



REVIEW

The Place and Value of Sodium-Glucose Cotransporter 2 Inhibitors in the Evolving Treatment Paradigm for Type 2 Diabetes Mellitus: A Narrative Review

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ABSTRACT

Over recent years, the expanding evidence base for sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapies has revealed benefits beyond their glucose-lowering efficacy in the treatment of Type 2 diabetes mellitus (T2DM), resulting in their recognition as cardiorenal medicines. While SGLT2is continue to be recommended among the second-line therapies for the

treatment of hyperglycaemia, their true value now extends to the prevention of debilitating and costly cardiovascular and renal events for high-risk individuals, with particular benefit shown in reducing major adverse cardiac events and heart failure (HF) and slowing the progression of chronic kidney disease. However, SGLT2i usage is still suboptimal among groups considered to be at greatest risk of cardiorenal complications. The ongoing coronavirus disease

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2019 (COVID-19) pandemic has intensified financial pressures on healthcare systems, which may hamper further investment in newer effective medicines. Emerging evidence indicates that glycaemic control should be prioritised for people with T2DM in the era of COVID-19 and practical advice on the use of T2DM medications during periods of acute illness remains important, particularly for healthcare professionals working in primary care who face multiple competing priorities. This article provides the latest update from the Improving Diabetes Steering Committee, including perspectives on the value of SGLT2is as cost-effective therapies within the T2DM treatment paradigm, with particular focus on the latest published evidence relating to the prevention or slowing of cardiorenal complications. The implications for ongoing and future approaches to diabetes care are considered in the light of the continuing coronavirus

pandemic, and relevant aspects of international treatment guidelines are highlighted with practical advice on the appropriate use of SGLT2is in commonly occurring T2DM clinical scenarios. The ‘SGLT2i Prescribing Tool for T2DM Management’, previously published by the Steering Committee, has been updated to reflect the latest evidence and is provided in the Supplementary Materials to help support clinicians delivering T2DM care.

Keywords: SGLT2 inhibitors; Oral glucose-lowering medicines; Type 2 diabetes mellitus; Prescribing tools; Heart failure; Chronic kidney disease; Diabetic kidney disease; Cardiovascular disease; Cardiovascular risk; Cardiorenal protection

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Key Summary Points

The Improving Diabetes Steering Committee has reviewed the wealth of evidence supporting the role of sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapies as cardiorenal and glucose-lowering medicines used in the management of Type 2 diabetes mellitus (T2DM).

Data from randomised cardiovascular outcomes trials and real-world studies have demonstrated the value of SGLT2i therapies in reducing cardiorenal events, with particular benefit shown regarding the slowing of disease progression in chronic kidney disease (CKD) and diabetic kidney disease as well as the avoidance of heart failure events.

The proven cost-effectiveness profile for SGLT2i therapies (previously based purely upon their glucose-lowering efficacy) has been strengthened by evidence from recent SGLT2i cardiovascular and renal outcome trials, in which costly adverse outcomes were reduced and subsequent improvements in quality of life were provided for people with T2DM.

The ongoing coronavirus disease 2019 (COVID-19) pandemic has heightened the challenges of T2DM management for many healthcare professionals (HCPs) and people living with the disease. The threat of severe COVID-19 infection emphasises the importance of maintaining good glycaemic control for people with diabetes. In this context, as clinically efficacious and cost-effective medicines, SGLT2i therapies can help people with T2DM reach their glycaemic targets.

As the evidence base for SGLT2i therapies continues to broaden and multiple treatment guidelines are adapted to reflect the latest data, HCPs may benefit from practical advice on the appropriate place of these medicines within the T2DM treatment pathway. The ‘SGLT2i Prescribing Tool for T2DM Management’, previously published by the Steering Committee, has been revised and developed further to provide a quick reference guide that aims to support HCPs working in the field of T2DM management and to encourage the appropriate use of SGLT2is in clinical practice.

THE ROLE OF THE IMPROVING DIABETES STEERING COMMITTEE

The Improving Diabetes Steering Committee was formed in 2017 and comprises a panel of clinical experts from across primary and specialist care who have worked alongside prominent professional organisations to improve the delivery of diabetes care. The Committee’s initial aim was to support healthcare professionals (HCPs) working in Type 2 diabetes mellitus (T2DM) medicine within the UK. However, the panel has recently welcomed European experts to the group, bringing new insights regarding the shared challenges faced by HCPs across Europe in T2DM management. The Committee is supported by an educational grant from Napp Pharmaceuticals Limited and Mundipharma Research Limited and endeavours to ensure that HCPs who prescribe diabetes medicines have access to balanced and accurate information and evidence concerning T2DM medicines, with a specific focus on the sodium-glucose cotransporter-2 inhibitor (SGLT2i) class. The group is committed to providing healthcare colleagues with clarity regarding the evidence base supporting SGLT2i agents and appropriate approaches to prescribing. Educational

materials and publications provided by the panel, such as the previously published consensus documents, are intended to increase confidence and understanding regarding the correct place of these medicines within the current T2DM treatment pathway [1–3].

This narrative review paper summarises the key topics that were discussed during a Steering Committee meeting held in July 2021 and aims to examine the accumulating evidence surrounding the cardiorenal benefits of SGLT2i medicines. The true value of these therapies in T2DM management is considered as well as the practicalities of prescribing SGLT2is in modern clinical practice, with emerging insights drawn from the era of the coronavirus disease 2019 (COVID-19) pandemic.

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 of 1964 and subsequent revisions and used protocols that had been approved by relevant Institutional Review Boards/Ethics Committees and included patients who had provided written informed consent.

THE CLINICAL EFFECTS OF SGLT2I THERAPIES: FROM GLUCOSE-LOWERING TO CARDIORENAL PROTECTION

Although initially approved as medicines for the treatment of hyperglycaemia in people with T2DM, the vast and rapidly developing evidence base for SGLT2i medicines has driven a paradigm shift in clinical perceptions regarding their place within the therapeutic pathway [4–36]. In addition to their proven efficacy in reducing hyperglycaemia, numerous large-scale randomised clinical trials (RCTs), real-world studies, systematic reviews and meta-analyses have revealed SGLT2i therapies to be effective cardiorenal medicines [4–36]. The protective effects of SGLT2is against the cardiovascular

(CV) and renal complications of T2DM appear to be independent of their glucose-lowering activity, with particular value being demonstrated in the reduction of risk regarding hospitalisation for heart failure (HHF) and progression of diabetic kidney disease (DKD) as well as lowering the incidence of major adverse cardiovascular events (MACE) [4–36]. Recently published reviews have described and explored the putative mechanisms underlying the cardiorenal benefits of SGLT2is, emphasising the direct and indirect effects that these medicines have on pathways that mediate inflammation, oxidative stress and endothelial cell dysfunction [37, 38].

Table 1 provides an overview of cardiorenal outcomes from randomised SGLT2i trials alongside the relevant study populations in which efficacy was demonstrated [4–36, 39–41]. CV outcome trials (CVOTs) examining the treatment effects of empagliflozin, canagliflozin and dapagliflozin, versus placebo, demonstrated significant reductions in CV events, including composite endpoints encompassing MACE (comprising non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality), HF and CV death, HHF and worsening HF events [4–7]. The ertugliflozin CVOT (VERTIS-CV) also demonstrated numerical reductions in some CV and renal events, with a significant decrease in HHF events shown [8]. Emerging data in people with HF with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) indicate that the benefits relating to reduction of HF events are relevant to high-risk populations with and without T2DM [8–15]. The protective CV effects of SGLT2is have been reaffirmed in the real-world setting through large observational studies that include the multinational CVD-REAL study, which showed that SGLT2i therapy was associated with a lower risk of HHF or death in people with or without CV disease (CVD), compared with other glucose-lowering therapies [17–20].

