Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2i) for Management of Heart Failure

Introduction

Dapagliflozin and empagliflozin are sodium glucose co-transporter 2 inhibitors (SGLT2i) traditionally prescribed for diabetes and indicated according to NICE guidance for the management of chronic heart failure and chronic kidney disease (CKD). This guidance focuses on the use of dapagliflozin and empagliflozin (herein referred to as 'NICE-approved SGLT2i') in patients **with heart failure** (HF) with and without diabetes mellitus (DM).

Recommendations

Initiation of dapagliflozin and empagliflozin in HFrEF

NICE technology appraisal (TA) TA679 and TA773, respectively, recommend dapagliflozin and empagliflozin, within their marketing authorisations, as an option for treating symptomatic chronic heart failure with reduced ejection fraction (HFrEF) in adults (defined by left ventricular ejection fraction (LVEF) less than or equal to 40%), as an add-on to optimised tolerated dose of standard care (see: South West London guidance on the pharmacological management of heart failure in adults):

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs) or sacubitril valsartan, AND
- Beta blockers, AND
- Mineralocorticoid receptor antagonists (MRAs), if tolerated

Initiation of dapagliflozin and empagliflozin in HFpEF or HFmrEF

NICE TA902 and TA929, respectively, recommend dapagliflozin and empagliflozin, within their marketing authorisations, as an option for treating symptomatic chronic heart failure with preserved ejection fraction (HFpEF, defined as LVEF 50% or greater) or mildly reduced ejection fraction (HFmrEF, defined as LVEF 41% to 49%) in adults. This is in addition to standard care (loop diuretics, and treatment for other conditions the person may have).

South West London (SWL) Formulary Status of Dapagliflozin and Empagliflozin (NICE- approved SGLT2i)

Heart failure reduced ejection fraction (HFrEF)

Dapagliflozin and empagliflozin in HFrEF have **Amber 1 formulary status** in SWL. Treatment may be initiated in primary care on the advice of a HF specialist (*nurse, doctor or pharmacist*) as recommended by NICE TA679 and TA773.

Heart Failure preserved/ mildly reduced ejection fraction (HFpEF), (HFmrEF)

Dapagliflozin and empagliflozin in HFpEF/HFmrEF have **Amber 1 formulary status** in SWL. Treatment may be initiated in primary care on the advice of a HF specialist (*nurse, doctor or pharmacist*) as recommended by NICE TA902 and TA929**.**

Roles and responsibilities

HF specialist team responsibilities

- **Shared decision**: support initiation of NICE-approved SGLT2i, following discussion with the patient – consider benefits and risks, clinical considerations, current co-morbidities, contra-indications, and side effects.
- Ensure the following is included in the discharge letter or outpatient letter:
    - **Indication for therapy**, including an updated HF management/ medicines optimisation plan.
    - Details of the shared decision-making process/counselling with the patient.
    - Baseline **renal function, liver function, blood pressure** (BP).
    - Baseline **glycated haemoglobin** (HbA1c).
    - **Patients with T2DM:** the glucose lowering effect should be considered (see Initiation and Monitoring Requirements). If appropriate, **advice on any adjustments of current diabetes medication**, and review date, should be provided.
    - **Contact details of HF specialist** and/or community HF team for advice, refer to Pharmacological Management of Heart Failure guidance.

Primary Care responsibilities

- **Initiate therapy** with the support of the HF specialist once discharge/outpatient clinic letter received.
- Follow initiation and monitoring requirements below and prescribing guidance on initiating NICE-approved SGLT2i.
- Ongoing monitoring and support of patient adherence (see below) unless adverse effects necessitate cessation of therapy. Discuss with the HF team before stopping medicines for HF unless there is a clear clinical reason to stop immediately.
- Ensure the indication for NICE-approved SGLT2i is linked to the patient record and added to the prescription e.g. “for the heart”, as well as the dispensing label in pharmacy, to avoid confusion and to ensure it is not inadvertently stopped as part of a routine diabetes or CKD review.
- Ensure the patient is coded on the HF register. Refer to Quality and Outcomes Framework guidance.

