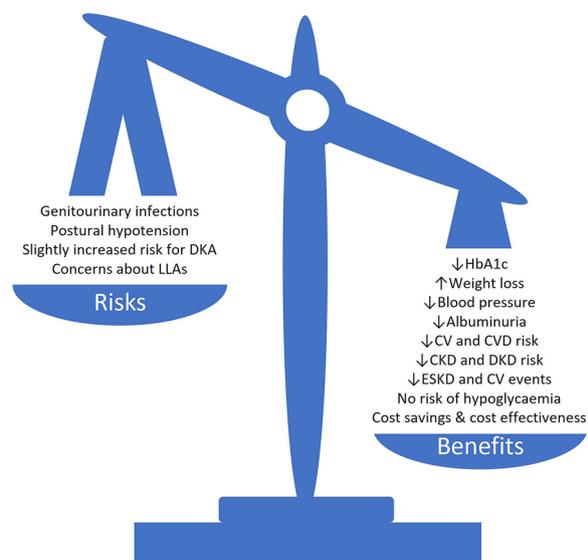


Fig. 2 Schematic representation of the relative risk and benefit profile for SGLT2i therapies based upon RCT and real-world data [2–4, 8, 9, 11, 17–31, 41, 49, 51, 56, 81, 82]. *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *DKA* diabetic ketoacidosis, *DKD* diabetic kidney disease, *ESKD* end-stage kidney disease, *LLAs* lower limb amputations, *RCT* randomised controlled trial

increase in absolute risk [9]. Published CVOTs reported DKA rates ranging between 0.1 and 0.6% in the SGLT2i treatment arm and <0.1 and 0.3% in the placebo arm across studies [9, 17, 18, 29, 53]. Ketoacidosis was not observed in non-diabetes subgroups participating in the DAPA-CKD trial and one case was reported in an individual without T2DM at baseline in the empagliflozin EMPA-KIDNEY study, indicating that such events are generally associated with the presence of T2DM itself [28, 31]. Clear written and verbal education regarding sick day guidance and the signs of DKA can help to manage and place the risk of this rare adverse event into context [84, 87]. The main signs include abdominal pain, nausea, vomiting, shortness of breath (Kussmaul breathing), drowsiness, confusion and sweet-smelling (pear drop) breath [84]. DKA can occur with euglycaemia (relatively normal glucose levels) during SGLT2i use and HCPs should be aware of this and check ketone levels in individuals who are unwell, even in the

setting of relatively normal blood glucose levels [84]. Individuals should be advised to seek medical guidance if they are feeling unwell, even if their blood glucose does not appear elevated [84]. SGLT2i treatment will need to be temporarily paused if symptoms develop, with the decision to restart (where a clear contributing factor has been identified) taken in discussion with the individual and clinical team when it has been established that the benefits of reintroducing an SGLT2i outweigh the risks [84, 87]. Where a person has paused SGLT2i treatment in line with specialist care instructions (e.g. fasting in preparation for surgery), instructions for restarting SGLT2i therapy should be clearly given. Current recommendations vary widely according to country and suggest that SGLT2is must be stopped 3–7 days prior to planned surgery or a procedure requiring nil by mouth [88, 89]. However, the IDSC would advise ceasing SGLT2i therapy the day before surgery and then restarting once normal oral intake has been established and the person's condition has stabilised.

Genital mycotic infections (vulvovaginitis and balanitis) can occur during SGLT2i treatment, with infections being more common in women than men and usually arising early in treatment [63–66, 87]. Severe bacterial urinary tract infections (such as pyelonephritis and urosepsis) are rare, and analysis of trial data and real-world evidence does not support a causal link with SGLT2i treatment [90, 91]. Standard topical or oral antifungal or antibiotic treatments are generally sufficient to manage minor genital infections and most people can continue taking their SGLT2i medication [87]. Glucosuria may cause urinary symptoms, including more frequent voiding, and people with diabetes should receive education regarding the importance of post-micturition genital hygiene and hydration [63–66, 87].

