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When to use SGLT2 inhibitors in type 2 diabetes

What and why

- SGLT2 inhibitors (SGLT2is) are oral glucose-lowering drugs that block reabsorption of glucose in the kidneys.
- SGLT2is were initially developed as glucose-lowering drugs and were demonstrated to have beneficial effects on BP and weight reduction. The cardiovascular outcome trials and studies in people with renal disease and heart failure have confirmed significant benefits in these co-morbidities, which appear to be independent of glucose-lowering, with the HF and CKD benefits demonstrated in people with and without T2D.
- SGLT2is remain underused in the UK, depriving people with T2D 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 the SU or insulin 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 guidelines from the European Society of Cardiology (ESC), Primary Care Diabetes Europe (PCDE) and Kidney Disease Improving Global Outcomes (KDIGO).

Although these guidelines differ in their recommendations for first-line glucose-lowering therapy (alongside lifestyle measures), they recommend the evidence-based use of SGLT2is or GLP-1 RAs for those with or at high risk of atherosclerotic cardiovascular disease (ASCVD), and SGLT2is preferentially for those with heart failure (HF) or diabetic/chronic kidney disease (CKD).

NICE (2015) and SIGN (2017) guidelines recommend stepwise intensification starting with metformin, unless contraindicated, and including SGLT2is. However, these guidelines are out of date as they do not take account of all the additional benefits seen in the cardiovascular outcome trials (CVOTs) that were mandated for all newer glucose-lowering drugs. The NICE guideline to T2D in adults is currently being updated.

Since 2018, use of SGLT2is in the UK has been guided by the ADA/EASD consensus on glycaemic management and its 2019 update, thus ensuring people with T2D receive the added beneficial effects on significant co-morbidities such as ASCVD, HF and CKD. This consensus also identifies that, amongst those with T2D who do not yet have any of these co-morbidities, there may be a compelling need to minimise hypoglycaemia, minimise weight gain or promote weight loss, and SGLT2is are treatment options in these scenarios too. Only when treatment costs are the overriding concern are SGLT2is not prioritised as an early treatment choice.

ADA Standards of Care 2021

In December 2020, within its "live" Standards of Medical Care for Diabetes, the ADA has slightly updated its algorithm for ASCVD, HF and CKD from the ADA/EASD consensus update. It is likely these changes will be incorporated into the ADA/EASD glycemic consensus shortly. For this reason, we have chosen to share the ADA (2021) recommendations as the basis for our guidance on where to use SGLT2is, and these are shown in full in the ***algorithm overleaf***.

Based on evidence from renal studies, the ADA has chosen to separate CKD into that comprising diabetic kidney disease (DKD)/albuminuria and that comprising other types of CKD. DKD can be defined as hyperglycaemia-induced glomerular disease resulting in gradually rising urine albumin:creatinine ratio, and a gradual decline in eGFR (see Winocour et al, 2020). In people with diabetes, if there is no other obvious cause for the declining renal function it is usually attributed to diabetes, especially if other microvascular complications such as retinopathy are present. However, hypertension and other conditions can damage the glomerulus or cause tubular or interstitial fibrosis and result in CKD in people with or without diabetes, so if no retinopathy is present, further investigation for underlying causes may be appropriate. When DKD is unlikely, it is the increased CVD risk associated with CKD that the ADA is recommending to be treated with either GLP-1 RAs or SGLT2is.