Initiation and Monitoring Requirements (by HF Specialist / Primary Care)

Initiation requirements

- **Check baseline BP** assessment and refer to cautions for further details.
- **Check baseline renal and hepatic function** and refer to prescribing guidance on initiating NICE-approved SGLT2i.
- **HF patients without T2DM:** check HbA1c prior to starting therapy to exclude undiagnosed T2DM. Refer to SWL guidance on T2DM management if HbA1c is above 48 mmol/mol.
- **HF patients with T2DM:** ensure HbA1c is checked prior to initiation. Seek advice on adjustment of existing diabetes medication to **prevent**

hypoglycaemia as appropriate according to medication class. Refer to SWL guidance on T2DM management, Frailty and SGLT2i drug information sheet.

- When a NICE approved SGLT2i is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea (e.g. gliclazide), **a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.** Refer to diabetes specialist teams for specific advice if appropriate.
  - Counsel patient on identification, prevention, and management of hypoglycaemia – see important side effects.
  - If estimated renal function (eGFR) is less than 45 ml/min/1.73m^2 then the NICE approved SGLT2i will have minimal effect on blood glucose (BG) however effects for HF and CKD remain.
- Note that HbA1c may not be reflective of current glycaemic levels in the presence of genetic, haematologic (e.g. anaemia) or illness-related factors that influence HbA1c and its measurement – refer to Diagnostic Criteria for Diabetes and factors that influence HbA1c and its measurement which provides further information.

- **Counsel on side effects and adherence**:
  - See additional cautions, contra-indications and important side effects.
  - Offer patient information leaflets available from manufacturers for dapagliflozin and empagliflozin.
  - Signpost to Pumping Marvellous for further patient support and HF guides.
  - See further guidance on medicines and fasting.
- **Counsel on sick day rules** – SGLT2i should be temporarily withheld in the following circumstances:
  - If hospitalised for major surgery or acute serious illnesses (see MHRA 2020). Blood ketone levels should be monitored (and be normal before restarting). Note SGLT2i may diminish excretion of ketone bodies in urine, making urine measurement of ketone bodies less reliable.
  - Pre-surgery: 24 hours prior to surgery and not restarted until the patient is eating and drinking normally, is not dehydrated, is not receiving variable rate intravenous insulin infusion, ketone levels are normal, and the patient's condition has stabilised. Seek advice from hospital teams.
  - Consider stopping in any other hospital admission, if acutely unwell, until patient well/stable. If unsure withhold and seek advice from named healthcare practitioner.
  - If patient develops or has inter-current conditions that may lead to volume depletion (e.g. vomiting/diarrhoea) or is not eating or drinking.
  - If patient has a severe infection.

  Treatment may be restarted once the patient's condition has stabilised, and they are eating normally for at least 24 hours (if no new contra-indications).

Ongoing Monitoring Requirements

Monitor as indicated and review the patient every 6 to 12 months in line with NICE HF guidance.

The frequency of monitoring should depend on the clinical status and stability of the person. The monitoring interval may be shortened to within days if the clinical condition has changed or within 2 weeks for medication changes (HF teams or specialist teams may support this), but monitoring is recommended at least 6-monthly for stable people with proven HF.

- **Blood pressure** – check as clinically indicated. Refer to cautions for further details.
- **Renal function** – check as clinically indicated and at least annually thereafter. If patient has chronic kidney disease (CKD), see SWL CKD and NICE TA775 and TA942.
- **HbA1c**
  - **HF without T2DM** – if clinically indicated.
  - **HF with T2DM** – Refer to diabetes team with any concerns. Routine monitoring is recommended 3-6 monthly (dependent on clinical circumstances) in line with management in T2DM NICE guidance.
- **BG levels:**
  - **HF without T2DM** – if clinically indicated.
  - **HF with T2DM**
    - If on insulin, sulfonylurea or repaglinide, ensure monitoring of BG levels. If patient is not currently testing, contact diabetes team/GP practice to arrange this. If concerns over BG levels or if patient experiences hypoglycaemia, review glycaemic medication. For advice, contact diabetes team.
    - If reduced dose of other diabetes medication on initiation, advise patient to check BG levels **daily for seven days**. Primary care teams to review levels and if no hypoglycaemic symptoms or significant glucose reduction, consider **gradually restoring to original doses over 2-3 weeks if appropriate**.
- **Liver function tests** – if clinically indicated.
- **Check for side effects and review adherence:**
  - Check as clinically indicated and at least annually.
  - If patient presents with intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness) monitor volume status (this includes physical examination, BP measurements) and laboratory tests including haematocrit and electrolytes, urea as clinically indicated.
  - See additional cautions, contra-indications and important side effect details.
- **Counsel on sick day rules** (see above) – ongoing basis.

