Doncaster and Bassetlaw Place Guideline for the Safe and Appropriate Use of Sodium Glucose Co-Transporter 2 inhibitors (SGLT2i's)

What are SGLT2 inhibitors?

SGLT2 inhibitors are an established class of medications for the treatment of type 2 diabetes, heart failure and chronic kidney disease which act by preventing the absorption of glucose and sodium, mainly from the proximal renal tubule in the kidney.

Glucose and sodium are, therefore, lost in urine. People do not become hyponatraemic (unless on diuretics as well) as most of the sodium is reabsorbed in the distal tubule.

What are the benefits of SGLT2 inhibitors?

Clinical trials using SGLT2 inhibitors have provided strong evidence in the trial populations for reduced risk of major cardiovascular, renal and heart failure events.

These medications are associated with weight loss of up to 3 kg of body weight and a reduction in systolic blood pressure of approximately 3–5 mmHg.

In addition, in people living with diabetes, they reduce HbA1c by up to 10 mmol/mol (1.0%) depending upon the initial HbA1c in people with an eGFR>45ml/min. When used alone or with agents that are not insulin, sulphonylureas or meglitinides they have minimal risk of hypoglycaemia.

Licences for the SGLT2i medications are changing rapidly. Always check the up-to-date licences. The information in this guidance was correct at the time of publication.

Which SGLT2 inhibitors do I use?

SGLT2 inhibitors have licences for treatment of insufficiently treated type 2 diabetes, chronic kidney disease (with and without type 2 diabetes) and symptomatic chronic heart failure with reduced ejection fraction (with or without type 2 diabetes). SGLT2s have also shown benefit in those with atherosclerotic cardiovascular disease (previous MI, previous stroke, and peripheral arterial disease) in people living with type 2 diabetes.

One significant co-morbidity

Diabetes	HF	CKD *
Dapagliflozin or Empagliflozin	Dapagliflozin or Empagliflozin	Dapagliflozin

Two significant co-morbidities

	Diabetes	HF	CKD*	CKD**	ASCVD***
Diabetes		Dapagliflozin or Empagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin
HF	Dapagliflozin or Empagliflozin		Dapagliflozin	Dapagliflozin or Empagliflozin	Empagliflozin
CKD*	Dapagliflozin	Dapagliflozin			Dapagliflozin
CKD**	Dapagliflozin	Dapagliflozin or Empagliflozin			
ASCVD***	Empagliflozin	Empagliflozin	Dapagliflozin		

Three or more significant co-morbidities (Diabetes and/or ASCVD and/or HF and/or CKD*)

Dapagliflozin

We would not advocate switching between SGLT2 inhibitors if co-morbidity changes. The above suggestions for initial therapy are based on licences and clinical trial data.

* With albuminuria: urine ACR ≥ 22.6mg/mmol and eGFR 25-75ml/min/1.73m^2 either attributed to diabetic and non-diabetic causes in someone living with diabetes or in someone not living with diabetes excluding those with polycystic kidney disease or someone on immunological therapy for renal disease

** with ACR<22.6mg/mmol and eGFR 25-75ml/min/1.73m^2

*** ASCVD is not a licenced indication and trial evidence for benefits in ASCVD in combination with other licenced indications have led to the choices in this guidance

Acknowledgment to Hannah Beba, RPS Approved Consultant Pharmacist for Diabetes Awaiting Credentialling. For preparing the original Leeds Citywide Guideline for the Safe and Appropriate Use of Sodium Glucose Co-Transporter 2 inhibitors (SGLT2i's) document prepared for Leeds Clinical Commissioning Group, Leeds Teaching Hospital and Leeds Community Healthcare (February 2022)

Looking to Start an SGLT2

Discuss individualised benefits of taking an SGLT2 and document the indication at initiation.