Data from the EMPA-REG Outcome Trial, CANVAS Program and DECLARE-TIMI 58 trial suggested that, compared with placebo, progression of kidney disease was significantly reduced with SGLT2i treatment, and meta-

Table 1 Key cardiovascular and renal outcomes from large-scale sodium-glucose cotransporter-2 inhibitor randomised studies [4–36, 39–41]

Study	N	Study population	Main treatment outcomes (relative risk reduction)						
			MACE	CV death and HHF	Renal composite endpoint	HHF	CV death	All-cause mortality	
CVOTS	CANVAS Program (canagliflozin)	10,1402	T2DM and CVD or CV risk	↓14%	↓22%	↓40%	↓33%	↓13%	↓13%
	DECLARE-TIMI 58 (dapagliflozin)	11,607	T2DM and CVD or CV risk	↓7%	↓17%	↓47%	↓27%	↓2%	↓7%
	EMPA-REG OUTCOME (empagliflozin)	7,020	T2DM and established CVD	↓14%	↓34%	↓46%	↓35%	↓38%	↓32%
	VERTIS-CV (ertugliflozin)	8,246	T2DM and established CVD	↓3%	↓12%	↓19%	↓30%	↓8%	↓7%
Renal outcomes trials	CREDESCENCE (canagliflozin)	4,401	T2DM and CKD	↓20%	↓31%	↓34%	↓39%	↓22%	↓17%
	DAPA-CKD (dapagliflozin)	4,304	CKD with/without T2DM		↓29%	↓39%		↓19%	↓31%
	SCORED ^a (sotagliflozin)	10,584	T2DM, CKD and CV risk	↓33%	↓23%	↓29%	↓33%	↓10%	↓1%
HF trials	DAPA-HF (dapagliflozin)	4,744	HFrEF with/without T2DM		↓25%	↓29%	↓30%	↓18%	↓17%
	EMPEROR-reduced (empagliflozin)	3,730	HFrEF with/without T2DM		↓25%	↓50%	↓31%	↓8%	↓8%
	EMPEROR-preserved (empagliflozin)	5,988	HFpEF with/without T2DM		↓21%	↓5%	↓27%	↓9%	No change
	SOLOIST-WHF ^a (sotagliflozin)	1,222	WHF and T2DM	↓28%	↓33%		↓36%	↓16%	↓18%

^aSotagliflozin is not currently approved for use in Europe, although it has been submitted to the US FDA for approval

Statistically significant relative reduction reported
 P value for relative risk value not reported or statistical significance not achieved
 No data reported/available

CKD chronic kidney disease, CV cardiovascular, CVD cardiovascular disease, HHF hospitalisation for heart failure, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, SGLT2i sodium glucose cotransporter-2 inhibitor, T2DM Type 2 diabetes mellitus, US FDA United States Food and Drug Administration, WHF worsening heart failure
 Adapted from Dashora et al. [44]

analysis of SGLT2i CVOTs confirmed these outcomes in people with and without atherosclerotic cardiovascular disease (ASCVD) [4–6, 21]. The CREDENCE trial was the first randomised SGLT2i study to show benefit in people with albuminuric chronic kidney disease (CKD) and T2DM [22]. Subsequently, the DAPA-CKD trial has shown benefits in CKD populations with and without diabetes [22, 23]. Data from other RCTs, real-world studies, post-hoc analyses and meta-analyses have consistently shown improvements in renal outcomes in people with diabetes across the SGLT2i class [23–36, 39–41].

THE USE OF SGLT2I THERAPIES IN CURRENT CLINICAL PRACTICE

The latest editions of clinical guidelines and position statements from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), Kidney Disease: Improving Global Outcomes (KDIGO), the Association for British Clinical Diabetologists (ABCD) and UK Kidney Association (UKKA) and the European Society of Cardiology (ESC) reflect the plethora of published data showing cardiorenal benefit with SGLT2i treatments in people with T2DM [42–46]. Publication of national guidelines may take longer, compared with international recommendations [47]. Modern guidelines typically recommend SGLT2is as a second-line option for T2DM therapy (after metformin), or as first-line therapy in cases where an individual is unable to tolerate metformin, with the aim of slowing CVD and CKD/DKD progression and reducing HF events [42–46]. KDIGO guidelines recommend starting treatment with metformin and SGLT2is for people with T2DM and CKD [43].

Despite the wealth of clinical evidence and guidance surrounding SGLT2i treatments, global and US data indicate that prescribing remains suboptimal for people with T2DM who have increased CV or renal risk [41, 48–53]. Country-level prescribing data are highly variable, but prescriptions for SGLT2i therapies are generally < 15% when comparing against other second-line T2DM treatments [41, 48–55].

Sulphonylurea (SU) treatments continue to be the most commonly prescribed second-line therapy, despite studies showing that newer glucose-lowering treatments (SGLT2is, glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) provide improved clinical outcomes when used with metformin, compared with SU–metformin combinations [41, 48–55]. Data from the DISCOVER study showed that people prescribed a newer glucose-lowering treatment alongside metformin demonstrated greater weight loss and fewer hypoglycaemic events than those receiving SU–metformin combination therapy [54]. The same study revealed that, compared with SU–metformin treatment, SGLT2i–metformin combination therapy was associated with improvements in health-related quality of life (QoL) measures over a 36-month follow-up [54].

Variability in local reimbursement arrangements presents a barrier to SGLT2i prescribing, and these medicines have only recently become available in countries such as France, where experience and confidence with SGLT2is may consequently be low [41, 55–57]. Some countries (e.g. Italy) require SGLT2i prescriptions to be initiated and reviewed by a specialist secondary care physician, and bureaucratic processes may hinder the use of newer medicines in other locations [55].

Caution in initiating SGLT2i therapies might, in part, be a consequence of the inconsistent approaches used in the reporting of safety outcomes from CVOTs [4–12]. The ongoing COVID-19 pandemic has dramatically impacted the delivery of healthcare services, particularly in primary care, with many medical consultations taking place virtually and clinical assessment becoming increasingly challenging. Most primary and secondary care services have struggled to address the current backlog in T2DM reviews and HCPs may feel uncomfortable starting newer classes of drug when face-to-face consultations or opportunities for monitoring are limited. In addition, the sheer number of new T2DM medications becoming available in recent years could have caused reasonable confusion among HCPs regarding the optimal place of each therapy within the ever more complex treatment pathway.

