



## 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.<sup>1,2</sup>

### Mechanisms of action<sup>1</sup>

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.<sup>2</sup>

#### 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.<sup>3</sup>
- 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  $\geq 10\%$ ).<sup>4</sup> See [Table 1](#) and [Figure 1](#)<sup>5</sup> for more information.

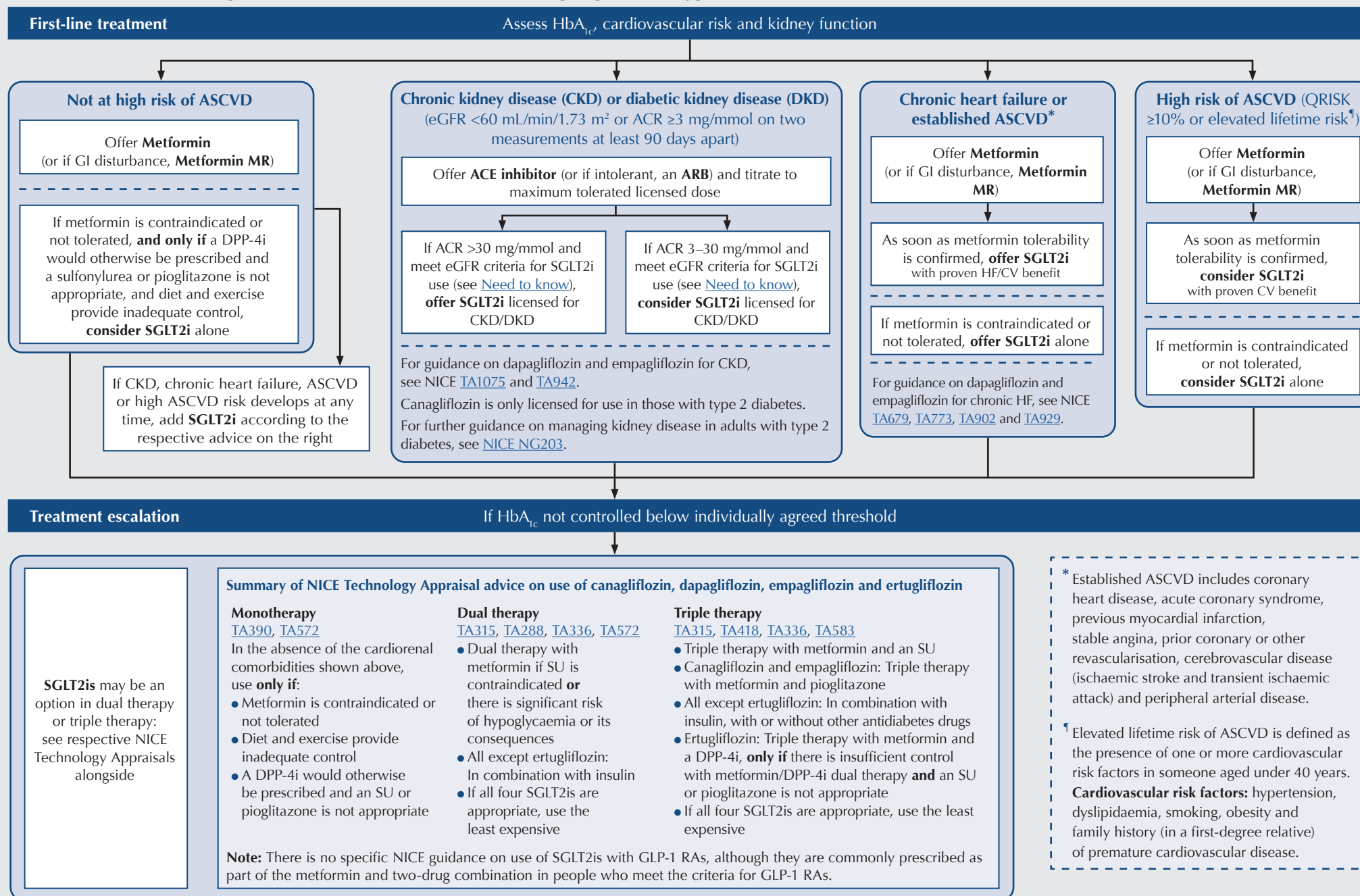
**Table 1. Summary of NICE recommendations on use of SGLT2 inhibitors for glycaemic control in type 2 diabetes (as an adjunct to diet and exercise).<sup>4</sup>**

	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 <a href="#">Figure 1</a> for more information			
Triple therapy	Yes – see <a href="#">Figure 1</a> for more information			
With insulin	Yes – see <a href="#">Figure 1</a> 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 m<sup>2</sup>.

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<sup>4</sup> by Brown, 2023)<sup>5</sup>





## 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<sup>6,7</sup>

**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<sup>2</sup>: 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 <b>Action:</b> Monitor and adjust antihypertensive
Other glucose-lowering agents	Increased risk of hypoglycaemia with sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists and insulin <b>Actions:</b> 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	<b>Atorvastatin:</b> Increased muscle effects when used after atorvastatin <sup>8</sup> <b>Rifampicin:</b> Decreases exposure to empagliflozin <b>Lithium:</b> Empagliflozin may increase lithium excretion.
Dapagliflozin	<b>Somatogon:</b> May increase blood glucose, opposing effect of dapagliflozin <sup>9</sup>
Canagliflozin	<b>Carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin:</b> Decrease exposure to canagliflozin
Ertugliflozin	<b>Somatogon:</b> May increase blood glucose, opposing effect of ertugliflozin <sup>10</sup> <b>Rifampicin:</b> 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 m<sup>2</sup> may occur within the first few weeks due to decreased hyperfiltration. This is normal.

### Glycaemic control (HbA<sub>1c</sub>)

- Check HbA<sub>1c</sub> 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<sub>1c</sub> 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.

## 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](#)

## Key summary table

<b>Efficacy</b>	High efficacy
<b>Hypoglycaemia risk</b>	Not unless combined with drugs causing hypoglycaemia
<b>Weight loss</b>	Modest effects (2–3 kg)
<b>Cardiovascular effects</b>	Benefits in ASCVD and heart failure: reduced risk of CV death and HHF, with or without type 2 diabetes
<b>Renal effects</b>	Benefits in CKD: reduced renal disease progression, with or without type 2 diabetes
<b>Cost</b>	High
<b>Formulations</b>	Oral
<b>Renal effects: need for dosage adjustments</b>	Neutral
<b>Renal impairment</b>	Adjustments required at eGFR <60; see <i>Table 1</i> and <i>Figure 1</i> for more information
<b>Severe hepatic impairment</b>	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.

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**References** can be found in the [online version](#) of this article.

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