When to use SGLT2 inhibitors in type 2 diabetes

What and why

- SGLT2 inhibitors (SGLT2is) are oral drugs that block reabsorption of glucose in the kidneys.
- SGLT2is were initially developed as glucose-lowering drugs and were noted to have beneficial effects on systolic BP and weight reduction. The cardiovascular outcome trials and studies in people with renal disease and heart failure confirm significant benefits in these comorbidities, which appear to be independent of glucose lowering, with the HF and CKD benefits demonstrated in people with and without T2DM.
- SGLT2is can be used at most stages of the T2DM pathway but remain underused in the UK, depriving people with T2DM of the added benefits for ASCVD, HF, CKD, weight loss and BP lowering.
- When prescribing SGLT2is, consider safety and tolerability.
- Although SGLT2is do not increase risk of hypoglycaemia, if adding an SGLT2i to insulin or a sulfonylurea, initially reduce the dose of insulin or SU to reduce risk of hypoglycaemia.

Many guidelines and guidance documents have informed the positioning of SGLT2 inhibitors since the previous version of this document was published. These include the 2022 update to NICE NG28 and the 2022 updated ADA/EASD consensus on glycaemic management.

These guidelines differ in their positioning of GLP-1 receptor agonists (GLP-1 RAs) since NICE did not revisit the evidence base for GLP-1 RA use for glucose lowering and did not find them cost-effective as a class for atherosclerotic cardiovascular disease (ASCVD) risk reduction due to differing cardiovascular benefit between drugs. Since advice on SGLT2i use is now similar between NICE and ADA/EASD guidelines, this article will focus on the 2022 update of NICE NG28.

As detailed in the **Algorithm overleaf**, NICE recommends the use of an SGLT2i as dual therapy with metformin (or alone if metformin is contraindicated or not tolerated) in people with established or high risk of ASCVD, and in combination with ACE inhibitors or ARBs in people with chronic kidney disease (CKD) or diabetic kidney disease (DKD).

SGLT2is are also options for monotherapy in some individuals who are not at high ASCVD risk, and as dual or triple therapy when other agents fail to control HbA_{1c} below the individual's agreed target.

Significant glucose lowering is unlikely if eGFR is <45, but other benefits in terms of heart failure, slowing CKD progression and ASCVD protection persist.

For more details of specific licensed indications and eGFR thresholds for initiation and stopping, see our Need to know guide and the SmPCs for individual drugs.

Before starting an SGLT2i, check whether the person is at increased risk of diabetic ketoacidosis (DKA), address modifiable risks for DKA, check whether suitable for an SGLT2i (see below), and fully counsel regarding sick day guidance (see page 3 of this article).

Safe use: SGLT2is and renal function

- Check electrolytes and eGFR prior to therapy; monitor annually unless eGFR is <60 mL/min/1.73 m^2, when eGFR should be checked every 3–6 months (see NICE NG203 guidance).
- Modest reductions in eGFR may occur when starting SGLT2is, but extra monitoring is not required unless unwell or starting another drug likely to impact renal function. eGFR will improve and, over the longer term, SGLT2is slow progression of CKD.
- See our Need to know guide for eGFR limits on initiating and stopping individual drugs for specific indications, as this is now complex.
- Dapagliflozin and empagliflozin are licensed for use in chronic symptomatic HFrEF and HFpEF.
- Dapagliflozin and empagliflozin are licensed to slow progression of DKD and CKD in people with and without type 2 diabetes. Canagliflozin is licensed to slow progression of DKD in people with type 2 diabetes.
- Glucose-lowering effects are minimal when eGFR is <45 mL/min/1.73 m^2, so additional glucose-lowering therapies may be needed.
- SGLT2is may increase the risk of dehydration and hypotension in those treated with thiazide or loop diuretics. **Caution is required particularly in older people.**

