Top Tips and Recommendations for use of Sodium Glucose Co-transporter 2 inhibitors (SGLT2i) in Adults with Type 2 Diabetes (T2DM) for Glycaemic Control

NHS Kent and Medway

INTRODUCTION & SCOPE

- Updated NICE T2DM guidelines [NG28, June 2022] highlight increased recommendations for SGLT2 inhibitor use for adults with T2DM
- The SGLT2i class have a growing evidence base for cardio +/- renal protective effects independent of glycaemic effectiveness. Further data is emerging rapidly, and this may be reflected in ongoing licensing changes for individual members of this class. *Please see section on "SGLT2i Use in HF and CKD"* on page 3 *for more information*

Aims of this document:

- To guide prescribing of SGLT2 inhibitors within each individual drug's current license for glycaemic control in T2DM alongside appropriate clinical guidelines, such as NG28
- To ensure safe prescribing of SGLT2 inhibitors for patients with type 2 diabetes for the management of glycaemic control
- To ensure these agents are prescribed appropriately and that the necessary safety information is given to all patients

**It is important to note this is only a guide and not exhaustive, appropriate clinical judgement and referral to other reference sources may be appropriate in individual patient cases*

What are SGLT2 Inhibitors?

- An established class of medications for the treatment of diabetes 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 also on diuretics) as most of the sodium is reabsorbed in the distal tubule
- This effect results in decreasing the blood glucose level, weight loss, an osmotic diuresis and a drop in blood pressure. These drugs have been licensed and used widely in people with T2DM and have shown significant cardiovascular and renal benefits in different subsets of this group of patients

When Initiating SGLT2 Inhibitors: Prescribing Considerations also see here

- Minimise risk of **hypoglycaemia**:
  - Review glucose lowering medications that may cause hypoglycaemia (e.g., insulin and sulphonylureas)
  - Consider dose reductions of above when SGLT2i initiated, particularly if HbA1c is already at target
- Minimise risk of **Diabetic Ketoacidosis (DKA)**, check if the person may be at increased risk, for example if:
  - They have had a previous episode of DKA
  - They are unwell with intercurrent illness
  - They are following a very low carbohydrate or ketogenic diet (20-50g/day of carbohydrate or <10% of a 2000 kcal/day diet)
- Minimise risk of **hypotension**:
  - Review diuretic and anti-hypertensives if hypertension improves or if there is postural hypotension

Monitoring Requirements

- Additional monitoring after starting SGLT2 inhibitors is **NOT** required
- Routine monitoring of kidney function should continue as part of routine care, frequency guided by national and local guidance for T2DM, and in line with person's other co-morbidities as appropriate. Additional routine tests are not required after starting SGLT2i
- Note glycaemic benefit will be limited for all SGLT2i below eGFR of 45ml/min as the glucose lowering efficacy of SGLT2i therapy is dependent on renal function. Further glycaemic control may be required.

Pregnancy and Breast-feeding

AVOID – toxicity in animal studies

When Initiating SGLT2 Inhibitors: Information for the Patient

Before initiating SGLT2 inhibitors the patient should be advised:

- What the **benefits** of taking SGLT2 inhibitors are to them as an individual
- What **side effects** may occur *(see "Class Side Effects" on page 3)* and **sick day rules** *(see box to right)* and when to stop taking their SGLT2 inhibitor due to associated risks with **dehydration and development of DKA**
  - To seek urgent medical attention if symptoms of DKA
  - To seek urgent medical attention if symptoms of Fournier's gangrene (e.g., severe pain, tenderness, erythema, swelling in genital or perineal area)
- About the importance of **routine preventative foot care**
- To **drink plenty of fluids** to avoid dehydration unless they have been told to restrict fluids by a healthcare professional, for example due to heart or kidney problems

Reducing Risk: Patient Education, Sick Day Rules

When a person with diabetes is not well and is unable to eat and drink as normal, some simple rules can prevent further deterioration or DKA Patients should be told the following:

- If **unwell** with diarrhoea, UTI, vomiting, fever or unusual drowsiness, STOP SGLT2 inhibitors and don't restart until feeling better and eating/drinking fluids normally
  - Restart only AFTER eating normally for AT LEAST 24 HOURS *AND* no longer acutely unwell
- Encourage patient to **avoid dehydration** with appropriate fluid intake
- ALL patients must be counselled on the **risk of ketoacidosis** and signs and symptoms of this (nausea, vomiting, abdominal pain, stupor, fatigue, difficulty breathing) and to STOP SGLT2 inhibitor if any symptoms develop
- Seek medical advice if particularly **unwell with infection or illness**
- To seek urgent medical attention if symptoms of **Fournier's gangrene** (e.g., severe pain, tenderness, erythema, swelling in genital or perineal area)
- Stop SGLT2 inhibitors prior to **surgery** - as advised by pre-op team

Top Tips and Recommendations for use of Sodium Glucose Co-transporter 2 inhibitors (SGLT2i) in people with Type 2 Diabetes (T2DM) For Glycaemic Control

Who is most likely to benefit most from SGLT2 inhibitor treatment?

