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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SGLT2i Prescribing Tool for Type 2 Diabetes Mellitus Management

The Prescribing Tool is designed to guide appropriate SGLT2i treatment in people diagnosed with T2DM. Further information regarding SGLT2i use in each of the clinical situations listed below can be found in the clinical summaries shown on pages 2–4. Please refer to the relevant individual SmPC before prescribing any SGLT2i therapy.

Category	Clinical situation	Relevant clinical summary [1–23]
SGLT2i therapy should be offered	First-line (metformin intolerant)	Box A: ADA/EASD and ABCD recommendations for SGLT2i therapy prescribing
	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	Box A: ADA/EASD and ABCD recommendations for SGLT2i therapy prescribing Box C: Renal disease, eGFR and reduced glucose-lowering (please review individual SmPC before prescribing)
	No history of lower limb amputation	Box H: Foot disease (limb ischaemia or ulceration)
	No history of PAD	
	Receiving loop diuretics	Box G: Drug-drug interactions (not recommended for all agents – please review individual SmPC before prescribing)
	Osteoporosis	Box I: Age/frailty/dementia Box H: Foot disease (limb ischaemia or ulceration)
	History of fractures	
SGLT2i therapy can be considered	Frail/elderly/cognitive impairment	Box I: Age/frailty/dementia
	History of PAD	Box H: Foot disease (limb ischaemia or ulceration)
	History of foot ulceration	
	Previous lower limb amputation	
	Existing diabetic foot ulcers	
	Ketogenic/low calorie/low carbohydrate diet	Box E: Diets and eating disorders Box D: Diabetic ketoacidosis
	BMI <25 kg/m^2	Box D: Diabetic ketoacidosis Box E: Diets and eating disorders Box J: High blood glucose levels despite oral diabetes medication
	High HbA1c levels (>86 mmol/mol or 10%)	Box D: Diabetic ketoacidosis Box J: High blood glucose levels despite oral diabetes medication
	Recurrent UTIs	Box F: Genital and urinary infections
	Recurrent genital mycotic infections	
	Receiving systemic steroid therapy	Box D: Diabetic ketoacidosis
SGLT2i therapy should not be prescribed	Acute illness	Box B: Sick day guidance Box D: Diabetic ketoacidosis
	DKA (or previous episode of DKA)	Box D: Diabetic ketoacidosis
	Excessive alcohol intake	
	Eating disorders	Box E: Diets and eating disorders Box D: Diabetic ketoacidosis
	Rapid progression to insulin (within 1 year)	Box J: High blood glucose levels despite oral diabetes medication Box D: Diabetic ketoacidosis
	Multiple pre-disposing risks for Fournier's gangrene	Box F: Genital and urinary infections
	Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding	Outside of licensed indication
	Recent major surgery	

Abbreviations:
ABCD, Association of British Clinical Diabetologists; ADA, American Diabetes Association; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; PAD, peripheral arterial disease; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; T2DM, Type 2 diabetes mellitus; UTIs, urinary tract infections

Considerations for Prescribing SGLT2i Therapy in Type 2 Diabetes Mellitus

The clinical summaries provided in boxes A–J aim to offer practical advice for healthcare professionals when prescribing SGLT2i therapies for the treatment of T2DM. Please refer to the relevant individual SmPC before prescribing any SGLT2i therapy.

Box A: ADA/EASD and ABCD recommendations for SGLT2i therapy prescribing [1–3]

- The latest ADA Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022 can be accessed online at: https://diabetesjournals.org/care/article/45/Supplement_1/S125/138908/9-Pharmacologic-Approaches-to-Glycemic-Treatment
- SGLT2i therapies are recommended as second-line therapy for adults with T2DM, after metformin, or first-line in cases of intolerance to metformin
- SGLT2is may be prescribed in combination with other glucose-lowering therapies, including GLP-1 RAs and insulin
- The decision to prescribe an SGLT2i therapy should be made independently of the baseline or target HbA1c for high-risk individuals with established T2DM in cases where the aim of treatment is to reduce MACE, HHF, CV mortality or CKD progression

T2DM populations most likely to benefit from SGLT2i prescribing:

- Established CVD or high CV risk
- CKD with albuminuria or high renal risk
- History of HF
- Inadequate glycaemic control with a need to minimise hypoglycaemia
- Inadequate glycaemic control and a requirement for weight loss or minimisation of weight gain

Box B: Sick day guidance [1–6]

Sick day guidance should be followed when a person with diabetes is suffering from an acute dehydrating illness or is unable to eat and/or drink normally. The guidance is intended for people taking oral T2DM therapies and insulins, with the aim of reducing the risk of DKA and blood glucose fluctuation during periods of illness. Advice should be given on what constitutes a 'sick day', with clear explanation of when and why specific medications should be paused. Access to glucose and ketone testing should be offered to individuals where this is deemed necessary.

