SGLT2 inhibitors: the new standard of care for cardiovascular, renal and metabolic protection in Type 2 diabetes - narrative review

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DECISION TOOL

Prescribing SGLT2i therapy for Type 2 Diabetes Mellitus Management

The SGLT2i Prescribing Tool has been independently prepared by the Improving Diabetes Steering Committee. A. Menarini Farmaceutica Internazionale SRL has fully funded the creation of this non-promotional document

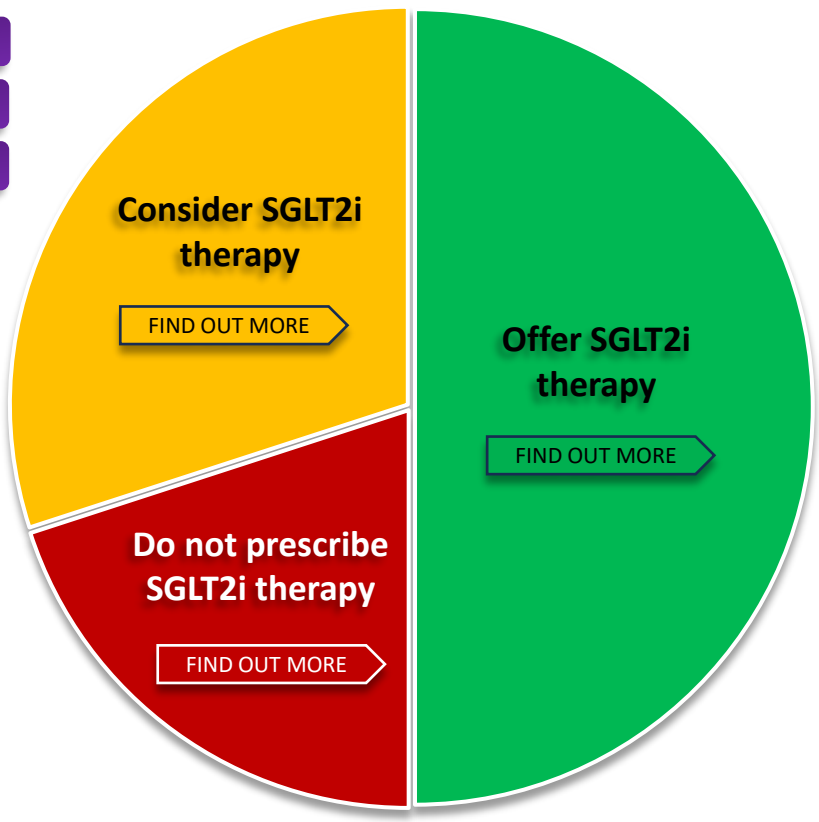
The NICE resource impact report for T2DM in adults suggests that around 1.7 million people with T2DM in England (approximately 50%) are eligible for SGLT2i treatment in accordance with current NICE guidelines [1,2]. However, given the weight of existing evidence and growing expert opinion, the Improving Diabetes Steering Committee estimates that up to 80% of people with T2DM would benefit from SGLT2i treatment, with some caveats that are summarized in this Decision Tool [1–53]. The Decision Tool aims to guide appropriate SGLT2i treatment in people diagnosed with T2DM. Before using this Tool, please determine the **QRISK®3 score** and **renal function** for the individual you are treating using up-to-date eGFR and UACR values. **Please refer to the relevant summary of product characteristics (SmPC) before prescribing any SGLT2i therapy.**

Key practice points [1-53]:

- *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.*
- *Discussion with an expert clinician is advisable for more complex cases.*

Initial assessment

- Go to QRISK®3 calculator
- Go to QRISK®3 lifetime calculator
- Kidney function (eGFR and UACR)



IMPORTANT – this decision tool is for guidance only. The final clinical decisions are the responsibility of the prescriber.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; ASCVD; atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; C_{max}, maximum serum drug concentration; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin A1c; HCP, healthcare professional; HF, heart failure; HFrEF, heart failure with ejection fraction; HHF, hospitalisation for heart failure; HHS, hyperosmolar hyperglycaemic state; LADA, latent autoimmune diabetes in adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; QRISK, cardiovascular risk score; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UKKA, UK Kidney Association; UTIs, urinary tract infections.

