PULSE Nursing IN PRACTICE

QUICK GUIDE

# Sodium-Glucose Cotransporter-2 Inhibitors for Type 2 Diabetes and Chronic Kidney Disease

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## Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have transformed the modern management of type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD) and chronic heart failure (CHF). SGLT2i provide heart and kidney benefits beyond their glucose lowering effect and are ideal for early initiation in many patients with T2DM and CKD. There has been a significant change in the UK SGLT2 prescription guidelines since 2022. This guide includes information from the National Institute for Health and Care Excellence (NICE) and UK Kidney Association (UKKA) guidelines to provide a quick reference guide for the use of SGLT2i both in patients with T2DM, those with CKD and patients with both conditions.

## SGLT2i in patients with T2DM: NICE criteria

While metformin remains the initial treatment of choice for people living with T2DM, NICE now recommends dual initial therapy in many patients (see indications).[1] When starting treatments sequentially, start with metformin and check tolerability.[1] Once metformin tolerability has been confirmed, you can start appropriate patients on SGLT2i;[1] this typically occurs within a month or two of starting metformin. Prescribe initial SGLT2i monotherapy where metformin is contraindicated.[1]

**Indications for offering initial SGLT2i therapy in patients with T2DM (strongest recommendation)**

- Co-morbid established atherosclerotic cardiovascular disease (CVD)[1]

– This may include coronary heart disease, prior myocardial infarction, acute coronary syndrome, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) or peripheral arterial disease[1]

- Co-morbid CHF[1]
- Co-morbid heavy albuminuric CKD (urinary albumin-to-creatine ratio [uACR] >30 mg/mmol)[1]

**Consider SGLT2i for T2DM patients:**

- with CKD who[1]

– are taking an angiotensin receptor blocker or an angiotensin-converting enzyme (ACE) that is titrated to the highest licensed tolerable dose
– have a uACR of 3–30 mg/mmol
– meet the criteria in the marketing authorisation[2,3]

- ≥40 years of age with a 10-year cardiovascular risk ≥10%[1]
- under 40 years of age with an elevated lifetime risk of CVD (defined as the presence of 1 or more cardiovascular risk factor)*[1]

*CVD risk factors include hypertension, smoking, dyslipidaemia, obesity and a first-degree relative with premature CVD.[1]

**Indications for SGLT2i add-on therapy[1]**

- People with T2DM who would benefit from cardio-renal protection and are not currently taking an SGLT2i
- For elevated glucose T2DM patients, particularly when:

– Haemoglobin A1c (HbA1c) is ≥58 mmol/mol (7.5%) and other oral antidiabetics are ineffective, not tolerated or contraindicated

**Choice of SGLT2i**

NICE recommends using an SGLT2i with proven cardiovascular protection (empagliflozin, dapagliflozin or canagliflozin) when used for its cardio-protective properties.[1]

**Benefits of SGLT2i for people with T2DM[4]**

- Improved glycaemic control
- Slowing CKD disease progression
- Weight reduction
- Reduced risk of major adverse cardiovascular events and heart failure

## SGLT2i in CKD

**UKKA guidelines**

I have chosen to focus on the UKKA guidelines for the management of CKD,[5] as these guidelines have been updated to incorporate the NICE technology appraisals of both SGLT2i treatments licensed for the management of CKD (empagliflozin and dapagliflozin).[6,7]

- SGLT2i are recommended for CKD management in people without diabetes if they have an estimated glomerular filtration rate (eGFR) ≥20 ml/min/1.73 m² and a uACR of ≥25 mg/mmol[5]
- Typically, patients requiring SGLT2i therapy will also benefit from maximum licensed and tolerated dose of renal angiotensin inhibition with either ACEs (e.g., ramipril) or angiotensin receptor blockers (e.g., losartan)[6,7]