Over the past decade, clinical experience, data from randomised controlled trials (RCTs), and real-world evidence have helped to enhance understanding of the risks associated with SGLT2is, particularly the rare but severe AEs such as Fournier's gangrene (FG), a perineal tissue infection, and lower limb amputations (LLAs) [92–95]. Yet, there is still uncertainty surrounding these potential side effects.

Continued placement of historical warnings regarding FG and LLAs on the UK Medicines and Healthcare Products Regulatory Agency (MHRA)/Department of Health (DoH) website as well as those in the British National Formulary (BNF) add further uncertainty for HCPs concerning actual risk levels for people who might otherwise be suitable for treatment [81, 82]. The MHRA, DoH and BNF statements are based upon outdated data, which have since been superseded by reassuring clinical outcomes from large scale CVOT and kidney disease trials conducted in high-risk populations [17, 18, 21, 53]. These studies showed that the incidence of FG was low and not confined to the active treatment arm, with higher incidence in the placebo arm in some trials (DAPA-CKD; DECLARE) [17, 18, 21, 28, 53]. Recent combined post hoc analysis from RCTs conducted in people with T2DM and high CV risk and/or CKD, the CANVAS Program and CREDENCE, showed that canagliflozin treatment did not affect the risk of non-genital skin and soft tissue infections compared with placebo [92]. People living with diabetes are inherently at elevated risk for LLA events [87, 96, 97]. Excess amputations were reported in one CVOT and were not replicated across subsequent trials [17, 18, 21, 28, 53, 98, 99]. Everyone with T2DM should be educated regarding the importance of preventative foot care and regular comprehensive assessment of lower limbs must be included in clinical reviews [8, 87, 96, 100]. Risk factors for LLAs include prior amputation, peripheral vascular disease and peripheral neuropathy, although these groups may gain advantage through the lowering of CVD risk associated with SGLT2is [87, 96, 100]. The Nuffield Department of Population Health Renal Studies Group meta-analysis stressed that the disease-modifying effects and absolute benefits of SGLT2i treatment outweighed any serious hazards of ketoacidosis or limb amputation [36]. Awareness of the key signs and symptoms is critical so that prompt and appropriate action can be taken when required for all people with T2DM. In addition, the osmotic diuretic effects of SGLT2i therapies may be advantageous for people who have limb-dependent oedema, even with active ulceration. Discussion with the local diabetes foot multidisciplinary team

(MDT) is warranted if SGLT2is are considered suitable in this situation. Experts across the field are currently working to develop a Delphi consensus statement regarding the diabetic foot, which will help in guiding appropriate use of medicines in high-risk individuals. It is hoped that the consensus will be available during the early part of 2024.

The risk factors discussed above are of particular relevance when considering the use of any glucose-lowering medicines in older people or those living with frailty [101]. Assessment of frailty level should be conducted regularly, as it is a dynamic parameter that changes over time, according to an individual's current circumstances [101]. Routine assessment of risk concerning urinary continence (due to potential urine infection), falls and perineal cutaneous infection must be conducted for older people with T2DM who are currently prescribed an SGLT2i. The decision to use an SGLT2i should consider the possibility of volume depletion and postural hypotension, which may increase the likelihood of falls, particularly in people who are also treated with diuretics or antihypertensives [17, 18, 53, 63–66, 101]. Older participants (aged >65 years) included in the CVOT studies typically demonstrated higher rates of volume depletion, compared with younger subgroups, although the overall rates were similar across the treatment and placebo arms in the DECLARE-TIMI (dapagliflozin) and EMPA-REG (empagliflozin) trials [18, 53, 102]. On the other hand, the CREDENCE and DAPA-CKD studies did not encounter any issues relating to concomitant use of SGLT2is and loop diuretics and some participants in the T2DM subgroups for HF trials (DAPA-HF and EMPEROR-reduced) were taking high-dose diuretics, and no dose reduction was necessary [20, 21, 28, 75, 103–105].

