When to use SGLT2 inhibitors in T2D

NICE and SIGN guidelines

Sodium–glucose cotransporter-2 inhibitors (SGLT2is) recommended as:

Monotherapy
Options as monotherapy instead of DPP-4 inhibitors, if sulfonylurea or pioglitazone not appropriate, where metformin contraindicated or not tolerated.

→

Dual therapy
Options in dual therapy with metformin.

→

Triple therapy
Options in metformin-containing triple-therapy regimens, including with insulin.

(Dapagliflozin is not approved for combination with pioglitazone.)

SIGN recommends that in established cardiovascular disease, SGLT2 inhibitors or GLP-1 RAs with proven cardiovascular benefit should be considered (SIGN, 2017).

NICE (2017) does not currently make specific recommendations for glycaemia management in those with established cardiovascular.

About this series

The aim of the "How to" series is to provide readers with a guide to clinical procedures and aspects of diabetes care that are covered in the clinic setting.

What and why

- SGLT2 inhibitors are a class of oral antidiabetes drug that block reabsorption of glucose in the kidneys.
- NICE and SIGN recommend their use in a process of stepwise intensification. The recent ADA/EASD consensus report suggests individualising SGLT2i use based on comorbidities and needs.
- When prescribing SGLT2 inhibitors, safety and tolerability should be considered for each individual based on the latest scientific evidence.

Citation: Brown P (2018) How to use SGLT2 inhibitors safely. *Diabetes & Primary Care* **20**: **173–4**

Author: Pam Brown, GP in Swansea.

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus report

Comprehensive lifestyle intervention management and metformin therapy

Established ASCVD or CKD — NO → **Without established ASCVD or CKD**

ASCVD predominates

either/or

- **GLP-1 RA** with proven CVD benefit
- **SGLT2i** with proven CVD benefit, if eGFR adequate

If HbA_{1c} above target

- Consider adding the other class (**GLP-1 RA** or **SGLT2i**) with CVD benefit; or
- Consider other drug with demonstrated CV safety

HF or CKD predominates

Preferably:
SGLT2i with evidence of reducing HF and/or CKD progression if eGFR adequate
or
If SGLT2i not tolerated or contraindicated, or if eGFR too low, add **GLP-1 RA** with proven CVD benefit

If HbA_{1c} above target

- Avoid TZD with HF

Choose agents with CV safety:

- Consider adding the **other class with CV benefit**
- **DPP-4i** (not saxagliptin) if HF (if not on GLP-1 RA)
- **Basal insulin**
- **SU**

Compelling need to minimise hypoglycaemia

Choice of **DPP-4i**, **GLP-1 RA**, **SGLT2i** or **TZD**.
If other drugs chosen and still above HbA_{1c} target, consider adding **SGLT2i**

Compelling need to minimise weight gain/ promote weight loss

either/or

- **GLP-1 RA** with good efficacy for weight loss
- **SGLT2i**

If HbA_{1c} above target

- **SGLT2i**
- **GLP-1 RA** with good efficacy for weight loss

When considering injectable therapies, if on an SGLT2i, these guidelines recommend continue this with injectables.

If at agreed glycaemic target, consider switching one therapy to SGLT2i or GLP-1 RA, or add one of these therapies and aim for lower target or reassess 3 monthly and add therapy as soon as above target.

Adapted from the ADA/EASD consensus report (Davies et al, 2018).
ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; DPP-4i=dipeptidyl peptidase-4 inhibitor; eGFR=estimated glomerular filtration rate; GLP-1 RA=glucagon-like peptide receptor agonist; HF=heart failure; SGLT2i=sodium–glucose cotransporter-2 inhibitor; TZD=thiazolidinedione.