Check that this is the right drug for the person

Caution in all in the following situations:

- People diagnosed with or at risk of frailty
- Those on loop diuretics (risk of hypotension and dehydration esp. in the elderly)

In addition to the above caution in people living with diabetes in the following situations:

- Person adhering to a ketogenic diet, recent weight loss or people intermittently fasting (more important if elderly or CKD or on diuretics) e.g., during Ramadan, should consider withholding medication or introducing ketone testing
- People on steroid therapy (either IV or oral)
- Body mass index under 25kg/m2 (under 23kg.m^2 in south Asian people)
- Person considered at high risk of acute effects of hyperglycaemia (such as dehydration due to non-adherence to medication)
- Person with very high HbA1c >86mmol/mol (~10% in old HbA1c)
- Cognitive impairment as it may interfere with the adequate understanding to take action to prevent and identify DKA

Avoid in all in the following situations:

- eGFR lower than allowed in the up-to-date licensing of the medication being considered
- Person with excess alcohol consumption or IVDU
- Unwell person, inpatient or otherwise (e.g.acute medical illness including sepsis, COVID-19, acute vascular event and still unstable, dehydration, surgery or planned medical procedure)
- Pregnancy or breast feeding (females of child-bearing potential should be counselled on risks in pregnancy and to withhold the medication if they are planning pregnancy)
- Eating disorder
- Age <18 years
- Active foot disease (infection, ulceration, or ischaemia) unless the specialist team have advised to continue or have reinitiated
- Organ transplant

In addition to the above avoid in people living with diabetes in the following situations:

- History of diabetic ketoacidosis unless a clear cause was identified, and the specialist teams involved believe that benefit outweighs risk of continued care
- Type 1 diabetes unless specifically indicated by specialist team (NB: now off liscence use)
- Any diagnosis or suspicion of diabetes due to other causes, including T1D, a latent autoimmune diabetes (LADA), other genetic causes of diabetes, known pancreatic disease or injury, or people who rapidly progressed to needing insulin within 1 year of diagnosis

If a person is suitable to start the SGLT2 then counsel them robustly, there are lots of benefits to these medications and much of the risk can be offset by this. This counselling should be

Discuss the most common side effects:

Genital mycotic infections: advise people this is common in both male and females. Provide genital hygiene advice and advice on how to self-treat. Most initial cases can be treated with topical antifungals and won't recur. The SGLT2is can be continued during treatment. Consider reviewing therapy or prophylactic antifungal therapy if recurrent infections.

Increased urination: advise people to expect Increased frequency and/or increased volume of urine

Volume depletion side effects discuss with people the signs (thirst, postural dizziness, hypotension and dehydration) and advise people that you will take particular care in someone who is frail/elderly. Discuss measuring blood pressure in lying and standing positions in those at risk of falls and those on diuretics

Discuss rare side effects:

Diabetic ketoacidosis (can be euglycemic): advise people that this is a rare side effect in people living with diabetes but that it can be serious if it does occur: Inform and advise people living with diabetes about how to prevent, recognise and how to get treatment for diabetic ketoacidosis (see BOX 1)

Amputation: advise people that this is an uncommon side effect. In people living with diabetes, it would be advisable to encourage routine preventative foot care and ask all people taking SGLT2is to report any wounds, discolouration, or tender/painful feet. If they discover any foot problems, they should seek medical attention immediately and therapy should be withheld if significant foot problems arise (such as infection or skin ulcers or ischaemia). Advise people that evidence for this comes only from the CANVAS trial (involving Canagliflozin) and not other SGLT2is. High risk people should receive standard education on relevant diabetes foot care.

Fournier's Gangrene: advise people this is a very rare side effect. People should remain alert to any perianal discomfort (pain or swelling) that is moderate to severe and may be accompanied by general malaise. Advise on good genital hygiene and how to seek help if they do develop symptoms.

Fracture Risk: advise people this is rare however in some cases it may be important to monitor bone parameters e.g., in people with CKD calcium, phosphate and PTH would be monitored. Advise people that evidence for this comes only from trial data involving Canagliflozin.

Discuss with people the importance of remaining well hydrated unless they are advised to restrict fluids.