## Guidance for initiating SGLT2i in patients with CKD

| | | SGLT2 inhibition to lower cardiovascular outcomes and kidney disease (those with type 1 diabetes, PKD, or kidney transplant were excluded from the definitive trials) eGFR (mL/min/1.73m²) | | | | |
|---|---|---|---|---|---|---|
| | | ≥60 | ≥45 <60 | ≥20 <45 | <20 | Dialysis |
| **uACR (mg/mmol)** | <25 | * | Suggested (in T2DM) | Advised ✓ | Suggested | Not advised** |
| | ≥25 | Advised ✓ | Advised ✓ | Advised ✓ | Suggested | Not advised** |

**PKD** Polycystic kidney disease
*It is not advised to use SGLT2 inhibition to lessen the progression of kidney disease for those with eGFR ≥60 mL/min/1.73m² and uACR <25 mg/mmol as it is out of the scope of the UK Kidney Association Guideline.
**Additional research on the role of SGLT2 inhibition in people on kidney replacement therapy is needed.
Note. Adapted from UK Kidney Association guidelines.[5]

### Prescribing considerations

SGLT2i may increase the risk of a number of issues. Before prescribing, it is important to consider the risks as well as the potential benefits of initiation. Risks include:

**1 Hypoglycaemia** – caution advised when prescribed alongside sulphonylurea drugs (e.g., gliclazide) or insulin[5]

**2 Hypovolaemia** – frail individuals and those on diuretics are at an increased risk of hypovolaemia[4,5]

**3 Genital mycotic infections** – consider history of recurrent genital thrush before prescribing[4,5]

**4 Urine infections** – consider history of recurrent urinary tract infections (UTIs) before prescribing[5]

**5 Ketoacidosis** – rates of ketoacidosis are much higher in T2DM,[5] particularly for those with a BMI ≤27 kg/m², for those who have rapidly progressed to requiring insulin therapy, or for those with high HbA1c (>86 mmol/mol).[5] Avoid if a patient has a history of previous diabetic ketoacidosis (DKA)[8]

**6 Lower limb amputations** – SGLT2i can theoretically reduce microvascular circulation. SGLT2i should be avoided in patients with active foot disease[5]

**7 Fournier's gangrene** – the UK Medicines and Healthcare Products Regulatory Agency (MHRA) has provided warnings on a possible association between SGLT2i and developing Fournier's gangrene[5]

Wilding et al (Diabetes Therapy 2018)[4] suggested a red/amber/green rating for the initiation of SGLT2i for people with T2DM (see below). I would suggest it as a useful guide for people with CKD; although the risk of ketoacidosis is lower than for those with diabetes.[5] In addition, the risk of mycotic infection decreases with a decrease in glycosuria.[5] →

## SGLT2i prescribing considerations

### Offer SGLT2i therapy if the patient

- Has CVD
- Has a history of HF
- Has previously had a stroke
- Is metformin intolerant as the first-line treatment
- Is on metformin (then SGLT2i can be a second-line or third-line treatment as an add-on therapy including combining with insulin and GLP-1 RA)
- Is overweight or obese
- Has renal impairment, DKD, or CKD
- Is receiving loop diuretics
- Has osteoporosis
- Has a history of fractures
- Has no history of lower limb amputation
- Has no history of PAD
- Is vulnerable to the effects of hypoglycaemia

### Think about SGLT2i therapy if the patient

- Has a history of PAD
- Has existing foot ulcers
- Has a history of foot ulceration
- Has previous lower limb amputation
- Is elderly, frail, or has cognitive impairment
- Is on a low calorie, low carbohydrate, or ketogenic diet
- Has had recurrent UTIs
- Has had recurrent genital mycotic infections
- Has a BMI of <25 kg/m²
- Has high HbA1c levels (>86 mmol/mol or 10%)
- Is receiving systemic steroid therapy

### Do not prescribe SGLT2i therapy if the patient

- Has an excessive alcohol intake
- Has an acute illness
- Has recently had major surgery
- Has had previous DKA
- Is planning a pregnancy, pregnant (or suspected pregnant) or breastfeeding
- Has an eating disorder
- Has several predisposing factors for Fournier's gangrene
- Has rapidly progressed to insulin usage (within a year)
- Has recently undergone major surgery

**DKD** Diabetic kidney disease. **GLP-1 RA** Glucagon-like peptide-1 receptor agonists. **HF** Heart failure. **PAD** Peripheral arterial disease.
Note. Adapted from Wilding, et al.[4]