SGLT2i agents appear to offer electrolyte sparing advantages, although the pathophysiological mechanisms remain poorly understood [104, 106–110]. In general, potassium, magnesium and sodium, levels seem to be unaffected by SGLT2i treatment [104, 106–110]. Meta-analysis from CVOT and renal outcomes trials including 50,000 people with T2DM and high CV risk or CKD reported

a 16% reduction of incident hyperkalaemia with SGLT2i treatment compared with placebo ($p < 0.001$) and no increase in hypokalaemia [108]. These properties may provide greater flexibility regarding dose optimisation for renin–angiotensin–aldosterone system inhibitor (RAASi) drugs and mineralocorticoid receptor antagonists (MRAs), which can be limited by hyperkalaemia, particularly with kidney function decline [108]. SGLT2i renal outcomes and HF trials have shown that the CVRM benefits associated with SGLT2i use occur independently of MRA use in high-risk patients, many of whom will be receiving polypharmacy (with RAASi and/or MRA agents) in clinical practice [20, 76, 111, 112]. Systematic review and network meta-analysis data have identified that SGLT2is or nonsteroidal MRAs, combined with RAASi drugs, resulted in a reduction in kidney-specific composite events and HHF in people with T2DM and CKD, compared with placebo [112]. The NICE NG28 guideline does not provide advice on whether a person should be taking SGLT2i therapy before or after initiating MRA therapy and this lack of clarity also extends to the use of other glucose-lowering medicines in the treatment pathway (e.g. GLP-1 RAs) [8, 113]. However, the NICE technology appraisal guidance for finerenone states that people with T2DM and CKD can be prescribed finerenone in addition to angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), if they are not working well enough, and could be offered before, after, or with an SGLT2i [114]. KDIGO recommendations also state that nonsteroidal MRA agents can be added to first-line therapy (including SGLT2is) for people with T2DM and high residual risk of kidney disease progression and CV events, as evidenced by persistent albuminuria [32].

Post hoc analyses of CVOT data and real-world studies have revealed that the use of SGLT2i therapy is associated with lower serum urate levels and reduced incidence of gout [115–119]. In addition, a recent cohort study indicated that people T2DM and gout were at lower risk of recurrent gout flares and mortality if they were treated with an SGLT2i, compared with other oral glucose-lowering therapies [120].

PRACTICAL TOOLS TO SUPPORT BETTER MANAGEMENT OF T2DM

Figure 3 provides a traffic light summary of the clinical situations in which the IDSC believes that SGLT2i therapy should be offered to people with T2DM (green), SGLT2is should be considered (amber) or SGLT2i treatment should not be prescribed (red). To provide support in navigating each of these clinical situations and the topics discussed throughout this review in clinical practice, further information and practical advice are provided in the revised IDSC SGLT2i Decision Tool, which can be downloaded in an interactive pdf format as a supplementary material associated with this article alongside a printable one-page A4 poster/wall chart summary.

Putting the evidence in to practice, the IDSC supports the implementation of a rapid sequential approach to T2DM management comprising early combination therapy with metformin and an SGLT2i agent for most people with T2DM, rather than gradual stepwise intensification of treatment over an extended period. Using this method, metformin should be initiated and titrated to an appropriate dose during the first month, with the SGLT2i agent added (unless contraindicated) after 4 weeks (supported by a telephone appointment, where possible) or by a review after 12 weeks (at latest). For high-risk individuals (high CV risk, CVD or kidney disease), an SGLT2i should be started at diagnosis, with or without other diabetes therapies, in line with ADA/EASD and KDIGO guidelines [9, 32].