Guidance should include:

- During periods of acute illness, blood glucose levels should be monitored and medical assistance must be sought if levels are persistently high or low
- If the person is vomiting, the following medications should be temporarily stopped (the SADMANS mnemonic may be a helpful reminder):
  - SGLT2is, ACEis, Diuretics, Metformin, ARBs, NSAIDs and SUs
- Maintain normal hydration and food, where possible
- Check for urinary ketones:
  - If a dipstick test shows ketones to be moderate (or above) or blood tests show that levels are >3 mmol/mol, (where blood ketone testing is available) immediate attendance at the Emergency Department is required
- Once vomiting has ceased or the individual is feeling better, oral medications can be restarted

Box C: Renal disease, eGFR and reduced glucose-lowering [7–13]

Some SGLT2is have shown cardiorenal benefits independent of their glucose lowering effect and have been granted extended licenses specifically for these indications (please refer to the individual SmPC for prescribing guidance).

- eGFR should be checked before starting therapy, with ongoing monitoring implemented according to CKD stage
- A reversible reduction in eGFR of up to 30% may occur when initiating therapy, which will usually stabilise with time and should not be a cause for concern as overall decline in eGFR will be slowed with ongoing treatment
- No additional eGFR monitoring is required unless the person is unwell or it is otherwise indicated (e.g. starting another therapy likely to impact on kidney function)
- Due to SGLT2i mechanism of action, glucose-lowering efficacy is inversely proportional to the degree of renal impairment. Therefore, the glucose lowering effect will be reduced when the eGFR falls <45 mL/min/1.73 m^2 and may be absent in those with severe renal impairment

Please refer to the relevant individual SmPC before prescribing any SGLT2i therapy.

Box D: Diabetic ketoacidosis [1–3,6,10–13]

DKA is a rare but serious complication that can occur in people treated with SGLT2is. Clinicians should be aware of the signs of DKA and the people who may be considered at greatest risk.

- SGLT2i therapies reduce insulin secretion and shift energy metabolism toward lipid oxidation, which can cause DKA during intercurrent illness as stress hormones increase insulin resistance and reduced oral intake can lead to starvation ketosis or increased ketone concentration (due to dehydration)
- Euglycaemic DKA (normal glucose and raised ketones) can occur in an insulin resistant individual when taking an SGLT2i therapy
- Key signs of DKA include excessive thirst, polyuria, dehydration, shortness of breath, abdominal pain, leg cramps, nausea and vomiting, mental confusion and drowsiness, ketones on the person's breath (pear-drop smell), ketones in the blood or urine
- Groups that should not be treated with an SGLT2i include those with T2DM and age-related pancreatic dysfunction and Type 3c diabetes or previous DKA. Dapagliflozin (5 mg) is the only SGLT2i currently approved for use in people with Type 1 diabetes
- Clear sick day guidance should be provided for people with T2DM (verbal and written format) with SGLT2i therapy suspended during intercurrent illness
- Individuals should be made aware of the signs and symptoms of DKA and know how/when to seek medical advice from an HCP

Box E: Diets and eating disorders [3,4]

- Conditions leading to restricted food intake or severe dehydration may predispose SGLT2i users to DKA
- Low carbohydrate, very low calorie and ketogenic diets are not recommended for SGLT2i recipients due to an increased risk of DKA
- SGLT2i therapy is not recommended for people living with T2DM and a co-morbid eating disorder (e.g. anorexia nervosa)
- Individuals with T2DM who follow an intermittent fasting diet (e.g. 5:2 diet) require a diabetes therapy review, with some therapies (including SGLT2is) being reduced in dosage or suspended on fasting days
- Please refer to advice on DKA for further information on the risk of DKA secondary to SGLT2i therapy

Box F: Genital and urinary infections [10–13]

SGLT2i therapy may be associated with an increased risk of genital mycotic infections (vulvovaginitis and balanitis) and urinary tract infections (UTIs).