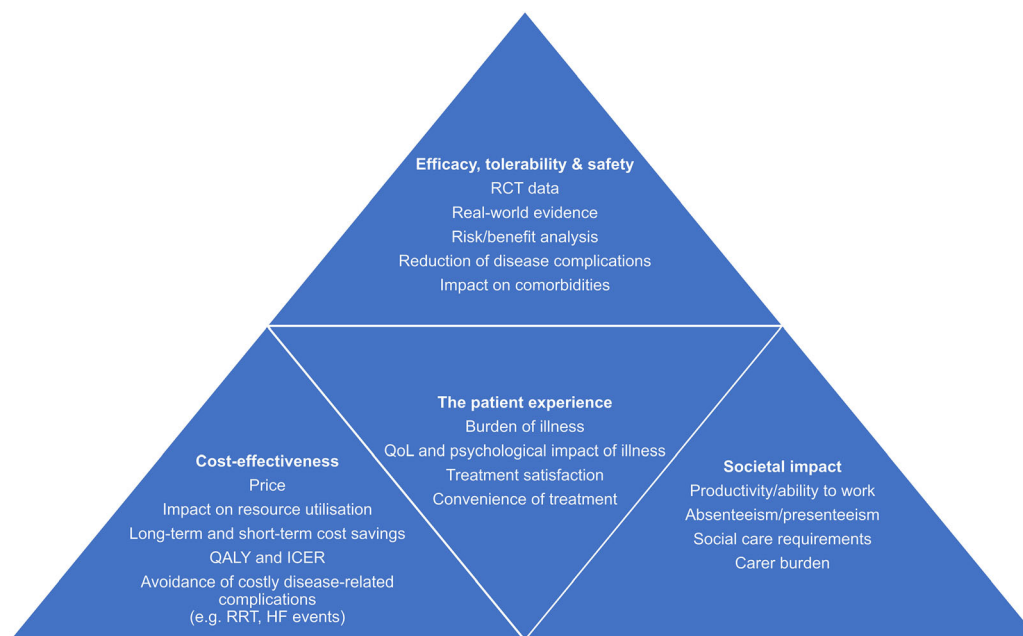


Fig. 1 An overview of key drivers of value relating to disease burden and pharmacological interventions [62–79]. The value of a pharmacological intervention encompasses many different parameters relating to the direct cost of treatment, avoidance of resource- and time-consuming adverse events or disease-related complications, the impact on recipient QoL (as well as the burden of illness for

family members and those who care for them) and the indirect implications of therapy on wider societal factors. *HF* Heart failure, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life years, *QoL* quality of life, *RCT* randomised controlled trial, *RRT* renal replacement therapy

Systematic review data show that therapeutic inertia typically increases with treatment intensification in T2DM management [41, 52]. Clinicians may welcome greater clarity and direction to support them in understanding the value that newer treatments can offer and the individuals most appropriate to receive such therapies.

THE VALUE OF SGLT2 INHIBITORS IN T2DM MANAGEMENT

Prior to the publication of outcomes from the CVOTs and the wealth of data that subsequently followed, internationally recognised reimbursement authorities considered the licensed SGLT2i treatments to be cost-effective in the management of T2DM, based upon their glucose-lowering efficacy [58]. It therefore seems reasonable to assume that the value or

cost-effectiveness of SGLT2i treatments should have increased given the evidence surrounding their protective cardiorenal effects and the revised licensed indications across the treatment class [59–61].

Considerations regarding value in primary care generally focus on drug acquisition cost rather than the long-term clinical advantages of treatments that lower the incidence of cardiorenal events, which are costly to manage and are associated with drastically reduced QoL for people with T2DM. In reality, the true value of a medicine will be represented by many different parameters, from the cost of a treatment through to the avoidance of undesirable clinical outcomes, the impact on QoL and other healthcare costs avoided due to the use of the medicine (e.g. reduced requirement for diabetic retinopathy management where glycated haemoglobin [HbA1c] has been effectively controlled) [62]. Outside of the healthcare system,

the broader societal impact of appropriate disease management may include factors such as productivity, absenteeism and presenteeism [62]. Figure 1 provides a summary of the key components of value for pharmacological interventions. While prescribing costs often drive treatment selection and formulary decisions, these represent < 10% of the total healthcare expenditure, and approximately 80% of spending in T2DM management is due to the complications of diabetes, many of which result in hospitalisation and are associated with extended lengths of stay [62–66]. The perceived value for the person with T2DM is also an important aspect of treatment. Interventions that improve QoL and assist in either avoiding or reducing the severity of adverse outcomes (e.g. the need for renal replacement therapy) must be considered of greater worth than treatments that are not able to provide such outcomes or may even be associated with potential harm (e.g. hypoglycaemia and weight gain with SU treatments). Patient-reported outcomes data are limited regarding SGLT2i treatments, although the DAPA-HF trial showed improvements in physical function and QoL relative to usual care in people with HFrEF with/without T2DM and another dapagliflozin study revealed improved treatment satisfaction compared with usual care in people with overweight/obesity and T2DM, with satisfaction significantly correlated to body weight loss [67, 68].

Taking a broader view, it seems clear that interventions capable of preventing cardiorenal events offer greater efficiencies within the treatment pathway and that these benefits comfortably off-set prescribing costs. In the UK, the latest National Institute for Health and Care Excellence (NICE) guidelines recognise this concept, stating that (although recommendations relating to the broader prescribing of SGLT2is in clinical practice may carry an associated cost impact) there was likely to be a long-term cost saving through the use of SGLT2is as CKD progression will be slowed and the number of CV and end-stage renal events reduced [47]. HCPs may underestimate the real value of SGLT2is when assessing them simply on their glucose-lowering properties, while ignoring the

breadth of data on adverse CV and renal event avoidance [4–36, 39–41]. Cost-effectiveness analyses suggest that SGLT2i therapies provide economic efficiencies over other T2DM treatments when comparing hospitalisations due to complications in people with and without pre-existing CVD [69–71]. Healthcare data indicate that the annual cost of managing each person with HHF could be as high as £3873/€4575, while respective DKD (Stage 3a) and dialysis costs are around £1580/€1866 and £27,270/€32,213 per person [41, 71, 72]. Studies comparing potential expenditure on care show that empagliflozin may offer annual savings of about \$1355/€1207 per person over dipeptidyl peptidase 4 inhibitor (DPP-4i) treatments due to reductions in the use of inpatient and outpatient services, shorter length of stay in hospital and fewer hospitalisations and emergency department visits [41, 73, 74]. Yearly cost reductions of approximately US\$1989/€1693 per person have been estimated to be associated with the avoidance of renal and CV events, based on outcomes from the canagliflozin CREDENCE study [41, 75]. Economic analysis has also shown positive results regarding dapagliflozin treatment for high-risk individuals with T2DM, based on outcomes from the DECLARE-TIMI 58 trial [76].

A recent study examining the cost of CKD in T2DM showed that, although the cost per person was especially high in those with advanced stages of CKD, direct healthcare expenditure was greatest during the initial phases of kidney disease due to the large number of individuals with T2DM in this group [77]. The study authors concluded that the economic impact of CKD in T2DM could be alleviated by timely and comprehensive approaches to management [77]. Some clinicians have stated the case for earlier use of SGLT2is and other newer glucose-lowering therapies in the T2DM treatment pathway, with the aim of delaying or avoiding CV or renal complications, reducing associated costs and improving long-term QoL for people with T2DM [78, 79]. The KDIGO guidelines reflect this approach, recommending SGLT2i use alongside metformin from the start of treatment in people with diabetes and CKD [43].