It is important to discuss the relative risks and benefits with the person being prescribed an SGLT2i to ensure that they broadly understand how these treatments work and have an opportunity to ask questions. To minimise the chances of experiencing an AE that will discourage an individual from persisting with newly initiated SGLT2i medication, advice should be given regarding the importance of maintaining good daily hydration and genital hygiene. Information about genital infections and the signs and symptoms of DKA should be communicated with an emphasis on the fact that ketoacidosis and FG are very rare events in usual practice. Counselling the individual about the

Key practice points:

- Discuss the relative benefits and risks of SGLT2i therapy with the person you are treating.
- Use dual first-line SGLT2i therapy with metformin (unless contraindicated). Initiate 4 weeks after metformin, post-date the SGLT2i prescription and do not wait for HbA1c assessment at 3 months after metformin initiation.
- Emphasise the importance of ongoing hydration and good personal hygiene.
- Give written information/electronic resources to support advice on the management of T2DM medicines during periods of acute or dehydrating illness.
- If symptomatic of hyperglycaemia, start rescue therapy and then reassess initiation of SGLT2i when symptoms resolved.
- For planned surgery or procedures requiring nil by mouth, advise on the importance of pausing SGLT2i treatment 3–7 days prior to surgery or liaise with pre-operative team.
- Please refer to the relevant SmPC before prescribing any SGLT2i therapy.
- Discussion with an expert clinician is advisable for more complex cases.

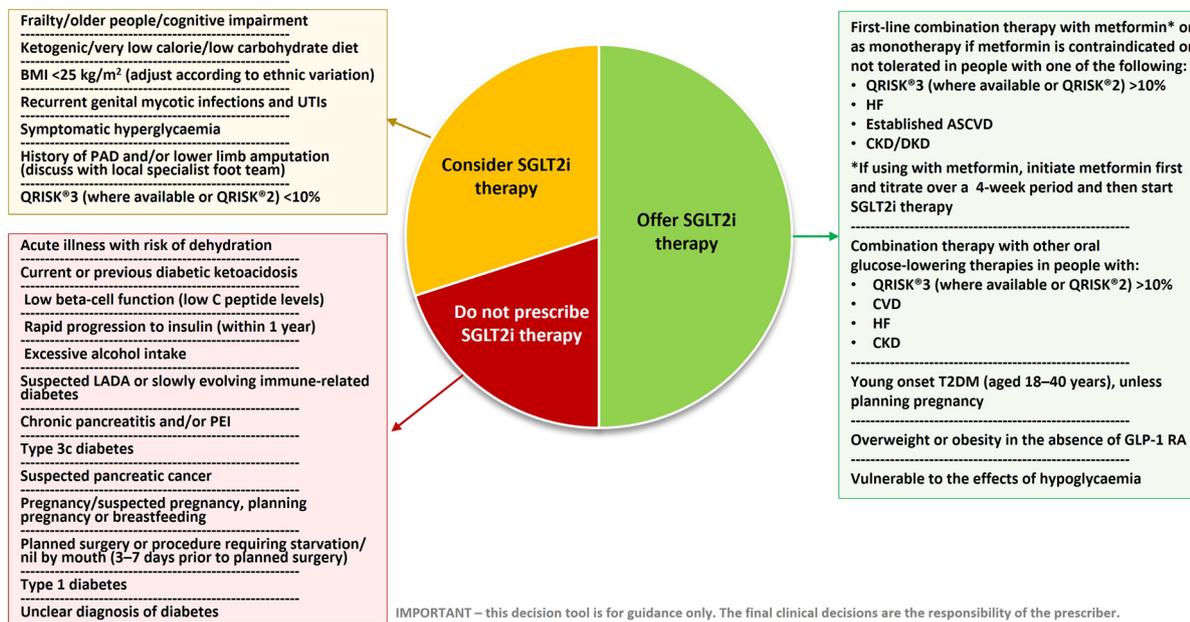
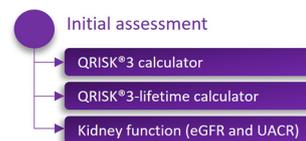