It is important to select the right patient for SGLT2 inhibitor therapy and avoid in others who may be at high risk of DKA
The following patients are likely to benefit most:

- Adults above 18 years with T2DM and one or more of the following:
  - established/high risk of atherosclerotic cardiovascular disease (NICE guidance NG28 advises SGLT2i use with proven cardiovascular benefit in people with QRISK2 of 10% or higher)
    - People who qualify for a statin due to diabetes will qualify for SGLT2i therapy
    - NICE define established atherosclerotic CVD as: coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
  - chronic kidney disease (CKD)
  - heart failure (HF)
  - inadequate glycaemic control with need to minimise hypoglycaemia
  - inadequate glycaemic control with need to minimise weight gain / encourage weight loss
- Patients with a clear understanding of the risks associated with SGLT2 inhibitors, how to reduce those risks and ability to follow sick day rules

Who is likely to be at risk with SGLT2 inhibitors?

Use with CAUTION in the following situations:

❑ **Patient Characteristics:**

- Body mass index <27 kg/m^2 although diabetes and other specialists may use them in people with lower BMI for potential cardiac or renal benefits
- Recent weight loss
- Potential for pregnancy
- People at risk of hypotension/hypovolaemia (e.g., on diuretic and/or multiple antihypertensive therapies, elderly)
- People diagnosed with or at risk of frailty
- Cognitive impairment or use of medication compliance aid (as this *may* imply inadequate understanding required to follow sick day rules and take action to prevent and identify DKA)

❑ **Other Past Medical History:**

- On long term or recurrent courses of steroids
- Raised haematocrit
- Severe hepatic impairment
- Recurrent urinary or genital tract infections

❑ **Diabetes History:**

- Long duration of diabetes (generally over 10 years from diagnosis)
- Person with very high level of HbA1c >86 mmol/mol
- Person considered at high risk of acute effects of hyperglycaemia (e.g., dehydration due to non-adherence to medication)
- Past history of active foot disease/foot ulceration – consider discussion with specialist, ensure regular preventative footcare*
- Existing diabetic foot ulcers*
- Previous lower limb amputation*
- History of peripheral arterial disease (PAD)*
- Taking sulphonylureas and/or insulin – increased risk of hypoglycaemia if commenced on SGLT2i

**Caution is in line with MHRA alert (see link below)* based on *CANVAS study on canagliflozin. Later studies and real world metanalysis for canagliflozin reported no increased risk of lower limb amputations. Not seen in other SGLT2i.*
https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-increased-risk-of-lower-limb-amputation-mainly-toes

AVOID in the following situations:

❑ **Patient Characteristics:**

- Age <18 years
- Pregnant, breastfeeding, female in their child-bearing years and sexually active without contraception
- Person with excess alcohol consumption or IVDU
- History of allergic reaction to SGLT2i or any of their excipients
- Person adhering to a fasting diet or ketogenic, low calorie, or low carbohydrate diet (including in context of strenuous exercise) (20-50g/day of carbohydrate or <10% of 2000 kcal/day diet)

❑ **Diabetes History:**

- Suspected or possible T1DM – unless under specialist advice, noting this is 'off-label' use
- Past history of diabetic ketoacidosis – unless under specialist advice, noting this is 'off-label' use
- Any diagnosis or suspicion of 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

❑ **Current Medical History:**

- Acutely unwell person (acute medical illness including COVID-19, surgery or planned medical procedure)
- Active foot disease
- Inpatient with acute vascular event who is not stable
- Eating disorder
- eGFR outside than allowed in the up-to-date licensing of the medication being considered
- Already on SGLT2 inhibitor for other co-morbidity
- Organ transplant
- Patients receiving dialysis