Real-world evidence is a critical tool in understanding the true value of pharmacological interventions within healthcare systems, providing additional insights concerning QoL measures, pharmacovigilance data, psychosocial factors, healthcare resource utilisation and treatment adherence and persistence. The Improving Diabetes Steering Committee strongly supports and encourages the use of T2DM registries and local audits to capture these data so that they can inform future economic models and clinical guidelines in T2DM management. The evidence base in this area is already rapidly expanding. The Manchester Community Diabetes Education and Support (CoDES) pilot provides an excellent example of a local project with the potential to influence best practice on a wider scale, due to the efficiencies and improvements in provision of care that were achieved [80]. The pilot demonstrated the benefits of holistic approaches to T2DM management in primary care, with integration of secondary and community care services and prescribing of cardio-protective medicines [80]. Financial modelling was included to understand the potential savings associated with a reduced requirement for specialist referrals and achievement of Quality Outcomes Framework (QOF) targets [80]. Retrospective analyses of real-world SGLT2i data conducted by clinicians in Italy have revealed early improvements in albuminuria, compared with other glucose-lowering therapies, and reductions in the composite endpoint of HbA1c, body weight and systolic blood pressure, versus DPP-4is [81–83]. In addition, SGLT2i use was associated with improved cardiorenal outcomes and reduced all-cause mortality, compared with DPP-4is [81]. Real-world data from the CVD-REAL Catalonia study (including 25,834 people with T2DM) demonstrated that SGLT2i use was associated with a lower risk of HF, all-cause mortality, modified MACE (all-cause mortality, myocardial infarction or stroke) and CKD compared with other glucose-lowering treatments ($P < 0.001$ for each outcome) [84].

Real-world models and examples that illustrate the value of newer T2DM treatments will become increasingly important as we move through the era of the COVID-19 pandemic, in

which HCPs are facing additional financial constraints imposed by payers within healthcare systems. HCPs may therefore feel resistant to the prescribing of medicines that are perceived to be more expensive than traditional therapies. Rebuilding services after COVID-19 will require a huge investment of HCP time, money and resources. However, those able to take a long-term view will understand that an investment in SGLT2i therapies is likely to reduce the overall expenditure required for the downstream management of the CV and renal complications of T2DM and relieve some of the associated financial burden.

REBUILDING TYPE 2 DIABETES CARE IN THE ERA OF COVID-19

Those involved in managing T2DM have met with many challenges during the COVID-19 pandemic due to cancelled face-to-face clinics and reduced access to health services across primary and secondary care. While HCPs continue to adapt to newer ways of interacting with patients under their care, the agile approach demonstrated by healthcare services and practitioners during the pandemic has seen services embrace the adoption of smarter approaches to care through the use of tools such as virtual technologies and telemedicine (e.g. telephone consultations).

The pandemic has had a varying impact on T2DM management, with outcomes influenced by local rates of infection and the ability of services to continue running during each of the lockdowns. Many people are likely to have ceased their T2DM medications due to periods of acute illness during the pandemic, and there may have been some hesitancy among HCPs in restarting treatments once individuals had recovered. It is important that people with diabetes re-establish their therapeutic regimen as soon as possible to ensure that they maintain good blood glucose control and manage their risk of complications. Studies are ongoing regarding the links between T2DM and the severity of COVID-19 disease, with some data suggesting that people with poorly controlled HbA1c may be at greater risk of adverse

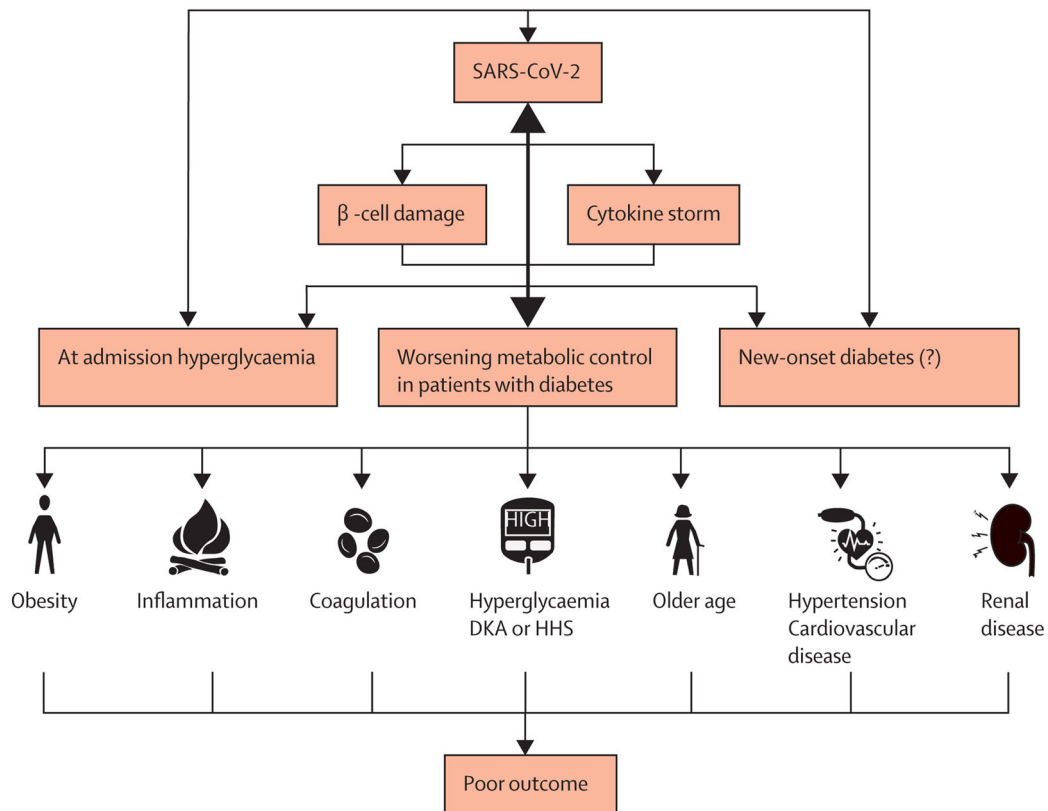


Fig. 2 Synopsis of the reciprocal effects of diabetes and COVID-19 [88]. The relationship between diabetes and COVID-19 is biunivocal. On one hand, people with diabetes have worse outcomes because of multiple associated conditions enhancing the risk. On the other hand, SARS-CoV-2, because of its tropism for the beta-cell, might cause new-onset diabetes or sustain hyperglycaemia at hospital admission. The impairment of beta-cell function along with the inflammatory cytokine storm

and counter-regulatory hormonal responses can precipitate further acute metabolic complications (DKA or HHS). New-onset diabetes, hyperglycaemia at admission, and acute metabolic deterioration, in turn, can further worsen COVID-19 outcomes. *DKA* Diabetic ketoacidosis, *HHS* hyperglycaemic hyperosmolar syndrome, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2. Reproduced with permission from Apicella et al. [88]

outcomes when hospitalised with COVID-19 infection, and elevated levels of systemic inflammation have been implicated in the underlying mechanisms of disease [85–89]. A reciprocal model has been proposed (Fig. 2) that links poor glycaemic control with associated inflammation, hypertension, CVD and other risk factors that increase the risk of progressive and severe COVID-19 infection [88]. Likewise, factors associated with severe COVID-19 disease may raise the risk of developing T2DM [88]. Biochemical stress due to infection could result in insulin resistance and insulin deficiency (caused by beta-cell damage), increasing the

likelihood of T2DM onset [88]. This disease model emphasises the need for well-managed blood glucose in people with T2DM and for interventions that lower the incidence of risk factors, such as having overweight/obesity, which are linked to poor COVID-19 outcomes and adverse CV events [88].

