Prescribing pearls: A guide to SGLT2 inhibitors

What are SGLT2 inhibitors?

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, also known as "Flozins", are a class of medication primarily used to manage type 2 diabetes. These drugs help lower blood glucose by targeting the kidneys and are also recognised for their protective effects on the heart and kidneys, often used in managing heart failure and chronic kidney disease.[1,2]

Mechanisms of action[1]

SGLT2 inhibitors work by reversibly inhibiting the sodium–glucose cotransporter 2 protein in the renal proximal convoluted tubule. This inhibition reduces reabsorption of glucose back into the blood, causing excess glucose to be excreted in the urine. This mechanism helps to lower blood glucose levels and, independently, provides cardiovascular and renal protective benefits.

Although the mechanisms behind the improved outcomes seen are not fully understood, they are hypothesised to include natriuresis and plasma volume reductions, which lower blood pressure and cardiac workload, and improved vascular function. Renal benefits involve reduced hyperfiltration and albuminuria, which protect kidney function. Additionally, the drugs shift metabolism to ketone bodies for heart and kidney energy, reduce inflammation and oxidative stress, and lower serum uric acid levels. These effects, alongside suppressed advanced glycation end-products, support potential broad organ protection. Studies exploring applications in non-diabetic kidney disease and heart failure with preserved ejection fraction are ongoing.

Licensed indications

Type 2 diabetes

- All four SGLT2 inhibitors available in the UK are licensed for the treatment of adults with insufficiently controlled type 2 diabetes, as an adjunct to diet and exercise. This class of drugs can be prescribed as monotherapy where metformin is not appropriate or tolerated, as well as in combination with other glucose-lowering agents.

Heart failure

- Dapagliflozin and empagliflozin are indicated for the treatment of symptomatic chronic heart failure regardless of ejection fraction in adults with or without type 2 diabetes. See NICE NG106 for further information.[2]

Chronic kidney disease

- Dapagliflozin and empagliflozin are licensed for the treatment of chronic kidney disease in adults without type 2 diabetes. See NICE NG203 for further information.[3]
- Canagliflozin is indicated for the treatment of kidney disease in adults but only in the presence of type 2 diabetes.

Positioning in guidelines

NICE NG28 advocates the use of SGLT2 inhibitors as second-line pharmacotherapy in addition to metformin for people who have established cardiovascular disease (CVD) or have a high risk of CVD (QRISK ≥10%).[4] See *Table 1* and *Figure 1*[5] for more information.

Table 1. Summary of NICE recommendations on use of SGLT2 inhibitors for glycaemic control in type 2 diabetes (as an adjunct to diet and exercise).[4]

	Empagliflozin (Jardiance®)	Dapagliflozin (Forxiga®)	Canagliflozin (Invokana®)	Ertugliflozin (Steglatro®)
Dose	**Initial dose**			
	10 mg daily	10 mg daily	100 mg daily	5 mg daily
	If additional glycaemic control is required			
	25 mg daily	–	300 mg daily	15 mg daily
Monotherapy	**People with heart failure, ASCVD or at high risk of CVD** Yes – when metformin is contraindicated or not tolerated			
	People not at high risk of CVD Yes – when metformin is contraindicated or not tolerated, and if a DPP-4 inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is unsuitable			
Dual therapy	Yes – see ***Figure 1*** for more information			
Triple therapy	Yes – see ***Figure 1*** for more information			
With insulin	Yes – see ***Figure 1*** for more information			
Use in renal impairment	Can be started in eGFR >60 Glycaemic benefit is diminished at eGFR <45; additional glucose-lowering agents may be required			Can be started in eGFR >60 Avoid if eGFR is persistently <45
	Limit to 10 mg daily if eGFR is <60 Avoid initiation if eGFR is <20	Avoid initiation if eGFR is <15	Limit to 10 mg daily if eGFR is <60 Avoid initiation if eGFR is <30	
Use in severe hepatic impairment	Avoid	5 mg may be used as a starting dose	Avoid	Avoid

eGFR presented in mL/min/1.73 m².