SGLT2 Inhibitor	Dose *(When using in T2DM for glycaemic control)*	Dose Adjustments *(When using in T2DM for glycaemic control. Please note licenses vary, for other indications please check individual drug SPC)*				
		eGFR > 60	eGFR 45-59	eGFR 30-44	eGFR <30	Hepatic Impairment
				Note glycaemic benefit will be limited for all SGLT2i below eGFR of 45ml/min as the glucose lowering efficacy of SGLT2i therapy is dependent on renal function. **Further glycaemic control may be required.**		
Canagliflozin PIL/SPC	100mg once daily. Increased if tolerated to 300mg once daily if required. Preferably before breakfast.	Initiate 100mg once daily, titrate to 300mg once daily if needed.	Initiate/continue with 100mg once daily only.	**Not recommended for glycaemic control in T2DM.** Initiate/continue with 100mg once daily. Further glycaemic control may be required.	**Not recommended for glycaemic control in T2DM.** Continue established treatment with 100mg once daily but do not initiate. Can continue until dialysis or transplant if ACR >30mg/mmol when eGFR falls below 30. **Stop if dialysis/transplant.** Further glycaemic control may be required.	No dose adjustment necessary if mild/moderate impairment. Therapeutic experience in severe hepatic impairment is limited and therefore use is not recommended by manufacturer.
Empagliflozin PIL/SPC	10mg once daily. Increased up to 25mg once daily if necessary. With or without food. *Initiation is not recommended in adults >85 years due to limited experience.*	Initiate 10mg once daily, titrate to 25mg once daily if required.	**Only initiate in those with established CVD, 10mg daily.** For those already taking empagliflozin, continue with 10mg only.	**Only initiate in those with established CVD, 10mg once daily.** Further glycaemic control may be required.	**Not recommended for glycaemic control in T2DM.** Can continue with 10mg once daily if person also has HF down to eGFR of 20ml/min. **Do not initiate/discontinue if already taking if eGFR <20ml/min.** Further glycaemic control may be required.	
Ertugliflozin PIL/SPC	5mg once daily. Increased to 15mg once daily if necessary and if tolerated. Dose to be taken in the morning.	Initiate 5mg once daily, titrate to 15mg once daily if needed.	**Do not initiate.** For those already taking ertugliflozin continue with 5mg once daily or 15mg once daily.	**Do not initiate.** **Discontinue if already taking.**		
Dapagliflozin PIL/SPC	10mg once daily. With or without food.	Initiate 10mg once daily.		**Not recommended for glycaemic control in T2DM.** Can continue with 10mg once daily if person also has HF or CKD down to eGFR of 15ml/min. **Do not initiate if eGFR <15ml/min.** Further glycaemic control may be required.		Initial dose 5mg daily in severe hepatic impairment, can increase to 10mg according to response/tolerability

SGLT2 Inhibitor Use in HF and CKD

- There is increasing use of SGLT2i in Heart Failure (**HF**) and Chronic Kidney Disease (**CKD**) in people with and without diabetes – check individual SPCs
- Check and document what **indication** the SGLT2i is being used for and document this to ensure appropriate monitoring and follow up
- These indications are currently outside the scope of this document
- Though it should be noted some patients may have multiple conditions for which an SGLT2i will confer benefit
- Use urine albumin to creatinine ratio (**ACR**) for people with **T2DM and CKD**, who are taking an ACE inhibitor or ARB at an optimised dose (titrated to the highest licensed tolerated dose):
    - **Consider** an SGLT2i when urine ACR confirmed between 3-30mg/mmol (in addition to the ACE inhibitor or ARB at maximum tolerated dose)
    - **Offer** an SGLT2i when urine ACR confirmed >30mg/mmol (in addition to the ACE inhibitor or ARB at maximum tolerated dose)
    - Criteria in the drug marketing authorisations should be met including eGFR thresholds *(see table above for dose adjustments / hyperlinks to drug SPCs)*
    - Monitor for volume depletion and eGFR decline
    - *Please note in November 2021, not all SGLT2 inhibitors were licensed for this indication*

Class Side Effects:

Common:

- Increased risk of UTI
- Polydipsia
- Polyuria
- Genito-urinary disorders
- Volume depletion effects (thirst, postural dizziness, hypotension, dehydration)
- Decreased eGFR
- Hypoglycaemia (increased risk if on sulphonylureas and/or insulin)

Uncommon but **serious**: *(see MHRA alerts in "Additional important safety information" below for more information)*

- DKA
- Fournier's Gangrene
- Potential for lower limb amputation - encourage regular preventative foot care

Please see individual drug monographs in BNF/SPC for a complete side-effect profile – see hyperlinks in table above

Additional Important safety information – Please see hyperlinks for more detailed advice:

- MHRA/CHM advice (updated April 2016): SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis (DKA)
    - People should be informed on the signs and symptoms of DKA, discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
    - Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal
- MHRA/CHM advice (MHRA/CHM advice March 2017): SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)
    - SGLT2i's may increase the risk of lower-limb amputation (mainly toes). All people taking an SGLT2i should be counselled on good preventive foot care. Review if lower limb complications develop (e.g. skin ulcer, osteomyelitis, or gangrene). Monitor people with risk factors for amputation.
- MHRA/CHM advice: SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) (February 2019)
    - If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required)
    - Fournier's gangrene is a rate but potentially life-threatening infection that requires urgent medical attention
- MHRA/CHM advice: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness (March 2020)
    - SGLT2 inhibitor treatment should be interrupted in people who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the person's condition has stabilised
- MHRA/CHM advice: Dapagliflozin (Forxiga): no longer authorised for treatment of type 1 diabetes mellitus
    - The authorisation holder for dapagliflozin has withdrawn the indication for type 1 diabetes mellitus. The removal of the type 1 diabetes indication is not due to any new safety concerns and the other indications of dapagliflozin are unchanged

References/Adapted from:
- GP Notebook, available via: www.gpnotebook.com [Accessed on 28th July 2021] [Updated and Accessed 14th October 2021]
- ABCD and DUK 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, Clinical Medicine Vol 21, No 3: 204-10
- NICE, NG28, Type 2 diabetes in adults. Available via https://www.nice.org.uk/guidance/ng28 [Accessed 29th July 2022]

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