Most people with T2DM are unlikely to experience severe COVID-19, but considerations should be in place for people with diabetes who contract the coronavirus. Better understanding is required of the pharmacological interventions with the potential to affect/improve outcomes for people with T2DM and

COVID-19 as retrospective studies suggest that mortality may be reduced for individuals treated with metformin, SGLT2is and GLP-1 RAs [90]. In an RCT (the DARE-19 trial), dapagliflozin showed numerical reductions in CV and renal events for people with COVID-19 with/without T2DM, although the difference was not significant [90]. This is a developing area of research, and more RCTs are needed to understand this phenomenon fully. In the meantime, it is recommended that people with T2DM who experience periods of acute dehydrating illness (due to COVID-19 or other conditions) follow the sick day guidance outlined by the ABCD and Diabetes UK [44, 92–96]. The guidance recommends that relevant treatments (including SGLT2is) are ceased while the individual is unwell and should be restarted once the person is able to eat and drink normally [44, 92–96]. Practical recommendations for the management of T2DM in people with COVID-19 have been published by various groups, including an international panel of experts in the field of diabetes and endocrinology and the Spanish Endocrinology Society [97, 98]. Diabetes UK has also developed a position statement to support HCPs and people living with diabetes during the COVID-19 pandemic, which includes advice on delivery of remote healthcare services [99]. This is particularly relevant as 49% of people surveyed by Diabetes UK did not have contact with their HCP during the pandemic [99]. Uptake of vaccinations against COVID-19 should improve the prognosis for people with T2DM who catch the virus. However, issues within healthcare systems relating to suboptimal outpatient care are likely to persist for some time and it will be necessary to establish practical strategies to improve disease outcomes and provide durable expenditure reductions. Within such a scenario, proper prescribing of medicines that may ensure good glycaemic control and provide cardiorenal protection should be encouraged in the attempt to enhance cost-effectiveness of treatment of people with Type 2 diabetes.

PRACTICALITIES OF PRESCRIBING SGLT2I TREATMENTS

The long-term management of T2DM and its associated complications/comorbidities represents a complex and challenging issue for clinicians, particularly in primary care where many practices are working to re-establish services after the initial impact of the coronavirus pandemic. HCPs with numerous competing priorities receive a continuous flow of prescribing and safety updates from international medicine regulators. In addition, local prescribing groups and committees will send regular updates on formulary decisions. There is pressure from payors to minimise disease management costs and HCPs must keep abreast of ongoing changes to clinical guidance from international and national bodies (e.g. International Diabetes Federation, NICE, Scottish Medicines Consortium) as well as relevant professional organisations (e.g. ABCD/UKKA, KDIGO, ADA, EASD). Although HCPs welcome data to support evidence-based prescribing, the volume of information emerging in the field of T2DM is vast and difficult to seamlessly apply in daily practice alongside existing clinical protocols.

As already discussed, the ever-expanding evidence base for SGLT2i treatments has resulted in changes to the licensed indications for some of the approved drugs in this class [59–61, 100]. The Improving Diabetes Steering Committee recommends that SGLT2i prescribing in T2DM should be implemented in accordance with the current ADA/EASD guidelines, which were developed in the context of the latest evidence [42]. The Steering Committee developed the ‘SGLT2i Prescribing Tool for T2DM Management’ in 2018 to support HCPs in the appropriate use of SGLT2is, and the Tool has been updated over subsequent years in line with the evolving evidence base. The latest version of the ‘SGLT2i Prescribing Tool for T2DM Management’ is provided in the Electronic Supplementary Material section of this paper and replaces those versions previously published [1–3]. In addition to the traffic light system, indicating the clinical situations in which SGLT2i therapy should be offered,

Category	Clinical situation
SGLT2i therapy should be offered	First-line (metformin intolerant)
	Second-line to metformin or third-line as add-on to other second-line therapies, including in combination with GLP-1 RA and insulin
	Established CVD
	History of HF
	Overweight or obesity
	Prior stroke
	Vulnerable to the effects of hypoglycaemia
	Renal impairment/CKD/DKD
	No history of lower limb amputation
	No history of PAD
	Receiving loop diuretics
	Osteoporosis
SGLT2i therapy can be considered	History of fractures
	Frail/elderly/cognitive impairment
	History of PAD
	History of foot ulceration
	Previous lower limb amputation
	Existing diabetic foot ulcers
	Ketogenic/low calorie/low carbohydrate diet
	BMI <25 kg/m ²
	High HbA1c levels (>86 mmol/mol or 10%)
	Recurrent UTIs
	Recurrent genital mycotic infections
	Receiving systemic steroid therapy
SGLT2i therapy should not be prescribed	Acute illness
	DKA (or previous episode of DKA)
	Excessive alcohol intake
	Eating disorders
	Rapid progression to insulin (within 1 year)
	Multiple pre-disposing risks for Fournier's gangrene
	Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding
	Recent major surgery

Fig. 3 A brief guide to SGLT2i prescribing in T2DM [4–36, 39–44, 59–61, 94, 95, 100]. The traffic light system indicates the appropriate approach for people with T2DM in each situation: green indicates when SGLT2i therapy should be offered; amber situations are when SGLT2i therapy can be considered; and SGLT2i therapy should not be prescribed for people within the red category. The full SGLT2i Prescribing Tool is provided in the Electronic Supplementary Material section. *BMI* body mass index,

CKD chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular diseases, *DKD* diabetic kidney disease, *eGFR* estimated glomerular filtration rate, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *LADA* latent autoimmune diabetes in adults, *PAD* peripheral arterial disease, *SGLT2i* sodium glucose cotransporter-2 inhibitor, *SmPC* summary of product characteristics, *T2DM* Type 2 diabetes mellitus, *UTIs* urinary tract infections

considered or avoided for people with T2DM, a series of clinical summaries has been provided to give further explanation and support for

prescribers. A brief overview of the situations included in the full Prescribing Tool are shown in Fig. 3. Prescribing of SGLT2i therapies must

be within the licensed indication for each drug and the relevant summary of product characteristics (SmPC) should be consulted accordingly [59–61, 100]. The key themes covered in the ‘SGLT2i Prescribing Tool for T2DM Management’ include sick day guidance, practical advice on the management of DKA risk, use of SGLT2i therapies in people with T2DM and renal disease, drug–drug interactions (DDIs), genital and urinary infections, foot disease, Fournier’s gangrene, frailty and declining cognitive function, varying body mass index (BMI) and duration of T2DM, and dietary implications (e.g. low-calorie diets, eating disorders). These themes are also outlined below in further detail.

People with Type 2 Diabetes Who are Most Likely to Benefit from SGLT2i Therapy

The ADA/EASD and ABCD/UKKA recommend the use of SGLT2is as second-line therapy to metformin (or first-line therapy in cases of intolerance to metformin) in adults with T2DM, while KDIGO guidelines recommend that people with T2DM and CKD are treated with metformin and an SGLT2i from the outset [42–44, 94]. Benefit may be gained from SGLT2i use among people with established CVD or high CV risk, CKD with albuminuria or high renal risk, a history of HF, inadequate glycaemic control with a need to minimise hypoglycaemia or inadequate glycaemic control with need to minimise weight gain/encourage weight loss [42–44, 94]. The decision to use an SGLT2i therapy with the aim of reducing MACE, HHF or progression of CKD should be made independently of baseline or target HbA1c [42–44, 94].