Discuss Sick Day rules (see Box 2) and other times when SGLT2i may need to be stopped (see Box 3)

Before you prescribe, a few checks. In people living with diabetes review medications that may cause hypoglycaemia, such as insulin, meglitinides and sulphonylureas. If someone is below or at their individualised blood glucose or HbA1c targets, or there is other cause for concern (e.g., high in day variability of blood glucose) consideration should be given to reduce doses when the SGLT2 inhibitor is started (a 50% reduction in dose of meglitinide or sulphonylurea or a 20% dose reduction in insulin may be appropriate). If the insulin requirement reduces considerably, one should be cautious of a higher risk of developing DKA. The healthcare professional should review diuretic and anti-hypertensive therapy periodically if hypertension improves or if there is postural hypotension. Before initiating, review licences for renal function (NB no additional renal function monitoring should be required for SGLT2 inhibitors above standard monitoring dictated by care plan):

	eGFR ≥60 ml/min/1.73m^2	eGFR 45 to <60 ml/min/1.73m^2	eGFR 30 to < 45 ml/min/1.73m^2	eGFR 15 to <30 ml/min/1.73m^2	eGFR<15 ml/min/1.73m^2
Canagliflozin					
Insufficiently controlled type 2 diabetes mellitus	Initiate with 100mg od and titrate to 300mg od if needed for glycaemic control	Initiate with 100mg od. Continue or reduce to 100mg for people already taking Canagliflozin	Initiate with 100mg od. Continue or reduce to 100mg for people already taking Canagliflozin. Note a reduced glycaemic effect is very likely at this eGFR.	Not recommended in the absence of DKD due to lack of glycaemic efficacy	Not recommended in the absence of DKD due to lack of glycaemic efficacy
Treatment of diabetic kidney disease (DKD) in adults with type 2 diabetes (UKKA have advised to have uACR ≥25mg/mmol and/or eGFR 25-60 ml/min/1.73m2 for use in people living with diabetes)	Initiate with 100mg od and titrate to 300mg od if needed for glycaemic control	Initiate with 100mg od. Continue or reduce to 100mg for people already taking Canagliflozin	Initiate with 100mg od. Continue or reduce to 100mg for people already taking Canagliflozin	Continue 100mg for patients already taking Canagliflozin only in those with a urinary ACR > 30mg/mmol .	Continue 100mg for patients already taking Canagliflozin only in those with a urinary ACR > 30mg/mmol. can continue until dialysis or renal transplantation.
Dapagliflozin					
Adults for the treatment of insufficiently controlled type 2 diabetes mellitus	Initiate with 10mg od	Initiate with 10mg od	Initiate with 10mg od. Note a reduced glycaemic effect is very likely at this eGFR.	Initiate with 10mg od. No glycaemic effect is expected at this eGFR	Do not initiate but can continue on 10mg od. Not recommended for those needing renal transplant but can be continued in dialysis. No glycaemic effect is expected at this eGFR.
Symptomatic chronic heart failure with reduced ejection fraction with or without diabetes	Initiate with 10mg od	Initiate with 10mg od	Initiate with 10mg od	Initiate with 10mg od	Do not initiate but can continue on 10mg od. Not recommended for those needing renal transplant but can be continued in dialysis
Chronic kidney disease (NICE have advised: for people with diabetes, you should have an eGFR 25-75ml/min/1.73m^2 and : type 2 diabetes or a uACR ≥22.6mg/mmol)	Initiate with 10mg od	Initiate with 10mg od	Initiate with 10mg od	Initiate with 10mg	Do not initiate but can continue on 10mg od. Not recommended for those needing renal transplant but can be continued in dialysis
Empagliflozin					
Insufficiently controlled type 2 diabetes mellitus	Initiate at 10mg od and titrate to 25mg od if needed	Only initiate in those with established CVD, 10mg od. Continue or reduce dose to 10mg od in those already taking Empagliflozin	Only initiate or continue in those with established CVD, 10mg od. Note a reduced glycaemic effect is very likely at this eGFR.	Do not initiate and discontinue in those already taking	Do not initiate and discontinue in those already taking
Symptomatic chronic heart failure with reduced ejection fraction with or without diabetes	Initiate at 10mg od	Initiate at 10mg od	Initiate at 10mg od	Initiate 10mg od if eGFR ≥ 20ml/min/1.73m2. Discontinue if eGFR < 20 ml/min/1.73m2	Do not initiate. Discontinue if already taking
Ertugliflozin					
Insufficiently controlled type 2 diabetes mellitus	Initiate at 5mg od and titrate to 15mg if needed for glycaemic control	Do not initiate. Continue established dose for those already on ertugliflozin	Do not initiate. Discontinue if already taking	Do not initiate. Discontinue if already taking	Do not initiate. Discontinue if already taking