Choosing who to treat with SGLT2 inhibitors

Low risk Evidence supports SGLT2i prescribing	**Moderate risk** Prescribe SGLT2i with caution	**High risk** Do not prescribe SGLT2i
First-line (if metformin intolerant/contraindicated*)	Frail/elderly/cognitive impairment	Acute illness
Second-line to metformin	History of peripheral arterial disease	DKA (or previous episode of DKA)
Third-line (add-on to second-line therapies), including in combination with GLP-1 RAs or insulin (avoid significant initial insulin reductions. Titrate insulin depending on glucose levels)	History of foot ulceration	Excessive alcohol intake
Established ASCVD¶	Previous lower limb amputation	Eating disorders
History of heart failure¶	Existing diabetic foot ulcer(s)	Rapid progression to insulin (within 1 year)
Overweight or obesity	Ketogenic/low-calorie/low-carbohydrate diet	Type 1 diabetes (diagnosed or suspected)
Prior stroke	BMI <25 kg/m^2	Multiple risk factors for necrotising fasciitis of the perineum (Fournier's gangrene)
Vulnerable to the effects of hypoglycaemia	High HbA_{1c} levels (>86 mmol/mol [10.0%])	Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding
Renal impairment/CKD/DKD (with ACEi/ARB)¶	Recurrent genital mycotic/urinary tract infections	Recent major surgery
No history of lower limb amputation	Receiving systemic steroid therapy	When renal function falls outside of licence (see Need to Know guide for summary)
No history of peripheral arterial diease		Diabetes due to pancreatic disease
Receiving loop diuretics		Severe hepatic impairment (dapagliflozin 5 mg can be initiated and, if tolerated, increased to 10 mg)
Osteoporosis		
History of fractures		

* See **algorithm overleaf**.

¶ Certain SGLT2 inhibitors are licensed for initiation at lower eGFR levels when used for DKD (canagliflozin, dapagliflozin, empagliflozin), CKD (dapagliflozin, empagliflozin), CVD (empagliflozin) or heart failure (dapagliflozin, empagliflozin). See our Need to Know guide for a summary of the licensed initiation and stopping eGFR values, for different clinical uses.

Note: Safety and tolerability concerns with SGLT2 inhibitors apply across the class unless documented specifically.

ACR=albumin:creatinine ratio; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; DKA=diabetic ketoacidosis; DKD=diabetic kidney disease; eGFR=estimated glomerular filtration rate.

Adapted from Wilding et al (2022).

Consult individual Summaries of Product Characteristics prior to prescribing.

Links to SmPCs: Canagliflozin 100 mg | Dapagliflozin 10 mg | Empagliflozin 10 mg | Ertugliflozin 5 mg

NICE guidance on SGLT2 inhibitor use in people with type 2 diabetes (adapted from NICE NG28)

First-line treatment — Assess HbA_{1c}, cardiovascular risk and kidney function

Not at high risk of ASCVD

Offer **Metformin** (or if GI disturbance, **Metformin MR**)

If metformin is contraindicated or not tolerated, **and only if** a DPP-4i would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate, and diet and exercise provide inadequate control, **consider SGLT2i** alone

If CKD, chronic heart failure, ASCVD or high ASCVD risk develops at any time, add **SGLT2i** according to the respective advice on the right

Chronic kidney disease (CKD) or diabetic kidney disease (DKD)

(eGFR <60 mL/min/1.73 m^2 or ACR ≥3 mg/mmol on two measurements at least 90 days apart)

Offer **ACE inhibitor** (or if intolerant, an **ARB**) and titrate to maximum tolerated licensed dose

If ACR >30 mg/mmol and meet eGFR criteria for SGLT2i use (see Need to know), **offer SGLT2i** licensed for CKD/DKD

If ACR 3–30 mg/mmol and meet eGFR criteria for SGLT2i use (see Need to know), **consider SGLT2i** licensed for CKD/DKD

For guidance on dapagliflozin and empagliflozin for CKD, see NICE TA1075 and TA942.

Canagliflozin is only licensed for use in those with type 2 diabetes.

For further guidance on managing kidney disease in adults with type 2 diabetes, see NICE NG203.