General Advice on SGLT2i Use During Periods of Acute Illness

Sick day guidance was developed to help people in managing their diabetes during intercurrent illness [92–96]. Throughout periods of acute illness (whether it is COVID-19 or any other illness), maintenance of glycaemic control can be challenging, and people with T2DM will be at increased risk of acute DKA and acute metabolic decompensation (i.e. hyperosmolar

hyperglycaemic state) resulting from a reduced intake of food and liquids and the physiological mechanisms that come in to play while the body is fighting an infection (e.g. hormonal response, inflammation) [92, 95, 96]. DKA is discussed in further detail below in the context of SGLT2i treatments. People with T2DM should be advised about sick day guidance, be informed of how to recognise the signs and symptoms of DKA, have access to glucose and/or ketone testing (where appropriate) and understand when to seek assistance [92, 95, 96]. Individuals should aim to stay well hydrated and maintain their carbohydrate intake when they are unwell and should seek medical assistance if vomiting is persistent or they are unable to eat for a prolonged duration [92, 96].

The ‘SADMANS’ medication list (Box 1) has been widely adopted as an aid in identifying the medicines that should be suspended during intercurrent illness to reduce the risk of kidney function decline and other adverse events [90–93]. Treatment should be re-started within 24 h, once eating and drinking has returned to normal so that glycaemic control can be optimised once more.

Box 1 SADMANS medication list [92–95]

S sulphonylureas
A ACE inhibitors
D diuretics, direct renin inhibitors
M metformin
A angiotensin receptor blockers
N nonsteroidal anti-inflammatory
S SGLT2i therapies
ACE Angiotensinogen converting enzyme

Diabetic Ketoacidosis in People with T2DM

Although usually undetectable in blood (< 0.6 mmol/L) and urine (negative on urine dipsticks), ketone levels can be increased with SGLT2i treatments because energy metabolism is switched from carbohydrate to lipid utilisation [94, 99]. During periods of acute illness, stress hormone levels rise, causing increased risk of insulin resistance. When this occurs in

combination with reduced endogenous insulin secretion, a state of relative insulin deficiency results that leads to free fatty acid breakdown and ketosis occurs [96, 101]. In a separate process, SGLT2is cause glycosuria and, therefore, continue to reduce plasma glucose concentration, which can lead to a state of normal glucose and raised ketones with acidosis, termed “euglycaemic DKA” [101]. Another theory suggests that rising sodium concentrations within the renal tubular fluid, due to reduced sodium reabsorption with SGLT2 inhibition, leads to an increased positive electrical charge within the tubular lumen and an influx of negatively charged ketone bodies. As a result, urinary ketone clearance will be reduced and plasma ketone levels will rise [101].

DKA is listed as a rare adverse event, affecting approximately 1 in 10,000 people with T2DM taking SGLT2i medications, as shown in CVOTs and renal studies for currently approved SGLT2is [5, 7, 11, 15, 22, 23, 102]. Low absolute incidence of DKA was reported in the canagliflozin CANVAS and CREDENCE studies, no imbalance was demonstrated for DKA episodes in the VERTIS CV trial (ertugliflozin), three episodes of DKA were reported in the dapagliflozin arms of the DAPA-HF study, two cases of ketoacidosis were reported in the placebo arm during the DAPA-CKD study and none were seen in either treatment arm for the EMPEROR-Reduced (empagliflozin) or DAPA-CKD (dapagliflozin) trials [5, 7, 11, 15, 22, 23, 102].

If DKA is suspected, HCPs should check ketone levels [96]. As recommended by the European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) and ABCD/UKKA, HCPs and people with T2DM should be aware of the key symptoms for DKA, which include in this setting nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet/metallic taste in the mouth or a different odour to urine or sweat [44, 96, 102]. While ketone monitoring may be variable (or absent) across practices, some people with T2DM may be given dipsticks to allow them to check their ketone levels at home. If DKA is suspected, blood ketone testing would ideally be used to

confirm (> 1.6 mmol/L) or exclude DKA [42, 96]. However, where blood ketone diagnostics are not readily available, HCPs and people with diabetes must be vigilant for the main signs of DKA so that urgent hospital admission can be implemented where DKA is suspected [96]. Groups that should not be treated with an SGLT2i due to DKA risk include those with T2DM with pancreatic dysfunction and Type 3c diabetes or previous DKA. For patients with Type 1 diabetes, only dapagliflozin 5 mg was previously approved, but has recently been withdrawn, due in part to ongoing concerns about risk of DKA [61]. Detailed discussion of SGLT2i use in Type 1 diabetes is beyond the scope of this review.

Monitoring of Kidney Function and Use of SGLT2i Therapies in People with Renal Dysfunction

The accumulation of robust data relating to the cardiorenal effects of SGLT2i treatments has resulted in the broadening of licensed indications for two of the currently available therapies, beyond the treatment of hyperglycaemia, to include people with reduced kidney function [59–61, 100]. Box 2 provides a summary of the current indications for people with impaired kidney function in the case of each approved SGLT2i therapy in Europe (N.B. the information provided is correct at the time of publication). The relevant product SmPC should be consulted before initiating therapy [59–61, 100]. Although SGLT2i treatments provide positive cardiorenal effects for people at high risk of HF and DKD, the glucose-lowering effect will be diminished in people with reduced kidney function due to their mechanism of action [59–61]. Local prescribing information should be reviewed to ensure that the appropriate dosage is given for people with T2DM and CKD [59–61]. Additional therapies may be required for people with T2DM and renal impairment in need of additional glycaemic control [59–61].

BOX 2

Licensed indications according to eGFR for SGLT2i therapies when used as glucose-lowering therapies in people with T2DM^a [59–61,100]

Please consult the individual SmPC or local prescribing information for dosing recommendations and specific indications before prescribing SGLT2i therapies.

Due to SGLT2i mechanism of action, glucose-lowering efficacy is inversely proportional to the degree of renal impairment. This becomes clinically relevant when the eGFR falls below 45–60 mL/min/1.73 m² and may be absent in those with severe renal impairment. However, the renoprotective effects of SGLT2is remain, even in the absence of glucose-lowering effect.

SGLT2i therapy	CKD stage (eGFR)				
	G1–G2 ≥60 mL/min/1.73 m ²	G3a 45–59 mL/min/1.73 m ²	G3b 30–44 mL/min/1.73 m ²	G4 15–30 mL/min/1.73 m ²	G5 <15 mL/min/1.73 m ²
Dapagliflozin	May be initiated and continued in people with an eGFR ≥15 mL/min/1.73 m ²				Do not initiate in people with eGFR <15 mL/min/1.73 m ²
Canagliflozin	May be initiated in people with eGFR ≥30 mL/min/1.73 m ²			Ongoing treatment can be continued until RRT/dialysis in patients with ACR >30 mg/mmol (>300 mg/g)	
				Do not initiate in people with eGFR <30 mL/min/1.73 m ²	
Empagliflozin	Therapy can be initiated in people with eGFR ≥60 mL/min/1.73 m ²	Ongoing empagliflozin (10 mg) treatment can be continued in people with eGFR ≥45 mL/min/1.73 m ²	Cease treatment if eGFR is persistently <45 mL/min/1.73 m ²		
Ertugliflozin	Ertugliflozin may be initiated in people with eGFR ≥60 mL/min/1.73 m ²	Ongoing ertugliflozin treatment can be continued when eGFR 45–60 mL/min/1.73 m ²	Discontinue ertugliflozin treatment when eGFR is persistently <45 mL/min/1.73 m ²		