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) or in combination with metformin	History of peripheral arterial disease	DKA (or previous episode of DKA)
Second-line to metformin	Osteoporosis or history of fractures	Eating disorders
Third-line (add-on to second-line therapies)	Frail/elderly; consider increased risk of volume depletion	Rapid progression to insulin (within 1 year)
Combination with basal insulin or multiple daily injections of insulin	Volume depletion: if suspected, correct before starting SGLT2i and monitor carefully	Latent autoimmune diabetes
Combination with GLP-1 RA	History of foot ulceration	Excessive alcohol intake
Established cardiovascular disease	Previous lower-limb amputation	Diabetes due to pancreatic disease
History of heart failure	Existing foot ulceration	Type 1 diabetes (diagnosed or suspected; dapagliflozin 5 mg for specialist use only)
No history of lower-limb amputation	CKD stage 3a (eGFR 45–60) or CKD stage 3b (eGFR 30–45) with ACR >30 mg/mmol†	Genetic diabetes
No history of peripheral arterial diease	Ketogenic diet	Acute illness
ACR >3 mg/mmol	High HbA_{1c} levels (86 mmol/mol or 10%)	Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding
eGFR ≥60 mL/min/1.73 m^2*	Systemic steroid therapy	Recent major surgery
Overweight or obese	Cognitive impairment	History of necrotising fasciitis of the perineum (Fournier's gangrene)
Vulnerable to the effects of hypoglycaemia	BMI <25	Empagliflozin not recommended in those ≥85 years
Prior stroke	Receiving loop diuretics	Severe hepatic impairment (dapagliflozin 5 mg can be initiated)
	Recurrent UTIs	
	Men with benign prostatic hypertrophy	
	Limited experience with ertugliflozin in those ≥75 years	

Adapted from Improving Diabetes Steering Committee (2020).

Consult individual Summaries of Product Characteristics prior to prescribing.

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

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

ACR=albumin:creatinine ratio; CKD=chronic kidney disease; DKA=diabetic ketoacidosis; eGFR=estimated glomerular filtraton rate.

*Canagliflozin is licensed for initiation at lower eGFR levels.

†Only canagliflozin 100 mg is currently licensed for initiation at eGFR <60; other SGLT2is should be stopped if eGFR is persistently less than 45 (do not use empagliflozin 25 mg or canagliflozin 300 mg doses below eGFR of 60). Dapagliflozin can be used to treat heart failure, but not for glucose-lowering, in those with an eGFR of ≥30.

When to use SGLT2 inhibitors

This how-to guide uses the ADA (2021) Standards of Diabetes Care as the basis of its recommendations. Use of SGLT2is in those with type 2 diabetes is expained in the algorithm below.

Lifestyle advice and metformin are recommended first-line.

SGLT2is are recommended:

- As an option instead of GLP-1 RAs (both with demonstrated CVD benefit) for those with or at high risk of ASCVD.
- For HF (preferentially SGLT2i with primary evidence in those with HF, or HF evidence from a CVOT).
- For those with DKD and albuminuria (preferentially SGLT2i with primary evidence for reducing CKD progression) and for those with CKD as an option instead of GLP-1RA to reduce CVD risk.
- As an option alongside DPP4is, GLP-1 RAs or TZDs when there is a compelling need to avoid hypoglycaemia
- As an option alongside a GLP-1 RA if compelling need to minimise weight gain or achieve weight loss.

American Diabetes Association (ADA, 2021) Standards of Care

Comprehensive lifestyle intervention management and metformin therapy
Consider initial dual therapy if HbA_{1c} is >16.5 mmol/mol above agreed target

High-risk or established ASCVD, CKD or HF*

YES

Consider independently of baseline HbA_{1c}, individualised HbA_{1c} target or metformin use†

Established ASCVD or high risk of ASCVD
(age >55 years with coronary, carotid or lower-extremity artery stenosis >50%, or LVH)

either/or

GLP-1 RA with proven CVD benefit[1] | **SGLT2i** with proven CVD benefit[1]

If HbA_{1c} above target

- Consider adding the other class; **OR**
- Consider another drug with demonstrated CV safety (**TZD**[2], **DPP-4i** (if not on GLP-1 RA), **basal insulin**[3], **SU**[4]

Established HF (particularly HFrEF: LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

*Action whenever these occur, regardless of background glucose-lowering medications.
†Most people in trials also received metformin at baseline.

Established CKD

DKD and albuminuria

YES

Preferably: SGLT2i with primary evidence of reducing CKD progression

OR
SGLT2i reducing CKD progression in CVOTs[5,6]
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i contraindicated or not tolerated

NO

For people with T2D and CKD (e.g. eGFR <60 mL/min/1.73 m^2) and thus at increased risk of CV events

either/or

GLP-1 RA with proven CVD benefit[1] | **SGLT2i** with proven CVD benefit[1,7]

NO

If HbA_{1c} above individualised target

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, add another from **SGLT2i**, **TZD**, **GLP-1 RA** or **DPP-4i** (do not combine GLP-1 RAs and DPP-4is)