SGLT2i therapy should be offered

First-line combination therapy with metformin* or as monotherapy if metformin is contraindicated or not tolerated in people with one of the following:

- QRISK®3 (where available or QRISK®2) >10%
- HF
- Established ASCVD
- CKD/DKD

*If using with metformin, initiate metformin first and titrate over a 4-week period and then start SGLT2i therapy.
[Box A; Box C; Box L]

Combination therapy with other oral glucose-lowering therapies in people with:

- QRISK®3 (where available or QRISK®2) >10%
- CVD
- HF
- CKD

[Box G; Box L]

Young onset T2DM (aged 18–40 years), unless planning pregnancy
[Box I]

Overweight or obesity in the absence of GLP-1 RA
[Box A]

Vulnerable to the effects of hypoglycaemia
[Box G]

REFERENCES

BOX A: NICE and ADA / EASD recommendations for SGLT2i prescribing

BOX C: Renal disease, eGFR and reduced glucose-lowering effect

BOX G: Drug-drug interactions

BOX I: T2DM in younger people (aged 18–40 years)

BOX L: The cost-effectiveness case for SGLT2is in T2DM

Check when SGLT2i therapy should be considered or not prescribed

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SGLT2i therapy should be considered

- Frailty/older people/cognitive impairment **[Box J]**
- Ketogenic/very low calorie/low carbohydrate diet **[Box E; Box D]**
- BMI <25 kg/m^2 (adjust according to ethnic variation) **[Box E; Box D]**
- Recurrent genital mycotic infections and UTIs **[Box F]**
- Symptomatic hyperglycaemia **[Box D; Box K]**
- History of PAD and/or lower limb amputation (discuss with local specialist foot team) **[Box H]**
- QRISK®3 (where available or QRISK®2) <10% **[Box A]**

SGLT2i therapy should not be prescribed

- Acute illness with risk of dehydration **[Box B; Box D]**
- Current or previous diabetic ketoacidosis **[Box D]**
- Low beta-cell function (low C peptide levels) **[Box K; Box D]**
- Rapid progression to insulin (within 1 year) **[Box K; Box D]**
- Suspected LADA or slowly evolving immune-related diabetes **[Box K; Box D]**
- Excessive alcohol intake **[Box K; Box D]**
- Chronic pancreatitis and/or PEI **[Box K; Box D]**
- Type 3c diabetes **[Box K; Box D]**
- Suspected pancreatic cancer **[Box K; Box D]**
- Planned surgery or procedure requiring starvation/nil by mouth (3–7 days prior to planned surgery) **[Box K; Box D]**
- Pregnancy/suspected pregnancy, planning pregnancy or breastfeeding **[Outside of license indication]**
- Type 1 diabetes **[Outside of license indication]**
- Unclear diagnosis of diabetes **[Outside of license indication]**

REFERENCES

BOX A: NICE and ADA / EASD recommendations for SGLT2i prescribing

BOX B: Sick day guidance

BOX D: Diabetic ketoacidosis

BOX E: Diets and eating disorders

BOX F: Genital and urinary infections

BOX H: Foot disease (limb ischaemia or ulceration)

BOX J: Older people / frailty / dementia

BOX K: High blood glucose despite oral diabetes medication

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Box A: NICE and EASD/ADA recommendations for SGLT2i prescribing [2-7]

For an overview of the NICE NG28 guidelines for the management of Type 2 diabetes in adults and the ADA/EASD consensus report on the management of hyperglycaemia in Type 2 diabetes click here.
Key points are highlighted below:

SGLT2i therapies are recommended as initial combination therapy, with metformin (once metformin tolerability has been established), for adults with T2DM who are likely to benefit from the cardiorenal protective properties of SGLT2is (chronic Heart Failure, ASCVD, CKD, high risk of CVD).