Fig. 3 SGLT2i decision tool—abbreviated summary [8, 9, 12, 17, 18, 21, 28, 31, 32, 41, 43, 51, 53–55, 62–66, 71, 74, 82–84, 87, 101, 110, 121–129]. The full SGLT2i Decision Tool can be viewed and downloaded in an interactive pdf format from the supplementary materials associated with this narrative review paper. *ASCVD* atherosclerotic cardiovascular disease, *BMI* body mass index, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DKD* diabetic kidney disease, *eGFR* estimated glomerular filtration

rate, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated haemoglobin A1c, *LADA* latent autoimmune diabetes in adult, *PAD* peripheral arterial disease, *PEI* pancreatic exocrine insufficiency, *QRISK* cardiovascular risk score, *SGLT2i* sodium glucose cotransporter-2 inhibitor, *SmPC* summary of product characteristics, *T2DM* type 2 diabetes mellitus, *UACR* urine albumin-to-creatinine ratio, *UTIs* urinary tract infections

importance of avoiding very low carbohydrate or ketogenic diets and ensuring continued hydration while taking an SGLT2i will help to reduce the risk of rare but serious events [84, 87]. Sick day guidance should be given, with clear instructions on pausing SGLT2i therapy while the person is unwell and they must be encouraged to contact their HCP if they need assistance in restarting treatment once they have recovered [121]. Box 1 provides a summary of key practice points to guide a T2DM consultation in which an SGLT2i agent is initiated. The answers to common FAQs are also provided in Box 2 to

support HCPs in answering their own questions about SGLT2is. Box 3 provides responses to queries that a person with T2DM may have when they are prescribed an SGLT2i. Finally, Box 4 contains links to key resources for HCPs and people with T2DM relating to SGLT2i treatment. Variation in approved SGLT2i product licences continues to be a cause for confusion among prescribers, particularly relating to eGFR, and the IDSC advocates the use of recently published summaries, such as those provided in ‘Prescribing SGLT2i therapy’ section in Box 4, which give

a useful and practical overview. Other areas covered by the links in Box 4 include current guidelines and information relating to DKA, genital infections and sick day guidance. Links to many of these materials are also provided via the SGLT2i Decision Tool (supplementary materials).

BOX 1. KEY PRACTICE POINTS FOR INITIATING SGLT2i THERAPY

[8, 9, 84, 87, 121]

- Consider an SGLT2i therapy at diagnosis (unless contraindicated) with long-term CVRM protection in mind
- If using combination therapy with metformin, use a rapid sequential approach:
Initiate SGLT2i therapy after 4 weeks, supported by a telephone appointment where possible, or at latest by a review after 12 weeks (unless contraindicated)
- Highlight the importance of good hydration
- Provide sick day advice and reiterate at every review
- Ensure the individual has a good understanding regarding the importance of genital hygiene
- Advise on the importance of seeking medical attention if severe pain, tenderness erythema or swelling occur in the genital region, accompanied by fever/malaise
- Advise against the use of very low carbohydrate or ketogenic diets with SGLT2i treatment
- Assess risk factors for DKA (low beta-cell reserve, sudden reductions in insulin, increased insulin requirements due to acute illness, surgery and alcohol abuse) and advise on key signs, which include abdominal pain, nausea, vomiting, shortness of breath (Kussmaul breathing), drowsiness, confusion and sweet-smelling (pear drop) breath
- As with all T2DM medications, provide footcare education and emphasise the importance of regular check

CVRM cardiovascular, renal and metabolic, *DKA* diabetic ketoacidosis, *SGLT2i* sodium glucotransporter-2 inhibitor, *T2DM* type 2 diabetes mellitus

BOX 2. FAQs RELATING TO SGLT2I TREATMENT FOR HCPS

[1–4, 8, 9, 11, 12, 17–40, 49, 51, 53–56, 61–66, 68–75, 83, 84, 87–89, 98–110, 121, 127–130]

Q Are SGLT2is associated with a greater risk of DKA?