- Infections are more common in women than men and usually occur early in treatment, but generally respond well to standard topical or oral treatments and most people are able to continue taking their SGLT2i therapy
- Glycosuria may cause urinary symptoms, including more frequent voiding
- Mycotic genital infections should be treated with antifungal medications and UTIs managed with standard antibiotics
- The risk of infections is reduced by maintaining good genital hygiene
- Fournier's Gangrene is a very rare but serious soft tissue infection of the genital area. Urgent medical attention should be sought if a person receiving SGLT2i therapy experiences severe pain, tenderness, worsening redness or widespread swelling in the genital or perineal area

Box G: Drug-drug interactions [10–21]

- SGLT2i therapies may be prescribed alongside other commonly used medications for the treatment of T2DM without clinically relevant interactions
- The label for each of the approved SGLT2is advises caution and monitoring of volume status when prescribed in combination with diuretic medicines due to potential dehydrating and hypotensive effects
- Some large-scale SGLT2i RCTs (e.g. CANVAS Program) and real-world studies (e.g. CVD-REAL 2) included people taking diuretics and showed CV and renal events to be reduced/slowed, regardless of diuretic use
- People taking insulin or insulin secretagogues (e.g. SU) should lower the dosage of these medicines initially when starting SGLT2i therapy to reduce the risk of hypoglycaemia

Please refer to the relevant individual SmPC before prescribing any SGLT2i therapy.

Box H: Foot disease (limb ischaemia or ulceration) [10–21]

One SGLT2i trial has demonstrated an imbalance in lower limb amputations (toe amputations). Subsequent SGLT2i trials, systematic reviews and meta-analyses have found no compelling evidence of a significant association with lower limb amputations.

- Those living with diabetic foot disease or peripheral vascular disease have inherently high CV risk and would benefit from therapies proven to reduce CV risk (such as SGLT2is)
- The osmotic diuretic effects of SGLT2i therapies are likely to be beneficial for those with limb-dependent oedema, even with active ulceration. Discussion with the local diabetes foot MDT is warranted if SGLT2is are considered suitable in this situation
- As with all people living with T2DM, SGLT2i users should check their feet regularly, follow preventative care and report any foot infection or ulceration to their HCP

Box I: Age/frailty/dementia [10–13,22]

Glucose-lowering therapies should be prescribed with the individual's age, degree of frailty and cognitive function in mind.

- Age: most SGLT2i therapies do not give specific ages for discontinuation in adults (please refer to the individual SmPC for prescribing guidance relating to age)
- Frailty: CVOTS demonstrated the delayed progression of CKD, HF, MACE, and hypoglycaemia risk (unless used with insulin and or SUs). Moderately or severely frail people may be 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 are important in this group
- Cognitive decline: pre-clinical trials have shown delays in the development of Alzheimer's disease and vascular dementia with SGLT2i therapies, but more robust clinical data are required. When used in individuals with impaired cognitive function, the benefits and challenges of SGLT2i therapies reflect those seen in frail individuals

Box J: High blood glucose levels despite oral diabetes medication [23]

Further clinical investigation is required when a person has persistently raised blood glucose levels, despite being treated with oral glucose-lowering medications, to understand if the cause is due to disease-related complications or whether an alternative diagnosis should be considered.

- Clinical records should be consulted to check the duration of T2DM since diagnosis
- BMI should be checked, with dietary advice and support provided to manage overweight/obesity
- Tests should be conducted to identify whether the person is beta-cell deficient and needs insulin replacement therapy. Insulin resistance may occur in people who have a normal BMI as well as those who have overweight/obesity
- Urinary or blood ketones should be checked (including after food) to identify any signs of DKA
- Assessment for LADA may be appropriate through antibody testing (GADA, IA2 and ZnT8)

Abbreviations:
ABCD, Association of British Clinical Diabetologists; ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; GADA, glutamic acid decarboxylase antibodies; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HCP, healthcare professional; IA2, islet antigen 2; LADA, Latent Autoimmune Diabetes in Adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; NSAIDs, non-steroidal anti-inflammatory drug; RCT, randomised clinical trial; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UTIs, urinary tract infections; ZnT8, zinc transporter 8

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