SGLT2i therapy alone may be given first-line when metformin is contraindicated or not tolerated.

SGLT2is may be prescribed in combination with other glucose-lowering therapies, including SUs, thiazolidinediones, GLP-1 RAs and insulin.

In people with T2DM and HF, CKD, established CVD, or multiple risk factors for CVD, the decision to prescribe SGLT2i therapy should be made independently of background metformin use and baseline or target HbA1c.

T2DM populations most likely to benefit from SGLT2i prescribing:

- Established ASCVD
- High risk of CVD.
- CKD/DKD or high renal risk.
- Current or prior HF.
- Inadequate glycaemic control with a need to minimise hypoglycaemia.

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Box B: Sick day guidance [3,8-12]

Sick day guidance should be followed when a person with diabetes has an acute dehydrating illness or is unable to eat and/or drink normally. The guidance is intended for people taking oral T2DM therapies with or without insulin, 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 must be paused. Access to glucose and ketone monitoring should be offered to individuals where this is deemed clinically necessary. If DKA is suspected, refer to Box D. Guidance should include the following:

- Offer the person advice on sick day guidance when initiating SGLT2is and remind them of this at every medication review. Patient information leaflets should be provided to support advice.
- Those with access to a glucose self-monitoring device (typically those on insulin or an SU) should check their glucose levels more frequently during periods of acute illness. Medical assistance must be sought if levels are persistently high or low.
- The following medications should be temporarily stopped if the person is unable to eat and drink normally and is at risk of dehydration or vomiting: SGLT2is, ACEis, diuretics*, metformin, ARBs and NSAIDs (the SADMAN mnemonic may be a helpful reminder).
- The person should maintain normal hydration and food, where possible. If this is not possible, oral fluids should be encouraged (≥100 mL/hour). Recommend sugar-free fluids if glucose levels are high or sugary fluids when glucose levels are low.
- Once eating and drinking normally and vomiting has ceased, or the individual is feeling better, oral medications (including SGLT2i therapy) can be restarted.

*** Decisions regarding the pausing of diuretics for HF should be based on current fluid status, as assessed by an HCP.**

Useful resources on sick day guidance can be found via the following links:

Down S. How to advise on sick day rules. Diabetes & Primary Care2020;22:47–8

TREND Diabetes

Diabetes UK (DUK)

EDEN

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Box C: Renal disease, eGFR and reduced glucose-lowering effect [2,3,13–18]

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). Recommendations on SGLT2i use have been published by the UKKA

- If the person has an eGFR <60 mL/min/1.73 m^2 or clinically significant proteinuria (UACR >3 mg/mmol) and is receiving the maximally tolerated dose of ACEi/ARB therapy, consider adding an SGLT2i for renal protection irrespective of glycaemic control. In addition, consider adding finerenone to the reduce the risk of adverse kidney and CV outcomes if significant proteinuria persists despite maximally tolerated ACEi/ARB and SGLT2i doses.
- Check eGFR 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 will be negligible if eGFR falls further. In these circumstances, if further glucose-lowering is required, an additional agent should be considered. A GLP-1 RA may be a useful add-on option to reduce albuminuria and retain glucose-lowering effect.

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Box D: Diabetic ketoacidosis [3,7,8,11,15-22]

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 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). Ketoacidosis occurring during SGLT2i use may be atypical and associated with euglycaemia (relatively normal glucose levels). Key resources on DKA can be found at: DUK, EDEN, TREND Diabetes and Diggle J, 2020.

Risk factors for DKA include:

- Low beta-cell function (e.g. those with T2DM and low C-peptide levels, LADA/slowly evolving immune-related diabetes or a history of pancreatitis). Ensure correct diagnosis of T2DM before initiating SGLT2i treatment.
- Restricted food intake (very low calorie or very low carbohydrate diet) or severe dehydration [see Box E for advice on intermittent fasting].
- Sudden reduction in insulin.
- Increased insulin requirements due to rising glucose levels (e.g. during acute illness).
- Surgery or surgical procedure that requires fasting.
- Alcohol abuse.
- Corticosteroid use.