A Incidence of DKA is low in general. Published CVOT data reported DKA rates to be between 0.1 and 0.6% with SGLT2i treatment and < 0.1 and 0.3% in placebo study groups. To reduce DKA risk, advise people to pause their SGLT2i if they are unwell and not able to eat and drink normally, then restart once recovered. SGLT2is should be avoided if LADA or pancreatitis associated diabetes is suspected. Pause SGLT2i use 3–7 days ahead of planned surgery and restart once the person has recovered and is eating and drinking normally again.

Q Does SGLT2i treatment need to be stopped prior to elective surgical procedures?

A Yes, treatment should be stopped ahead of planned surgical procedures and those requiring nil by mouth or starvation. Opinion varies regarding timing, but the literature indicates that treatment should be suspended from 3–7 days prior to surgery. This may also depend on local guidance. SGLT2i therapy should be restarted when postoperative stress has resolved and oral intake has returned to normal.

Q Can SGLT2i treatments be prescribed for older people?

A Most approved SGLT2i licences do not stipulate an upper age limit for prescribing. The SOLD study found SGLT2is to be effective and well tolerated in people aged > 70 years with T2DM and the associated delay in progression of CKD, HF, MACE is a potential benefit for this group. Moderately/severely frail people are at risk of weight loss resulting in sarcopenia, candidiasis and UTIs, possible urinary incontinence, fluid volume depletion, and subsequent DKA. Regular monitoring and sick day education should be conducted.

Q Does renal function need rechecking soon after SGLT2is are initiated?

A A person's eGFR can drop within the first few weeks after SGLT2i initiation. This is believed to be due to correction of glomerular hyperfiltration with SGLT2i treatment and is not associated with kidney injury. HCPs should not alter management or continuation of therapy in response to eGFR reductions early in treatment. SGLT2is do not cause electrolyte abnormalities and may lower the risk of hyperkalaemia. Routine renal function monitoring in line with diabetes reviews is suitable unless there is a clinical concern regarding volume depletion.

Q Can SGLT2i therapies be prescribed alongside loop diuretics?

A Renal studies and HF studies specifically included high-risk people with T2DM and kidney disease or HF, many of which were already taking loop diuretics. No issues associated with concomitant use were reported. Diuretic dosing may require modification because SGLT2is increase diuretic effect.

Q Can SGLT2is be used in women who are planning pregnancy?

A No, SGLT2i therapies are not licenced for use during pregnancy or breastfeeding. Any woman living with T2DM planning pregnancy should be referred to their local specialist diabetes team for pre-conception care.

- Q Can SGLT2is be used in people with T2DM who are under the age of 40 years?
- A SGLT2i treatment can be used in this group based on individual licences. People with young onset T2DM (especially those living with obesity) have a higher lifetime CVD risk compared with older onset diabetes and may benefit from the perspective of CVD prevention. However, women of child-bearing age should only be prescribed SGLT2is if they confirm that they are not planning pregnancy and that they are using reliable contraception after discussion of risks and benefits.
Note that the QRISK[®]2 tool should only be used to estimate CV risk in people aged above 40 years. The QRISK[®]3 tool is for use in people aged above 25 years. The QRISK[®]3-Lifetime tool may be more appropriate for assessment of people aged 18–40 years.
- Q Can I prescribe an SGLT2i for a person with active foot ulcers?
- A One SGLT2i trial showed an imbalance in LLAs (toe amputations), although subsequent SGLT2i trials, systematic reviews and meta-analyses have found no compelling evidence of a significant association. People living with diabetic foot disease or peripheral vascular disease have inherently high CV risk and would benefit from therapies proven to reduce CV risk and osmotic diuretic effects. Discussion with the local diabetic foot MDT is warranted if SGLT2is are considered suitable and, as with all people living with T2DM, individuals should check their feet regularly, follow preventative care and report any foot infection or ulceration to their HCP.
- Q Is FG risk an important consideration when prescribing SGLT2i treatment?
- A No causative link has been shown between FG and SGLT2is. Incidence of FG is very low and the risk is raised slightly in T2DM.
- Q Are the benefits of SGLT2is a class effect?
- A The CVRM disease benefits of SGLT2is appear to be relatively consistent across the treatment class. However, as highlighted in some guidelines, the significant reduction in CVRM risk has been specifically proven in CVOTs and renal trials for canagliflozin, dapagliflozin and empagliflozin.