## SGLT2i dosing recommendations

### Empagliflozin[2]

- Start empagliflozin at 10 mg and titrate up to 25 mg if additional glycaemic improvement is required in those with an eGFR ≥60 mL/min/1.73 m²

**i.e., G1–G2**

- Start or continue empagliflozin (10 mg) in those with an eGFR <60 mL/min/1.73m²
- Limited experience means that it is not recommended to start empagliflozin in those with an eGFR <20 mL/min/1.73m²

### Canagliflozin[9]

- Initiate or continue at 100 mg in those with an eGFR ≥30 mL/min/1.73m²

**i.e., G1–G2, G3a and G3b**

- Titrate up to 300 mg if additional glycaemic improvement is required in those with an eGFR ≥60 mL/min/1.73m²

**i.e., G1-G2**

- Do not start treatment in those with an eGFR <30 mL/min/1.73m²
- However, treatment can continue until dialysis/RRT in those with uACR >30 mg/mmol

### Ertugliflozin[10]

- May be started at 5 mg and titrated up to 15 mg if additional glycaemic improvement is required in those with an eGFR ≥45 to <60mL/min/1.73 m²

**i.e., G1–G2**

- Do not initiate in those with an eGFR <45 mL/min/1.73 m²

**i.e., G3b, G4 and G5**

- Stop treatment when eGFR is consistently <30 mL/min/1.73m²

**i.e., G4 and G5**

### Dapagliflozin[3]

- May be started and continued (10 mg) in those with an eGFR ≥15 mL/min/1.73m²

**i.e., G1–G2, G3a, G3b and G4**

- Do not initiate in those with an eGFR <15 mL/min/1.73m²

**i.e., G5**

**Chronic kidney disease stage (eGFR)**

**G1–G2** = ≥60 mL/min/1.73 m²
**G3a** = 45–59 mL/min/1.73 m²
**G3b** = 30–44 mL/min/1.73 m²
**G4** = 15–30 mL/min/1.73 m²
**G5** = <15 mL/min/1.73 m²

**RRT** Renal replacement therapy

Note. Adapted from Wilding et al.[4]

## Dosing

Above is a summary of the dosing recommendation based on eGFR. Please note that only empagliflozin and dapagliflozin are licensed for CKD in people without diabetes.[6,7]

## Monitoring

- Routine early assessments of kidney function are not required after initiation of SGLT2i[5]
- If early kidney function assessment is performed in the weeks post SGLT2i initiation, changes in eGFR must be interpreted with caution and in light of expected drug effects[5]
- Monitor blood glucose and HbA1c levels in people with T2DM (on insulin or sulphonylurea drugs)
- Check for signs of side effects and adjust therapy accordingly

## Patient education

Ideally provide the following advice in both a verbal and written format:

- Importance of adherence to medication and lifestyle changes
- Awareness of side effects and when to seek medical help
- How and when to self-monitor
- Dietary advice regarding ketogenic/very low carbohydrate diets and SGLT2i

Patient information leaflets highlighting sick day guidance as well as signs and symptoms of DKA and Fournier's gangrene are available from UKKA and can be found within some GP clinical systems (e.g., Ardens).

## Conclusion

SGLT2i offer significant benefits for the management of T2DM and CKD, especially in patients with additional cardiovascular risk factors. Adherence to NICE guidelines and the UKKA recommendations ensures optimised patient outcomes. Careful selection of suitable patients, regular monitoring and patient education are pivotal for the effective and safe use of these medications.

**Resources for patients**

- UKKA SGLT2i patient information leaflet for people with diabetes https://guidelines.ukkidney.org/wp-content/uploads/2022/10/Example-patient-information-sheet-for-a-person-being-initiated-on-an-SGLT-2-inhibitor-who-also-has-diabetes.pdf
- UKKA SGLT2i patient information leaflet for people without diabetes https://guidelines.ukkidney.org/wp-content/uploads/2022/10/Example-patient-information-sheet-for-a-patient-being-initiated-on-an-SGLT-2-inhibitor-who-does-not-have-diabetes.pdf

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