Chronic heart failure or established ASCVD*

Offer **Metformin** (or if GI disturbance, **Metformin MR**)

As soon as metformin tolerability is confirmed, **offer SGLT2i** with proven HF/CV benefit

If metformin is contraindicated or not tolerated, **offer SGLT2i** alone

For guidance on dapagliflozin and empagliflozin for chronic HF, see NICE TA679, TA773, TA902 and TA929.

High risk of ASCVD (QRISK ≥10% or elevated lifetime risk¶)

Offer **Metformin** (or if GI disturbance, **Metformin MR**)

As soon as metformin tolerability is confirmed, **consider SGLT2i** with proven CV benefit

If metformin is contraindicated or not tolerated, **consider SGLT2i** alone

Treatment escalation — If HbA_{1c} not controlled below individually agreed threshold

SGLT2is may be an option in dual therapy or triple therapy: see respective NICE Technology Appraisals alongside

Summary of NICE Technology Appraisal advice on use of canagliflozin, dapagliflozin, empagliflozin and ertugliflozin

Monotherapy
TA390, TA572
In the absence of the cardiorenal comorbidities shown above, use **only if**:
- Metformin is contraindicated or not tolerated
- Diet and exercise provide inadequate control
- A DPP-4i would otherwise be prescribed and an SU or pioglitazone is not appropriate

Dual therapy
TA315, TA288, TA336, TA572
- Dual therapy with metformin if SU is contraindicated **or** there is significant risk of hypoglycaemia or its consequences
- All except ertugliflozin: In combination with insulin
- If all four SGLT2is are appropriate, use the least expensive

Triple therapy
TA315, TA418, TA336, TA583
- Triple therapy with metformin and an SU
- Canagliflozin and empagliflozin: Triple therapy with metformin and pioglitazone
- All except ertugliflozin: In combination with insulin, with or without other antidiabetes drugs
- Ertugliflozin: Triple therapy with metformin and a DPP-4i, **only if** there is insufficient control with metformin/DPP-4i dual therapy **and** an SU or pioglitazone is not appropriate
- If all four SGLT2is are appropriate, use the least expensive

Note: There is no specific NICE guidance on use of SGLT2is with GLP-1 RAs, although they are commonly prescribed as part of the metformin and two-drug combination in people who meet the criteria for GLP-1 RAs.

* Established ASCVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

¶ Elevated lifetime risk of ASCVD is defined as the presence of one or more cardiovascular risk factors in someone aged under 40 years. **Cardiovascular risk factors:** hypertension, dyslipidaemia, smoking, obesity and family history (in a first-degree relative) of premature cardiovascular disease.

Safety issues with SGLT2 inhibitors

Diabetic ketoacidosis (DKA) – see MHRA (2016)

- May be euglycaemic with only slight increases in blood glucose: <14 mmol/L. Test blood ketones even if glucose levels are normal.
- May be associated with dehydration, low food intake, weight loss, infection, surgery, vomiting, decreased insulin dose, poor glycaemic control.
- Suspect if nausea, vomiting, anorexia, abdominal pain, thirst, difficulty breathing, confusion, or unusual fatigue and sleepiness.
- Warn to seek medical care immediately if these develop. Most people will require admission.
- Pause SGLT2i drugs during acute illness and prior to surgical procedures – see **Sick-day guidance** alongside.
- Do not restart an SGLT2i if DKA occurs unless there was a clear precipitating factor.
- Pause treatment in those hospitalised for surgery or acute illness.
- Factors in history that may predispose to DKA include low beta-cell reserve, sudden reductions in insulin, increased insulin requirements due to acute illness, surgery and alcohol abuse.
- Warn against combining an SGLT2i with a very-low-carbohydrate/ketogenic diet, as these greatly increase DKA risk; people eating this way are not suitable for an SGLT2i.