ASCVD=atherosclerotic CVD; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate.

NICE guidance on SGLT2 inhibitor use in people with type 2 diabetes (adapted from NICE NG28[4] by Brown, 2023)[5]

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 for adults with CKD, see NICE TA775.

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 heart failure, see NICE TA679, TA773 and TA902.

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.

Principal effects

Glycaemic control

SGLT2 inhibitors reduce glucose levels by preventing the reabsorption of glucose through the urinary tract. They can be used alone or with other agents for a synergistic glucose-lowering effect at licensed doses.

Additional benefits[6,7]

Reduction in body weight: Provide a modest but consistent weight reduction, typically ranging between 2–3 kg in clinical trials. This weight loss effect is generally attributed to increased urinary glucose excretion and slight reductions in body fluid volume.

Reduction in kidney disease progression: Reduce the risk of kidney disease progression by 37% in patients with chronic kidney disease, whether they have diabetes or not.

Reduction in cardiovascular death or hospitalisation for heart failure: Reduce the combined risk of cardiovascular death and hospitalisation for heart failure by 23% (relative risk [RR] 0.77; 95% CI 0.74–0.81). These benefits were consistent in people with and without diabetes, with relative risks of 0.77 in those with diabetes and 0.79 in those without.

Reduction in cardiovascular death: Also lower the risk of cardiovascular death alone by 14% (RR 0.86; 95% CI 0.81–0.92), showing similar effects between people with and without diabetes.

Contraindications

- **Type 1 diabetes** due to an increased risk of diabetic ketoacidosis.
- **Severe renal impairment:** avoid in people with an eGFR below the specific cut-offs stated in ***Table 1***.
- **Hypersensitivity** to any SGLT2 inhibitor or to any of their excipients.
- Current or recent **diabetic ketoacidosis**, due to the risk of worsening this condition.
- **Pregnancy or breastfeeding:** limited information.

Cautions

- Elderly population.
- Hypotension.
- Hypovolaemia or at risk of hypovolaemia.
- Complicated urinary tract infections (empagliflozin).
- Raised haematocrit (canagliflozin).
- People adhering to a ketogenic/low-calorie/low-carbohydrate diet.
- Glycaemic effect is reduced below eGFR 60 mL/min/1.73 m^2: additional glucose-lowering agents may be required.

Adverse effects

- **Common:** Increased risk of urinary infections, dizziness, urinary disorders, thirst, hypoglycaemia (when combined with insulin or sulfonylureas), skin reactions, genital infections.
- **Uncommon:** Hypotension, hypovolaemia, angioedema.
- **Rare:** Diabetic ketoacidosis, fracture risk, lower limb amputation, Fournier's gangrene.

Drug interactions

- There is an increased risk of hypotension when SGLT2 inhibitors are used with drugs that may cause hypotension.
- There is an increased risk of hypoglycaemia when SGLT2 inhibitors are used with other glucose-lowering agents (especially sulfonylureas and insulin).
- Other drug specific interactions (not an exhaustive list) are stated in ***Tables 2 and 3***.

Table 2. Class-effect drug interactions with SGLT2 inhibitors.

	Reported adverse effect and actions
Antihypertensive agents (including drugs that may cause hypotension)	Increased risk of hypotension **Action:** Monitor and adjust antihypertensive
Other glucose-lowering agents	Increased risk of hypoglycaemia with sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists and insulin **Actions:** Monitor and adjust dose of sulfonylurea, GLP-1 RA or insulin. Monitor for hypoglycaemic symptoms with DPP-4 inhibitors

Table 3. Drug interactions with specific SGLT2 inhibitors.