Signs of DKA include abdominal pain, nausea, vomiting, shortness of breath (Kussmaul breathing), drowsiness, confusion and sweet smelling (pear-drop) breath.

- Provide clear verbal and written sick day guidance [Box B].
- Explain the signs and symptoms of DKA and the need to temporarily pause SGLT2is and seek immediate medical advice if symptoms develop.

If DKA develops while taking an SGLT2i, the agent should be stopped. The decision to restart where a clear contributing factor has been identified should be taken in discussion with the individual and clinical team to establish whether the benefits of reintroducing an SGLT2i outweigh the risks.

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Box E: Diets and eating disorders [8,23-25]

Conditions leading to restricted food intake or severe dehydration may predispose SGLT2i users to DKA [Box D].

- 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 comorbid eating disorder (e.g. anorexia nervosa, diabulimia).
- Individuals with T2DM who follow an intermittent fasting diet (e.g. 5:2 diet) require a diabetes therapy review, with some treatments (including SGLT2is) being reduced in dosage or suspended on fasting days.
- For advice on SGLT2i use during Ramadan, refer to the IDF-DAR guidelines and/or the SAHF guidelines.
- SGLT2i users should receive information relating to the risk of DKA [Box D] and sick day advice [Box B].

Urgent medical attention must be sought if a person receiving SGLT2i therapy is unwell and tests positive for ketones.

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Box F: Genital and urinary infections [15-18,26,27]

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

- Infections are more common in women than men and usually occur early in treatment but generally respond well to standard topical or oral medications and most people can continue taking their SGLT2i therapy.
- Glycosuria may cause urinary symptoms, including more frequent voiding.
- Treat mycotic genital infections with antifungal medications and UTIs with standard antibiotics. Patient information is available via TREND.
- The risk of infections is reduced by maintaining good genital hygiene. Advise SGLT2i users on genital health and hydration.
- Fournier's Gangrene is a very rare but serious soft tissue infection of the genital area. Risk factors include diabetes, local trauma, male gender, obesity, older age, immunosuppression, HIV infection, end-stage renal or liver failure, smoking and alcohol abuse. Until 2019, 6 yellow card reports of Fournier's Gangrene had been received by the UK MHRA for an estimated exposure to SGLT2i treatment of 548,565 patient-years

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.

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Box G: Drug-drug interactions [2-6,15-18]

SGLT2i use within a polypharmacy setting is highly likely when prescribed according to NICE and ADA/EASD recommendations. Drug interaction studies indicate that SGLT2is have no clinically relevant effect on the pharmacokinetics of metformin, other oral glucose-lowering therapies, oral contraceptives, glibenclamide, paracetamol, hydrochlorothiazide, statins or warfarin. However, when concomitantly prescribed, SGLT2is can have dosing implications in the following situations:

- Diuretic dosing may require modification because SGLT2is increase the diuretic effect of thiazide and loop diuretics and raise the risk of dehydration and hypotension. Diuretic effect with SGLT2is can be more pronounced in those with poor metabolic control and people with T2DM and high HbA1c.
- Insulin and insulin secretagogues (including SUs) may require dose reduction to lower the risk of hypoglycaemia. SGLT2is are not licensed for use in people with Type 1 diabetes.
- Antihypertensive medications may need adjustment due to potential induction of diuresis (particularly in people with higher glucose levels) and reduced systolic (approximately 4 mmHg) and diastolic (approximately 2 mmHg) blood pressure. Monitor individuals with a history of CVD or hypotension, or older people. Prioritise maintenance of stable RAAS inhibitor dosing and reduce doses of other antihypertensives, if needed.
- Empagliflozin and dapagliflozin may increase renal lithium excretion and decrease blood lithium levels, with more frequent monitoring of serum concentration and potential dose changes required.
- Monitoring of digoxin levels (or other cardiac glycosides) is required with canagliflozin due to potential increases in AUC and C_{max}.