Lower limb amputations – see MHRA (2017)

- Amputations are eight times more likely in those with diabetes than those without.
- Increased risk of amputation with canagliflozin in CANVAS trial programme but not in CREDENCE.
- Increased amputations across the ertugliflozin studies, notably with the 15 mg dose.
- Warnings remain on the SmPCs for these two drugs.
- No increased risk identified with empagliflozin (Inzucchi et al, 2018) or dapagliflozin (Bonaca et al, 2020).
- Proposed risk factors include previous amputation, peripheral vascular disease and neuropathy, but no specific mechanisms confirmed.
- Footcare education should be provided at initiation and during SGLT2i therapy.
- Many clinicians pause SGLT2i therapy during active foot ulceration, infection, osteomyelitis or gangrene.
- Meta-analysis of 15 randomised controlled trials involving 63 716 people with and without type 2 diabetes did not identify any increased risk of amputation with SGLT2is (See et al, 2022).

References

Bonaca MP et al (2020) *Circulation* **142**: 734–47

Inzucchi SE et al (2018) *Diabetes Care* **41**: e4–5

MHRA (2016) *SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis*

MHRA (2017) *SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)*

MHRA (2019) *SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)*

See RM et al (2022) *Pharmacology* **107**: 123–30

Wilding JPH et al (2022) *Diabetes Ther* **13**: 847–72

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Acknowledgement: The author thanks Samina Ali and Nicola Milne for their contributions and feedback on this article.

Citation: Brown P (2023) How to use SGLT2 inhibitors safely and effectively. *Diabetes & Primary Care* **25**: 113–5

Update history: Last updated July 2025 to reflect changes to NICE TA guidance for dapagliflozin and empagliflozin.

Sick-day guidance for type 2 diabetes

Blood glucose can rise during illness even if the person is not eating. When ill and at risk of dehydration, people with T2DM should be advised to:

- Temporarily stop **SADMANS** drugs (**S**GLT2is, **A**CEis, **D**iuretics [individualise in those with HF], **M**etformin, **A**RBs, **N**SAIDs and **S**Us*), and if unable to eat or drink, or persistent vomiting or diarrhoea, to contact their GP or specialist nurse for advice.
- If they are unsure how to self-manage during illness, encourage the person to contact their practice or diabetes specialist team, or seek emergency medical advice.
- If not able to eat normally, replace meals with high-carbohydrate snacks or drinks.
- Stay well hydrated (2–3 L of fluid per day) and eat little and often.
- **Advise to keep taking insulin and all other diabetes medicines (apart from SADMANS drugs) even if not eating.**
- Give people taking SGLT2i drugs specific advice about the risk of euglycaemic DKA and to consult if they become ill, even if blood glucose levels are not high. Primary care teams should be aware of the need to test blood glucose **AND** ketones in this situation.
- See *How to advise on sick day rules*.

*For SUs, consider stopping if unable to eat or drink but be guided by results of self-monitoring of blood glucose.

Genital and urinary infections

- Thrush-type genital infections are common.
- Infections are more common early in treatment and when glucose levels are high (even without SGLT2is). Providing hygiene information may reduce risk and improve treatment continuation.
- Treat with topical or oral antifungals.
- Most people can continue SGLT2i treatment.
- Glycosuria may cause urinary symptoms and more frequent voiding.
- UTIs are relatively rare but urosepsis may occur; manage with standard antibiotics. If recurrent, stop SGLT2i treatment.

Fournier's gangrene (necrotising fasciitis of the perineum) – see MHRA (2019)

- Rare but serious and potentially life-threatening. Diabetes and SGLT2i treatment are risk factors.
- May be preceded by urogenital infection or perineal abscess.
- Advise to seek urgent medical attention if severe pain, tenderness, erythema or swelling in genital area accompanied by fever or malaise.
- Usually occurs mainly in men but with SGLT2i treatment can occur in women.

Bone fractures

- Small increased fracture risk and changes in bone mineral density (BMD) seen in those treated with canagliflozin compared with placebo in the CANVAS (but not CANVAS-R or CREDENCE) trial, and with ertugliflozin, but not identified in empagliflozin or dapagliflozin studies.
- Fractures occurred mainly early in treatment and may have been linked to increased falls due to volume depletion and hypotension.