CKD chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *CVOT* cardiovascular outcomes trial, *CVRM* cardiovascular renal and metabolic, *DKA* diabetic ketoacidosis, *eGFR* estimated glomerular filtration rate, *FAQs* frequently asked questions, *FG* Fournier's gangrene, *HCP* healthcare professional, *HF* heart failure, *LADA* latent autoimmune diabetes in adult, *LLA* lower limb amputation, *MACE* major adverse cardiovascular events, *MDT* multi-disciplinary team, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *T2DM* type 2 diabetes mellitus, *UTI* urinary tract infection

BOX 3. FAQs RELATING TO SGLT2I TREATMENT FOR PEOPLE LIVING WITH TYPE 2 DIABETES MELLITUS

- Q Should I stop taking my SGLT2i if I am unwell?
- A Yes. If you are unwell and you are not able to eat and/or drink properly or you are vomiting or dehydrated, you should not take your SGLT2i. You should restart the SGLT2i when you are recovered and eating and drinking normally.
- Q Can I start a low carbohydrate or ketogenic diet whilst taking my SGLT2i?
- A This is not advisable, please speak to your healthcare team for a medication review before embarking on a low carbohydrate or ketogenic diet.
- Q Why have I been started on metformin and an SGLT2i together?
- A People with T2DM are at a higher risk of heart attacks, strokes and kidney disease, which can affect long-term health and quality of life. Metformin will help to manage your glucose levels along with the SGLT2i, but the SGLT2i will also protect your heart and your kidneys. Using two medications together soon after diagnosis will help to prevent problems in the future, compared to using just one medication on its own. Your healthcare professional will most likely start the metformin first and then add the SGLT2i a month later.
- Q Will the SGLT2i give me genital thrush?
- A SGLT2is work by making you pass more sugar in your urine and sometimes, when you first start taking this type of medicine, this can increase the likelihood of genital thrush (a fungal infection) or balanitis (fungal infection under the foreskin in men). As glucose levels improve this is likely to get better. Thrush can be treated with over-the-counter medications or treatment from your general practitioner. A one-off episode of thrush should be treated fully but should not be a reason to stop taking the medication. It is recommended to wash daily and maintain good personal hygiene.
- Q Should I be concerned about the increased frequency of urination?
- A Increased frequency of urination is expected when taking an SGLT2i because of the way that this type of medicine works. It may be more noticeable when you first start taking it if your glucose levels are particularly raised. As the glucose levels improve, the increased urinary frequency should ease.
- Q Can my blood sugar levels run low with SGLT2is?
- A SGLT2is do not commonly cause hypoglycaemia (low blood sugar) on their own. However, some people may need to monitor their glucose levels regularly, especially if they are taking other diabetes medications in addition to an SGLT2i, such as insulin and/or gliclazide/glimepiride.
- Q Will I get a urinary tract infection if I take an SGLT2i therapy?
- A There may be a slight increase in the risk of a urinary tract infection when taking an SGLT2i medicine. You can reduce the risk by making sure that you stay well hydrated (drink at least 2 litres of water/fluid each day), maintain good personal hygiene and consult your healthcare professional if you experience signs or symptoms such as a burning sensation when urinating.