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Box H: Foot disease (limb ischaemia or ulceration) [15-18, 28-35]

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.

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.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; ASCVD; atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; C_{max}, maximum serum drug concentration; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin A1c; HCP, healthcare professional; HF, heart failure; HFrEF, heart failure with ejection fraction; HHF, hospitalisation for heart failure; HHS, hyperosmolar hyperglycaemic state; LADA, latent autoimmune diabetes in adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; QRISK, cardiovascular risk score; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UKKA, UK Kidney Association; UTIs, urinary tract infections.

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Box I: T2DM in younger people (aged 18–40 years) [2,36]

Prevalence of T2DM in younger people has increased over recent decades. Evidence suggests that younger people with T2DM have high lifetime CVD risk. Diabetes-related complications appear early and progress rapidly in this group. Intensive treatment should therefore be implemented from an early stage in the therapeutic pathway. NICE NG28 guidance recommends SGLT2i therapy for people with T2DM under the age of 40 years with ≥1 CV risk factor, comprising hypertension, dyslipidaemia, smoking, obesity, and family history (first-degree relative) of premature CVD.

- Initiate SGLT2i therapy with first-line therapies [Box A] and provide advice regarding contraception for women of childbearing age. SGLT2is are not licensed for use during pregnancy and should only be given if contraception is being used.
- Education should be given regarding reduction in CV risk through lifestyle factors (e.g. diet, exercise).
- The QRISK®2 tool is only designed for use with people aged above 40 years and uses a 10-year risk calculation instead of lifetime risk. SGLT2i treatment should not be stopped when a person reach 40 years of age as they will continue to benefit from the protection offered by this therapeutic class of agent regarding CV, renal and metabolic complications of T2DM.
- The QRISK®3 tool can be used in people aged >25 years. The QRISK®3-Lifetime tool may be more appropriate for assessment of people aged 18–40 years.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; ASCVD; atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; C_{max}, maximum serum drug concentration; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin A1c; HCP, healthcare professional; HF, heart failure; HFrEF, heart failure with ejection fraction; HHF, hospitalisation for heart failure; HHS, hyperosmolar hyperglycaemic state; LADA, latent autoimmune diabetes in adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; QRISK, cardiovascular risk score; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UKKA, UK Kidney Association; UTIs, urinary tract infections.

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Box J: Older people/frailty/dementia [37-39]

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

Older people: most SGLT2i therapies do not give specific ages for discontinuation in adults (please refer to the individual SmPC for prescribing guidance relating to age). The SOLD study found that SGLT2is were an effective and generally well-tolerated therapeutic option with a good safety profile in people aged above 70 years and living with T2DM. However, some caution was suggested, especially in those who were most frail mainly due to UTIs and worsening renal function.

Frailty: CVOTs have demonstrated delayed progression of CKD, HF and MACE, and reduced hypoglycaemia risk with SGLT2is (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 [Box B] are important in this group.

HF and frailty: a pre-specified analysis of data from the DELIVER trial found health-related improvements in quality of life occurred early with SGLT2i treatment. Improvements were greatest in people with higher levels of frailty.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; ASCVD; atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; C_{max}, maximum serum drug concentration; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin A1c; HCP, healthcare professional; HF, heart failure; HFrEF, heart failure with ejection fraction; HHF, hospitalisation for heart failure; HHS, hyperosmolar hyperglycaemic state; LADA, latent autoimmune diabetes in adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; QRISK, cardiovascular risk score; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UKKA, UK Kidney Association; UTIs, urinary tract infections.

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Box K: High blood glucose levels despite oral diabetes medication [40,41]

While there is no evidence-based consensus regarding the upper HbA1c threshold for SGLT2i initiation (or to signal the pausing/stopping of use), high HbA1c due to low beta-cell function increases the risk of DKA [Box D].