Prescribing Guidance on Initiating NICE-approved SGLT2i

(SPC link: dapagliflozin and empagliflozin)

Dapagliflozin

- **Dosage:** 10mg once a day.
- **Renal function:** avoid initiation if estimated glomerular filtration rate (eGFR) is less than 15 ml/min/1.73m^2. See SWL guidance on use of SGLT2i in CKD.

- **Hepatic Impairment:** Mild and moderate (defined as Child-Pugh A & B): 10 mg once a day. Severe (Child-Pugh C or if alanine aminotransferase (ALT) /aspartate transaminase (AST) is greater than three times the upper limit of normal (ULN) or bilirubin is greater than two times the ULN): Start 5 mg once a day and increase to 10mg if tolerated.
- **Age:** licensed for 18 years and older.

Empagliflozin

- **Dosage:** 10mg once a day.
- **Renal function:** avoid initiation if eGFR is less than 20 ml/min/1.73m^2. Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis. There is insufficient data to support use in these patients.
- **Hepatic Impairment:** Mild and moderate (as above): 10 mg once a day. Severe: Not recommended for use due to lack of experience.
- **Age:** licensed for 18-85 years. The manufacturer does not recommend its use in those 85 years and over due to limited therapeutic experience.

Contra-indications and Cautions (full list dapagliflozin: BNF and SPC, empagliflozin: BNF and SPC)

Do not prescribe NICE approved SGLT2i in the following patients:

- Pregnancy and breastfeeding.
- Severe hepatic impairment with empagliflozin - see Prescribing guidance.
- Severe renal impairment - see Prescribing guidance.
    - If eGFR falls **below 20ml/min/1.73m^2 for empagliflozin** and **15ml/min/1.73m^2 for dapagliflozin -** consider specialist/renal advice and co-prescribed medications/co-morbidities that may affect eGFR.
- Hypersensitivity to active substance or excipients.
- Galactose intolerance or total lactase deficiency (tablets contain lactose).
- Already taking another SGLT2i.
- Type 1 diabetes: SGLT2i are contra-indicated and not licensed. Refer to MHRA 2021.
- History of diabetic ketoacidosis (DKA) – refer to DM specialist.
- Active foot ulceration.

Prescribe NICE approved SGLT-2 inhibitor with caution in people with:

- Severe hepatic impairment with dapagliflozin – refer to Prescribing guidance.
- Patients undergoing surgical procedures –- risk of DKA in the peri-operative period: temporarily withhold and monitor ketone levels – MHRA guidance for further information and sick day rules.
- History of urinary tract infections or recurrent thrush. Uro-genital infection or perineal abscess may predispose to necrotising fasciitis.
- Low weight/ weight loss.
- Increasing age: elderly patients are at greater risk for volume depletion.
- Systolic BP less than 95mmHg or if symptomatic hypotension, particularly in:
    - Elderly (greater than 65 years) or frail patients.
    - Patients on anti-hypertensive therapy with a history of hypotension.

    - Patients prescribed diuretics – at risk of hypotension or dehydration and may require additional monitoring.

  Refer to HF specialist if there are any BP or diuretic concerns.
- HF with T2DM: discuss with the diabetes team in the following circumstances:
    - Recurrent or problematic hypoglycaemia.
    - Risk factors for diabetic ketoacidosis (DKA):
        - Previous DKA
        - Those with very high HbA1c levels (86 mmol/mol or 10%)
        - Low reserve of insulin secreting cells
        - Rapidly progressed to requiring insulin (within one year of diagnosis).
        - Clinical features of significant insulin deficiency (e.g. weight loss, symptoms of hyperglycaemia).
        - Conditions that restrict food intake or can lead to severe dehydration.
        - A sudden reduction in insulin or an increased requirement for insulin due to illness, surgery, or alcohol abuse
        - Ketone prone T2DM.
        - Presence of blood or urine ketones.
        - Diabetes due to pancreatitis or past history of pancreatitis.
        - Patients on very low calorie or carbohydrate diets.