Agent	Reported adverse effect and actions
Empagliflozin	**Atorvastatin:** Increased muscle effects when used after atorvastatin[8] **Rifampicin:** Decreases exposure to empagliflozin **Lithium:** Empagliflozin may increase lithium excretion.
Dapagliflozin	**Somatrogon:** May increase blood glucose, opposing effect of dapagliflozin[9]
Canagliflozin	**Carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin:** Decrease exposure to canagliflozin
Ertugliflozin	**Somatrogon:** May increase blood glucose, opposing effect of ertugliflozin[10] **Rifampicin:** Decreases exposure to ertugliflozin

Monitoring

Renal function (eGFR)

- Monitor eGFR before initiating treatment and then at least annually thereafter, especially in people with renal impairment or those at risk of kidney dysfunction.
- An initial, reversible eGFR reduction of 5–8 mL/min/1.73 m² may occur within the first few weeks due to decreased hyperfiltration. This is normal.

Glycaemic control (HbA_{1c})

- Check HbA_{1c} levels 3 months after starting treatment to evaluate efficacy, and then annually.

Ketones

- Monitor ketone levels during treatment interruptions, such as for surgery or acute serious medical conditions, to reduce the risk of euglycaemic diabetic ketoacidosis, even if blood glucose is near normal.

Signs and symptoms of diabetic ketoacidosis

- Educate patients to monitor for DKA symptoms, including nausea, vomiting, abdominal pain, excessive fatigue and difficulty breathing, and to seek urgent medical care if these symptoms appear.

Blood pressure

- Regularly assess blood pressure, as SGLT2 inhibitors can lower this; adjustments in antihypertensive medication may be required. Measure at baseline and then at least annually.

Hydration and blood volume status

- Monitor hydration status, especially in elderly patients or those with renal impairment, as SGLT2 inhibitors increase urinary excretion and may lead to dehydration or hypotension.

Body weight

- Track weight periodically, as weight loss is a common effect and may indicate improved metabolic control.

Tolerance

- Review side effects, adherence and sick day rule understanding at each review.

Prescribing tips

Minimising risk of hypoglycaemia

Review glucose-lowering agents and consider dose reductions to reduce the likelihood of hypoglycaemia with concomitant use, especially if HbA_{1c} is already at target.

Minimising risk of diabetic ketoacidosis

Review DKA risk factors and address modifiable risk factors such as low-calorie or ketogenic diets. Note that DKA can occur with normal glucose levels with SGLT2 inhibitors. The risk of this is higher during acute illness.

Minimising risk of hypotension

Review diuretic and antihypertensive therapies periodically if hypertension improves, and adjust doses accordingly.

Sick day rules

Counsel on sick day rules and side effects upon initiation, and review patients' understanding of how to identify features of acute illness periodically.

Key summary table

Efficacy	High efficacy
Hypoglycaemia risk	Not unless combined with drugs causing hypoglycaemia
Weight loss	Modest effects (2–3 kg)
Cardiovascular effects	Benefits in ASCVD and heart failure: reduced risk of CV death and HHF, with or without type 2 diabetes
Renal effects	Benefits in CKD: reduced renal disease progression, with or without type 2 diabetes
Cost	High
Formulations	Oral
Renal effects: need for dosage adjustments	Neutral
Renal impairment	Adjustments required at eGFR <60; see *Table 1* and *Figure 1* for more information
Severe hepatic impairment	Dapagliflozin 5 mg can be used in severe hepatic impairment; other SGLT2 inhibitors should be avoided

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; CVOT=cardiovascular outcome trial; CKD=chronic kidney disease; HHF=hospitalisation for heart failure.

Additional safety information

MHRA (April 2016): Updated advice on the risk of diabetic ketoacidosis

MHRA (March 2017): Updated advice on increased risk of lower-limb amputations (mainly toes)

MHRA (February 2019): Reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)

MHRA (March 2020): Monitor ketones in blood during treatment interruptions for surgical procedures or acute serious medical illness

See also

Need to know guide: SGLT2 inhibitors: Indications, doses and licences in adults

How to: How to use SGLT2 inhibitors safely and effectively

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References can be found in the online version of this article.