- Reliability of the test. Any condition that affects the lifespan of the red blood cell will affect HbA1c.
- Consider red flags for pancreatic malignancy.
- Is the T2DM diagnosis correct/secure? Consider LADA/slowly evolving immune-related diabetes or significant decline in beta-cell function and insulin deficiency.
- Check adherence to the current treatment regimen (and lifestyle changes).
- Is there a possibility of DKA or HHS?
- Are new medications raising blood glucose levels (e.g. steroids, antipsychotics)?
- Have any recent or current infections or comorbidities potentially contributed to raised blood glucose?
- If a person has a high HbA1c and is osmotically symptomatic, rescue therapy (see NICE NG28) may be appropriate initially, with reassessment for SGLT2i treatment at a later date.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; ASCVD; atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; C_{max}, maximum serum drug concentration; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin A1c; HCP, healthcare professional; HF, heart failure; HFrEF, heart failure with ejection fraction; HHF, hospitalisation for heart failure; HHS, hyperosmolar hyperglycaemic state; LADA, latent autoimmune diabetes in adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; QRISK, cardiovascular risk score; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UKKA, UK Kidney Association; UTIs, urinary tract infections.

Box L: The cost-effectiveness case for SGLT2is in T2DM [1-4,28-53]

SGLT2is have an extensive evidence base supporting their use in T2DM management, with increasing data demonstrating their clinical benefit in reducing the risk of CKD progression and CVD outcomes, independent of metabolic control. Evolving clinical guidelines support a broad positioning of SGLT2is within the T2DM treatment paradigm and the health economic profile of this class of medicines has been extensively evaluated.

Systematic review data have demonstrated the cost-effectiveness of SGLT2is. The economic value of SGLT2i therapy has also been illustrated in the treatment of people with/without T2DM who live with HFrEF and CKD (with varying degrees of albuminuria). Since there is considerable clinical overlap across T2DM, HFrEF and CKD, the proven therapeutic value and benefit of SGLT2is across the three disease areas mandates a holistic approach to assessment of true value for money that encompasses measures of CV, renal, HF and metabolic outcomes.

Current UK NICE guidelines (NG28) advocate the early use of SGLT2is across a wide range of people with T2DM, particularly those with comorbid HF and CKD. Economic analyses supporting the NG28 guideline considered evidence from recent CVOTs but excluded CKD trial data. It is likely that SGLT2is offer value beyond that described in the NG28 guideline, based upon data from three major dedicated outcome studies in people with T2DM with/without albuminuria (CREDENCE, EMPA-Kidney and DAPA-CKD), which showed the impact of SGLT2is in delaying progression of kidney disease, reducing HHF and incidence of ESKD, CV events, CV mortality and all-cause mortality.

A recent economic evaluation study examining SGLT2i use in line with NICE NG28 recommendations concluded that these agents were highly cost-effective with the potential to realise cost savings within 2 years in high-risk groups. The determinants of the economic value were driven by the combined effect of a reduction in CV event rate and HHF and avoiding ESKD events. Pharmacy expenditure associated with widespread SGLT2i uptake is likely to be more than offset by reductions in the cost of managing related health complications and the release of greater capacity/resource within the healthcare system, ultimately translating into system-level savings.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARBs, angiotensin receptor blockers; ASCVD; atherosclerotic cardiovascular disease; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; C_{max}, maximum serum drug concentration; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin A1c; HCP, healthcare professional; HF, heart failure; HFrEF, heart failure with ejection fraction; HHF, hospitalisation for heart failure; HHS, hyperosmolar hyperglycaemic state; LADA, latent autoimmune diabetes in adult; MACE, major adverse cardiac event; MDT, multidisciplinary team; MHRA, Medicines and Healthcare products Regulatory Agency; NSAID, non-steroidal anti-inflammatory drug; QRISK, cardiovascular risk score; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium glucose cotransporter-2 inhibitor; SmPC, summary of product characteristics; SU, sulphonylurea; T2DM, Type 2 diabetes mellitus; UACR; urine albumin to creatinine ratio; UKKA, UK Kidney Association; UTIs, urinary tract infections.

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