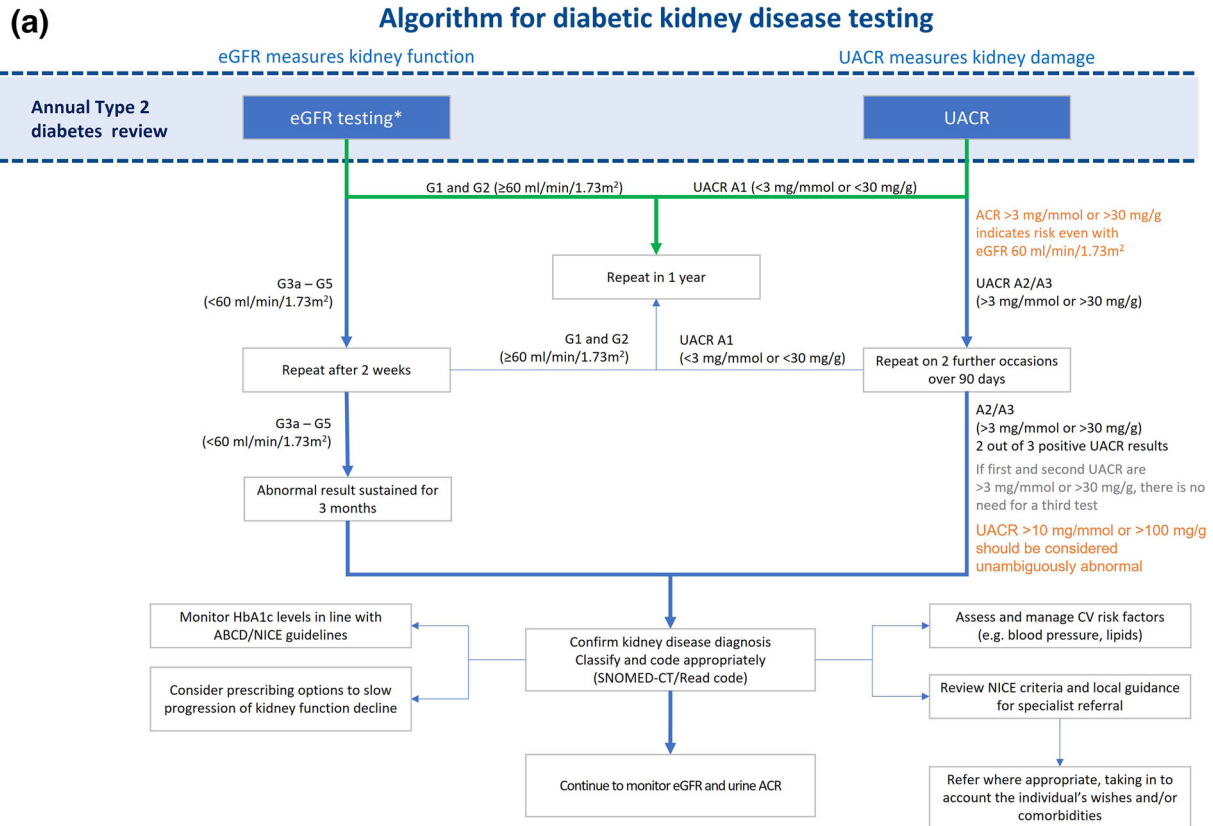
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; T2DM, Type 2 diabetes mellitus.

^aThe renal indications provided were correct at the time of publication. Each SmPC was consulted ahead of publication on 16th December 2021.

Monitoring of kidney function is usually recommended prior to initiating SGLT2i therapy and periodically during treatment [59–61, 100]. It is usual to see an initial acute reduction in estimated glomerular filtration rate (eGFR) at the start of SGLT2i treatment, which is typically followed by an overall slowing in the decline of eGFR over time and a reduction in other markers of kidney function deterioration [5, 26–29]. In most cases (> 98%), the dip in eGFR will be < 30% and the renal or CV prognosis will not worsen [5, 26–28, 103]. ABCD/UKKA recommend against early testing of kidney function following SGLT2i initiation on the

basis that withdrawal of the therapy due to an initial decline in eGFR is inappropriate [44, 46].

The algorithm for DKD testing developed by Winocour et al. [105] (adapted in Fig. 4) was based on NICE and KDIGO recommendations and provides a useful reference regarding the appropriate frequency of eGFR and urine albumin to creatinine ratio (UACR) monitoring [43, 104, 105]. NICE and KDIGO recommend that baseline eGFR and UACR should be recorded and then eGFR monitored at least annually, or more frequently if eGFR falls below 30 mL/min/1.73 m² [3, 43, 104, 105]. ADA guidelines recommend that patients with diabetes and urinary albumin > 30 mg/mmol creatinine



(b)

eGFR ml/min/1.73m ²	Albuminuria categories Albumin : Creatinine ratio spot urine		
	A1 <3 mg/mmol <30 mg/g	A2 3–30 mg/mmol 3–300 mg/g	A3 >30 mg/mmol >300 mg/g
G1 ≥ 90	≤ 1	1	≥ 1
G2 60–89	≤ 1	1	≥ 1
G3a 45–59	1	1	2
G3b 30–44	≤ 2	2	≥ 2
G4 15–29	2	2	3
G5 <15	4	≥ 4	≥ 4

Fig. 4 Diagnostic monitoring for CKD/DKD in people with T2DM. **a** Algorithm for DKD testing, **b** frequency of monitoring per year by eGFR and adverse risk category for people with (or at risk of) CKD [43, 104, 105]. *ABCD* Association of British Clinical Diabetologists, *AKI* acute kidney injury, *NICE* National Institute for Health and

Care Excellence, *UACR* urine albumin:creatinine ratio. Adapted from Winocour et al. [105] (<https://diabetesonthenet.com/diabetes-primary-care/testing-for-kidney-disease-in-type-2-diabetes-consensus-statement-and-recommendations/>)

and/or an eGFR of 30–60 mL/min/1.73 m² should be monitored twice annually to guide therapy [42]. As eGFR and UACR are each independent risk factors for adverse outcomes and mortality, the Winocour et al. algorithm suggests that both should be monitored at least annually and more regularly in cases where UACR is > 30 mg/mmol (300 mg/g) and eGFR < 45 mL/min/1.73 m² [105]. Acute kidney injury is not a concern for SGLT2i therapies [22, 27, 28, 32, 106].

Drug–Drug Interactions and Use of Loop Diuretics Alongside SGLT2i Therapies

SGLT2i therapies can be prescribed alongside other commonly prescribed medications in T2DM management with no clinically relevant interactions expected [59–61, 100]. However, the label for each of the approved SGLT2i therapies advises caution and monitoring of volume status when prescribing in combination with diuretic medicines due to potential dehydrating and hypotensive effects [59–61, 100]. It is therefore important to check the individual SmPC before prescribing SGLT2i treatments alongside diuretics. People initiating SGLT2i therapy should be encouraged to drink plenty to maintain hydration and lower the risk of hypotension, with closer monitoring used for elderly individuals or those at risk of falls.