Add the third drug class, if appropriate, if still above HbA_{1c} target

If HbA_{1c} above target

Consider adding a **later-generation SU**[4] or **basal insulin**[8] with lower hypoglycaemia risk

Compelling need to minimise weight gain/ promote weight loss

GLP-1 RA with good efficacy for weight loss[9], or **SGLT2i**

Add the other class if HbA_{1c} remains above target

HbA_{1c} above target or SGLT2i/GLP-1 RA contraindicated/not tolerated

Preferably **DPP-4i** (if not on GLP-1 RA)

If DPP-4i not tolerated or already on GLP-1 RA, consider **SU**[4], **TZD**[2] or **basal insulin**

Cost is a major issue[10]

SU[4] or **TZD**[10]

Add the other class if needed

Add lowest-cost **basal insulin** or consider other therapies based on cost, if needed

1. Proven CVD benefit means a label indication of reducing CVD events.
2. Low dose may be better tolerated though less well studied for CVD effects.
3. Degludec and U-100 glargine have demonstrated CVD safety.4. Lower risk of hypoglycaemia with later-generation SU; glimepiride similar CVD safety to DPP-4i.
5. SGLT2i labelling regarding eGFR for initiation and continued use varies by region and drug.
6. Empagliflozin, canagliflozin and dapagliflozin have shown reductions in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary HF outcome data.
7. Proven benefit means a label indication of reducing HF in this population.
8. Degludec/glargine **U-300** < glargine **U-100**/detemir < NPH insulin.
9. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
10. Consider cost of drugs. Substitute DPP-4i if cheaper than TZDs.

See full ADA (2021) Standards of Care section 9 for additional treament options

How to use SGLT2 inhibitors safely

Genital and urinary infections

- Thrush-type genital infections are common.
- Infections are more common early in treatment; providing hygiene information may improve treatment continuation.
- 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. If recurrent, stop SGLT2i treatment.

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 (bit.ly/2QcKnnR).
- Absolute risk is low, but appears higher in those with previous amputation.
- Risk does not appear to be dose-dependent.
- MHRA has advised that all people treated with an SGLT2i should receive advice regarding preventative foot care, including to inspect feet regularly and to report wounds, discolouration or pain and to stay well hydrated.
- Ideally avoid SGLT2i in those with active foot ulceration or previous amputation.

Diabetic ketoacidosis (DKA)

- MHRA (2016) and EMA (2016) have issued warnings regarding a small risk of DKA, which may be euglycaemic. 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** alongside.

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 or CREDENCE trials), 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.

Sick-day rules 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 T2D should be advised to:

- Temporarily stop **SADMANS** drugs (**S**GLT2is, **A**CEis, **D**iuretics, **M**etformin, **A**RBs, **N**SAIDs and **S**Us*), and if unable to eat or drink, or persistent vomiting or diarrhoea; contact their GP or specialist nurse for advice.
- If unsure how to self-manage during illness, encourage them to contact their practice or diabetes specialist team or seek emergency medical advice if unsure what to do.
- Stay well hydrated (2–3 L of fluid per day) and eat little and often.
- If not able to eat normally, replace meals with high carbohydrate snacks or drinks.
- **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 for ketones as well as blood glucose in this situation.
- "How to advise on sick day rules" (**Down, 2020**).

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

Safe use: SGLT2is and renal function

- Check electrolytes and eGFR prior to therapy; monitor annually unless eGFR <60 mL/min/1.73 m^2, when eGFR should be checked 3–6 monthly.
- 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 usually improve and, over the longer term, SGLT2is may slow progression of CKD.
- Dapagliflozin, empagliflozin and ertugliflozin may be initiated provided eGFR ≥60. Empagliflozin (10 mg), ertugliflozin and dapagliflozin (10 mg) can be continued if eGFR is 45–60. These drugs should be stopped if the eGFR is persistently <45. Dapagliflozin can be used to treat HF if eGFR is ≥30.
- Canagliflozin is licensed to slow progression of diabetic kidney disease and can be initiated at eGFR ≥45, or ≥30 if albuminuria is ≥30 mg/mmol. It should not be initiated if eGFR is <30 but can be continued if already initiated until renal replacement is required. Glucose-lowering effects decrease at lower eGFRs, 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 particularly in older people.

References

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