Q	Do SGLT2is help with weight loss?
A	Because these medicines work by causing more glucose/sugar to leave the body via the urine, less calories will be absorbed by the body and weight loss may happen over a period of time. If you experience very rapid weight loss, nausea and dizziness contact your healthcare professional straightaway.

FAQs frequently asked questions, *SGLT2i* sodium-glucose cotransporter-2 inhibitor

BOX 4. KEY RESOURCES FOR HCPS AND PEOPLE WITH T2DM

[8, 9, 32, 62, 68, 72, 73, 83, 84, 87, 121, 122, 124–126, 131–136]

Resources for HCPS. Follow the links below to access the resources

Prescribing SGLT2i therapy: useful summaries

Interactive IDSC SGLT2i Decision Tool (available in the supplementary materials for this article)

[Brown P. SGLT2 inhibitors: Indications, doses and starting/stopping recommendations](#)

[Brown P. How to use SGLT2 inhibitors safely and effectively](#)

[Fernando K. SGLT2is in extra-glycaemic indications: use in people with renal impairment](#)

Guidelines for people with T2DM

[Fernando K. Medscape UK. Guidelines summary. 2022](#)

[NICE NG28 guideline: type 2 diabetes in adults: management](#)

[ADA/EASD consensus report. 2022](#)

[KDIGO 2022 Diabetes in CKD guideline](#)

[UKKA clinical practice guideline: SGLT2is in adults with kidney disease. 2021](#)

[2019 ESC/EASD Guidelines on diabetes, pre-diabetes, and CVDs](#)

[Centre for Perioperative Care. Guideline for people with diabetes undergoing surgery. 2022](#)

Sick day guidance: useful summaries

[Down S. How to advise on sick day rules](#)

[EDEN infographic – sick day rules for T2DM](#)

DKA: useful summary

[Diggle J. Ketones and diabetes](#)

Diabetes and fasting: key guidelines

[IDF-DAR Practical Guidelines 2021: Diabetes and Ramadan](#)

[South Asian Health Foundation \(UK\) Guidelines for managing diabetes during Ramadan: 2020 Update](#)

Risk calculators

[QRISK^{®3}](#)

QRISK[®] 3-Lifetime

Resources for people with T2DM. Follow the links below to access the resources

Sick day guidance

[TREND Diabetes: What to do when you are ill](#)

[Diabetes UK: Diabetes when you're unwell](#)

DKA

[TREND Diabetes: T2DM and ketoacidosis](#)

[Diabetes UK: What is DKA \(diabetic ketoacidosis\)?](#)

Genital infections

[TREND Diabetes: How to reduce your risk of genital fungal infection](#)

Diabetic foot

[TREND Diabetes: Looking after your feet when you have diabetes](#)

[Diabetes UK: How to look after your feet](#)

All links were correct at the time of publication

ADA American Diabetes Association, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DKA* diabetic ketoacidosis, *EASD* European Association for the Study of Diabetes, *ESC* European Society for Cardiology, *HCP* healthcare professional, *IDF-DAR* International Diabetes Federation and Diabetes and Ramadan collaboration, *IDSC* Improving Diabetes Steering Committee, *KDIGO* Kidney Disease: Improving Global Outcomes, *NICE* National Institute for Health and Care Excellence, *SGLT2i*, sodium-glucose cotransporter-2 inhibitor, *T2DM* type 2 diabetes mellitus, *UK* United Kingdom, *UKKA* UK Kidney Association

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Declarations

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Ethical Approval. This article is based upon previously conducted studies and does not involve any new studies of human or animal subjects. Some authors were involved in studies discussed within the paper that included human subjects, all of which complied with the tenets of the Declaration of Helsinki and used protocols that had been approved by relevant

Institutional Review Boards/Ethics Committees and included patients who had provided written informed consent.

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