Large-scale RCTs and real-world studies examining SGLT2i medicines in people with T2DM and high CV or renal risk included people taking loop diuretics and thiazide diuretics [4–6, 27, 94, 107, 108]. In the CANVAS Program, individuals taking diuretic therapy at baseline showed a greater relative risk reduction for MACE with canagliflozin treatment compared with those not on baseline diuretics with no increase in renal or other adverse events [108]. Likewise, the CVD-REAL study showed that the rate of renal function decline was slowed with SGLT2i treatments, regardless of whether loop diuretics were co-administered [28].

The dosage of insulin or insulin secretagogues (e.g. SU therapies) should be initially lowered for individuals starting SGLT2i therapy

to reduce the risk of hypoglycaemia [59–61, 100].

Genital and Urinary Infections

Genital mycotic infections and urinary tract infections (UTIs) may occur with SGLT2i treatment, particularly during the initial stages of treatment [94]. Women and individuals with previous genital mycotic infections are at higher risk of developing genital fungal infections with SGLT2i therapy [59–61, 100]. Genital infections following SGLT2i initiation are typically mild to moderate in nature and respond well to the conventional therapy, usually one single dose of oral fluconazole [94]. The appearance of genital candidiasis does not imply the withdrawal of SGLT2i treatment. Analysis of real-world data and meta-analysis of safety data from randomised trials did not suggest an increased risk of harm with SGLT2i inhibitors over placebo or active comparators with respect to UTIs [106, 109, 110]. Genital infections and UTIs should be treated with antifungals or antibiotics, respectively, with advice on hydration as well as hygiene given. SGLT2is should be stopped if infections are recurrent [44]. Urinary frequency/urgency may be increased with SGLT2i therapy [59–61, 100].

Fournier's Gangrene

Fournier's gangrene (necrotising fasciitis of the perineum) is a rare adverse event [111, 112]. In 2019, the UK Medicines and Healthcare products Regulatory Agency (MHRA) estimated that experience with SGLT2i treatment in the UK had accumulated to reach 548,565 patient-years, with just six yellow card reports relating to Fournier's gangrene [44, 111]. Predisposing conditions for Fournier's gangrene include diabetes and associated comorbidities, such as obesity, CKD and congestive HF [112]. Among the 17,160 people included in the DECLARE-TIMI 58 trial, five incidents of Fournier's gangrene were reported in the placebo group and one in the dapagliflozin group [6]. One case was reported in the empagliflozin arm of the EMPEROR-reduced study, which included 5988

participants [10, 113]. Patients treated with SGLT2is should be made aware of this very rare but serious infection and advised to seek urgent medical attention if they experience severe pain, tenderness, worsening redness or swelling in the genital or perineal area [44, 111].

Foot Disease and Lower Limb Amputations

Among the numerous RCTs and real-world studies examining the efficacy and safety of SGLT2i therapies, excess amputations were reported in one randomised trial and low incidence has been shown across all published RCTs (0–2 additional events per 1000 person-years) [4–6, 22]. Current ADA/EASD guidelines recommend that the relative risks should be discussed fully with people who have active foot disease or those at elevated risk for amputation, with the decision to prescribe an SGLT2i therapy being shared between the clinician and individual with T2DM [42]. People with T2DM, including those treated with SGLT2is, must be educated regarding preventative foot care, and comprehensive checks should be conducted regularly. The individual must contact their HCP promptly in cases where wounds, discoloration or pain are identified and therapy ceased if significant problems occur (e.g. infection) [42, 44, 94].

Frailty and Declining Cognitive Function

SGLT2i treatments should be used with caution in people who are living with moderate or severe frailty because of increased risk of weight loss favouring sarcopenia, genital candidiasis and UTIs, urinary incontinence, fluid volume depletion and dehydration [114]. Volume depletion can cause hypotension and postural dizziness that increase the chances of experiencing falls and bone fractures [114]. Blood pressure monitoring should be conducted, particularly for those at risk of falls and for people taking diuretic medicines [43]. Advice should be given to the individual and those who care for them regarding the importance of remaining well-hydrated and reporting any symptoms of

dizziness [44, 114]. Research using animal models suggests that SGLT2i therapies may slow the development of Alzheimer's disease; however, further studies are required to fully understand the effects of these treatments in this setting and their influence on the mechanisms of disease [115, 116].

Cases of High Blood Glucose Despite Oral Diabetes Medication

In cases where blood glucose remains high, despite therapy, the person's clinical history should be checked to establish whether an underlying undiagnosed condition that is also associated with hyperglycaemia is likely (e.g. inflammatory disease) and requirement for insulin replacement therapy should be evaluated. Assessment of BMI should be conducted and any signs of recent weight loss noted. Individuals may also require assessment for latent autoimmune diabetes in adults (LADA) via testing for antibodies against glutamic acid decarboxylase antibodies (GADA) and possibly islet antigen 2 (IA2) and zinc transporter 8 (ZnT8) [117].

People with T2DM who have progressed to the stage of requiring insulin therapy and/or insulin secretagogues may have to reduce the dosage of these medicines when initiating SGLT2i therapy to reduce the risk of hypoglycaemia and should be guided by their HCP [44, 94]. If insulin requirement reduces significantly over time with SGLT2i therapy, monitoring for DKA should be implemented (testing for urinary and/or blood ketones, where diagnostics are available) [42].

Dietary Implications

Individuals with T2DM taking SGLT2i medication who restrict their food or fluid intake for any reason will risk becoming severely dehydrated and being at greater risk of developing ketoacidosis [42]. When an individual is unable to eat or drink regularly due to illness, they should cease their SGLT2i medication until they are able to take food and fluids normally again [42, 92, 95]. People on low carbohydrate, very

low calorie or ketogenic diets should not be selected for SGLT2i treatment due to their increased risk of developing ketoacidosis [44]. Similarly, SGLT2i therapy is not recommended for people living with T2DM and a co-morbid eating disorder (e.g. anorexia nervosa) or elderly people with unreliable eating patterns. Individuals with T2DM who choose to follow an intermittent fasting diet (e.g. 5:2 diet) must have their diabetes regimen reviewed, with therapies such as SGLT2is stopped or their dosage reduced on fasting days. As highlighted above, people with T2DM must be educated regarding the key signs and symptoms of DKA and understand when they should seek urgent medical advice/assistance [44, 96].

CONCLUSION

As the prevalence of T2DM continues to increase alongside the enduring global obesity epidemic, HCPs are faced with increasing numbers of people who have associated CV and renal risk factors or established disease. Interruptions to the provision and continuity of care caused by the ongoing COVID-19 pandemic have increased pressure on already overstretched services. As a result, access to effective treatment options that help to avoid serious, costly and debilitating cardiorenal events are a higher priority than ever. The abundance of evidence supporting the protective cardiorenal effects of SGLT2i therapies has driven a shift in perceptions among the clinical community regarding their value in treating high-risk T2DM populations, and the newly revised therapeutic indications for the available SGLT2is reflect their efficacy within these settings. By addressing the practicalities of SGLT2i prescribing in clinical practice in this article and through the provision of the newly created the 'SGLT2i Prescribing Tool for T2DM Management', the Improving Diabetes Steering Committee hopes to support HCPs in advancing their understanding regarding the appropriate place of SGLT2i treatments within the T2DM treatment pathway with the aim of improving patient care.

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