Interactions

- Documented interactions are related to the potential effects of synergistic hypotension with medications that lower blood pressure, and these parameters should be monitored.
- Rare risk of increased renal lithium excretion with concurrent prescribing of SGLT2i with lithium, which may lead to decreased blood lithium levels. Serum concentration of lithium should be monitored more frequently after SGLT2i initiation and dose changes.
- Full list of interactions:
    - British National Formulary: Dapagliflozin | Interactions | BNF content published by NICE, Empagliflozin | Interactions | BNF content published by NICE.
    - **Dapagliflozin**: section 4.5 of the SPC; **empagliflozin:** section 4.5 of SPC.

Side Effects

Always discuss stopping therapy with a HF specialist unless there is an urgent clinical need to stop immediately. Important side effects that require immediate cessation of therapy are suspicion of Fournier's gangrene or DKA.

For full side effect profile see dapagliflozin: section 4.8 of SPC; **empagliflozin:** section 4.8 of SPC. **Important side effects include:**

- **Hypoglycaemia (T2DM patients)**: more likely to occur when patient taking medications with a higher risk of hypoglycaemia e.g. insulin, sulfonylureas or repaglinide.

    - If on insulin, sulfonylurea or repaglinide, ensure patient is monitoring BG levels. If patient is not currently testing, please contact diabetes team/GP practice to arrange this.
    - Counsel on prevention, identification, and management of hypoglycaemia.
    - Ensure patient has been counselled on driving rules – see DVLA rules or contact diabetes team for further advice if required.
    - If patient experiences hypoglycaemia, please review glucose-lowering medications. Contact the diabetes team for further advice if required.
- **Diabetic ketoacidosis (DKA)**: this has not yet been reported in patients without diabetes, but it is important to be aware of and inform patients of the signs and symptoms of metabolic acidosis, as patients with undiagnosed T2DM may be at risk of DKA.
    - Signs and symptoms of metabolic acidosis include rapid weight loss, excessive thirst, nausea, vomiting, anorexia, abdominal pain, difficulty breathing or fast and deep breathing, confusion, unusual fatigue and sleepiness, sweet smelling breath, sweet or metallic taste in the mouth or a different odour to urine or sweat. **Advise to stop therapy and immediately seek medical advice if signs and symptoms occur**.
    - If patients present with symptoms of metabolic acidosis, assess for DKA and stop therapy. Do not restart treatment with any SGLT2i in patients who experienced DKA during use, unless another cause for DKA was identified and resolved. Ketoacidosis can occur with normoglycaemia
- **Mycotic genital infections**: commonly occur (particularly at the start of therapy) but can be managed with antifungals – reassure patient and ensure adequate genital hygiene; if problematic/recurrent, stop therapy.
- **Urinary tract infections (UTIs)**: common; stop therapy if significant UTIs such as pyelonephritis or urosepsis.
- **Fournier's gangrene (necrotising fasciitis of the genitalia or perineum):** very rare; **therapy should be stopped immediately and emergency treatment organised** – advise patients to seek medical attention if onset of genital pain, tenderness or swelling with fever or malaise (MHRA guidance).
- **Rash**: rare; eliminate possible other causes and if persists, consider stopping therapy.
- **Angioedema**: rare; requires cessation of therapy.
- **Tubulointerstitial nephritis**: very rare.

References/resources

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Document History

Version: V 1.0

Author: **SWL Cardiovascular Working Group**

Acknowledgement: Patient Information leaflet with permission from North London and South London Cardiac Operational Delivery Network
Approved by: Integrated medicines committee (IMOC)
Approval date: February 2023
Review Date: 2 years from approval date or sooner where appropriate.

Version: V 2.0
Author: **SWL Cardiovascular Working Group**
Approved by: Integrated medicines committee (IMOC)
Approval date: May 2024
Review Date: 2 years from approval date or sooner where appropriate.