How to use SGLT2 inhibitors

Low risk Evidence supports SGLT2i prescribing	Moderate risk Prescribe SGLT2i with caution	High risk Do not prescribe SGLT2i
First-line (metformin intolerant)	History of PAD	Previous lower-limb amputation
Second-line to metformin	Osteoporosis	Existing diabetic foot ulcers
Third-line (add-on to second-line therapies)	Frail/elderly	DKA (or previous episode of DKA)
Combination with basal insulin or multiple daily injections of insulin	History of foot ulceration	Eating disorders
Established cardiovascular disease	History of fractures	Rapid progression to insulin (within 1 year)
No history of lower-limb amputation	GLP-1 receptor agonist combination	Latent autoimmune diabetes
No history of PAD	Ketogenic diet	Excessive alcohol intake
Microalbuminuria	High HbA_{1c} levels (86 mmol/mol or 10%)	Diabetes due to pancreatic disease
eGFR ≥60 mL/min/1.73 m^2	Steroid therapy	Stage 3 CKD/eGFR <60 mL/min/1.73 m^2
Overweight or obese	Cognitive impairment	Type 1 diabetes (diagnosed or suspected)
Vulnerable to the effects of hypoglycaemia	BMI <25	Genetic diabetes
Adapted from Wilding et al, 2018 (https://bit.ly/2DkWlZZ)	Receiving loop diuretics	Acute illness
		Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding
		Recent major surgery

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

CKD=chronic kidney disease; DKA=diabetic ketoacidosis; LLA=lower-limb amputation; PAD=peripheral arterial disease.

Genital and urinary infections

- Thrush-type genital infections are common.
- Infections are more common early in treatment; providing information may improve continuation of treatment.
- Treat with topical or oral treatments.
- Most people can continue SGLT2i treatment.
- Glycosuria may cause urinary symptoms and more frequent voiding.
- UTIs are relatively rare; manage with standard antibiotics.

Lower-limb amputations (LLAs)

- European Medicines Agency (EMA) has advised caution in using SGLT2is in those at high risk of LLA, as a class effect cannot be ruled out (https://bit.ly/2QcKnnR).
- Absolute risk is low (0.6 per 100 person-years in cardiovascular outcome trials), but appears higher in those with previous amputation.
- Risk does not appear to be dose-dependent.
- MHRA has advised all should receive advice and ongoing monitoring regarding preventive foot care.
- Ideally avoid SGLT2i in those with active foot ulceration or previous amputation.

Bone fractures

- Small increased fracture risk and changes in bone mineral density (BMD) seen in the CANVAS trial compared with placebo (but not in the CANVAS-R population), 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.

Diabetic ketoacidosis (DKA)

- MHRA (https://bit.ly/24eXtSC) and EMA (https://bit.ly/2SDJYwg) have issued warnings regarding a small risk of euglycaemic DKA. Discuss this prior to and during SGLT2i therapy.
- Risk is higher:
  - if relatively insulin deficient
  - when insulin doses are reduced suddenly
  - when there is increased need for insulin (e.g. illness, alcohol abuse)
  - with restricted food intake, particularly carbohydrates
  - if dehydrated.
- Symptoms of DKA include nausea, vomiting, abdominal pain, generalised malaise and shortness of breath.
- Symptoms may be atypical and glucose may not be elevated.
- Stop SGLT2i drugs during acute illness and prior to surgical procedures – see **Sick day rules** below.

Sick day rules for T2D

When ill and at risk of dehydration, people with T2D should be advised to:

- Stop taking SGLT2i, metformin, GLP-1 RA, SUs, ACEI/ARBs and diuretic medicines if unable to eat or drink, or persistent vomiting or diarrhoea; contact their GP or specialist nurse for advice.
- Contact their practice, diabetes specialist team or emergency medical advice if unsure what to do.
- Stay well hydrated (2–3 L of fluid/day) and eat little and often.
- If not able to eat normally, replace meals with high carbohydrate snacks or drinks.
- Keep taking insulin and most other diabetes medicines 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 for ketones as well as blood glucose in this situation.
- "How to give sick day advice" (**https://bit.ly/2yNUt7X**).

Safe use: SGLT2i and renal function

- Check electrolytes and eGFR prior to therapy; monitor annually unless levels are <60 and, if so, check eGFR 3–6 monthly.
- Modest reductions in eGFR may occur when starting SGLT2is and ACEIs. These usually improve.
- All three SGLT2i drugs may be initiated provided eGFR ≥60 mL/min/1.73 m^2.
- If eGFR falls but remains ≥45 mL/min/1.73 m^2, canagliflozin and empagliflozin can be continued at their lower doses.
- Stop canagliflozin and empagliflozin if eGFR falls below 45, and dapagliflozin if eGFR <60.
- SGLT2is are not currently recommended for use with loop diuretics – check why loop diuretic in use and if it is needed.
- For those on other types of diuretic, review need and whether alternative treatments could be used (e.g. for blood pressure).

References

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