BOX 1: Diabetic Ketoacidosis (DKA)

Explain that DKA is an uncommon and serious side effect caused by the build-up of ketones which are being produced due to insulin deficiency (absolute or relative). Inform people of the common causes as part of a preventative strategy:

1. Acute Illness/infections
2. Starvation/fasting
3. Carbohydrate deficient diet i.e., ketogenic diets (50-130g of carbohydrate per day)
4. Excessive exercise
5. Alcohol
6. Surgery
7. Illicit drugs
8. Reduced insulin dose (if on insulin)
9. Dehydration

With SGLT2 inhibitors DKA may occur with normal glucose levels

Be aware and make your patient aware of the signs and symptoms of DKA: Nausea, vomiting, abdomen pain, stupor, fatigue, and difficulty breathing.

Ketones need to be tested urgently if DKA is suspected. DO NOT Use urine ketone testing Test capillary ketones if you have access to a ketone meter and if not refer to the hospital for blood ketone testing. If ketones >1.5mmol/L then further tests may be needed to ascertain if the person has a DKA.

BOX 3: When to stop SGLT2 inhibitors

When there is an increased risk of DKA:

a. Acute medical illness, including for COVID-19 infection
b. Admission for elective surgery or procedure requiring starvation
c. Vomiting and/or diarrhoea
d. Dehydration

Restart only AFTER the patient has been eating and drinking normally for 24 hours AND no longer acutely unwell. You may need to commence alternative treatments in the interim.

BOX 2: Sick Day Rules

To be used when a person with diabetes is not well and unable to eat and drink as normal

1. If ill with diarrhoea, vomiting or fever stop the SGLT2 inhibitor and do not restart until eating/drinking fluids normally.
2. When people with diabetes who take insulin are not able to eat, it might be possible for them to consume milk, fruit juice, yoghurt or soup in place of meals and adjustments may need to be made to usual medication regimens e.g., insulin.
3. Drink plenty of water/sugar free fluids to avoid dehydration for up to 24 hours. If not resolved > 24 hours seek medical advice
4. Seek medical advice if seriously unwell with infection or illness

Useful Resources for people living with diabetes:

TREND leaflets (free to register) https://trenddiabetes.online/resources/

- Diabetes and your Kidneys
- How to reduce your risk of genital fungal infection
- Type 2 DKA
- Type 2 Diabetes: what to do when you are ill

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https://e7fvz575be6.exactdn.com/wp-content/uploads/pdf/dotn024ae8fb1b78500b7bc752b98e9b6d92.pdf

ABCD SGLT2 information

https://abcd.care/sites/abcd.care/files/site_uploads/Images/ABCD_A4_Leaflet_Final%20%28002%29.jpg

References:

Dashora U, Gregory R, Winocour P, Dhatariya K, Rowles S, Macklin A, Rayman G, Nagi D, Whitehead K, Beba H, De P, Patel DC; ABCD executive committee and Diabetes UK. Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021). Clin Med (Lond). 2021 May;21(3):204-210. doi: 10.7861/clinmed.2021-0045. PMID: 34001571; PMCID: PMC8140708.

APC approved July 2022 Review July 2025