Guideline for the use of the sodium glucose co-transporter 2 inhibitors (SGLT2i) dapagliflozin and empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF) without diabetes mellitus

Initiation Flowchart

NICE approved SGLT2 inhibitors dapagliflozin▼and empagliflozin▼ may be prescribed in patients with HFrEF, defined by left ventricular ejection fraction ≤40% **without** diabetes mellitus (DM). For further information on medicines optimisation in patients with heart failure see: SEL Pharmacological Management of HF guidance.

Patient: with symptomatic HFrEF (NYHA class 2 to 4) and LVEF ≤40% **without diabetes**

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Prescribed a maximum tolerated dose of:
Angiotensin-converting enzyme (ACEI) **OR** angiotensin-2 receptor blocker (ARB) **OR** Sacubitril valsartan (ARNI)
With a beta-blocker (BB)
And, if tolerated, a mineralocorticoid receptor antagonist (MRA)

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Use of NICE approved SGLT2i in HFrEF is Amber 1 in SEL joint formulary: treatment may be initiated in primary care on the advice of a HF specialist (*nurse, doctor or pharmacist*) **(as recommended by NICE TA773 and TA679)**
Refer to initiation checklist below and prescribing guidance *on page 2* for choice of SGLT2i agent

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Initiation checklist:

1. Shared decision: HF specialist supports initiation of NICE approved SGLT2i for each patient, following a discussion with the patient- consider benefits and risks, clinical considerations listed below, current co-morbidities (*including a check for diabetes where possible*) and contra-indications to this therapy (*see page 2*). *See page 4 for side effects* to consider in the patient consultation

2. Check baseline renal function: *See page 2* for a comparison between NICE approved SGLT2i and renal function at initiation according to summaries of product characteristics for dapagliflozin and empagliflozin (SPC)

3. Check baseline blood pressure (BP): Caution if SBP <95mmHg for elderly ≥65 years and if symptomatic hypotension. NICE approved SGLT2i can lead to a reduction in BP (up to 5mmHg SBP depending on baseline BP- higher drops seen in those with a higher baseline SBP >130mmHg)[5]- consider also volume depletion/dehydration with diuretic therapy and review of other medications affecting BP. Refer to HF specialist for advice if required

4. HbA1c: It is good practice to check for diabetes prior to starting a NICE approved SGLT2i to exclude undiagnosed type 2 diabetes mellitus (T2DM). Refer to DM team/guidance if HbA1c is above 48 mmol/mol (6.5%) See NICE guidance for T2DM.

5. Check baseline liver function: *See page 2* for dosing considerations in severe liver impairment

6. **Good Prescribing Practice:** Ensure the indication for the NICE approved SGLT2i is added to the prescription e.g. "for the heart" and that this is added to the dispensing label in pharmacy and the patient's clinical record

7. Communication (heart failure management plan)**:** If initiated in hospital, prescribing will transfer to primary care and patients will be monitored by the initiating HF team or referred to the community HF team. Patients initiated on NICE approved SGTL2i in outpatient clinics and in primary care on the advice of a HF specialist will be followed up by the community HF team (*see monitoring requirements on page 3 and roles/responsibilities on page 4*).

7. Referral to community pharmacy for discharge medicines service: It is good practice to inform a patient's community pharmacist of medication changes and the patient referred to their local pharmacy for further counselling/adherence support through the discharge medicines service (NHS DMS). Always communicate medication changes with community pharmacy and primary care for blister pack patients to reduce the risk of medication errors and to safeguard patients.

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London: South East London Clinical Commissioning Group (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLAM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

Prescribing guidance

Practical advice on prescribing of NICE approved SGLT2 inhibitors, dapagliflozin and empagliflozin, in heart failure with reduced ejection fraction (EF ≤ 40%) in NYHA class II-IV (see SPC link: dapagliflozin and empagliflozin):

	Dapagliflozin	Empagliflozin
Dosage	10 mg once a day	10 mg once a day
Renal function [a]	eGFR ≥ 15 mL/min *Dapa-CKD study showed a benefit in eGFR ≥15ml/min in patients with CKD co-morbidity (eGFR <60ml/min) and is licensed for use in CKD*	eGFR ≥ 20 mL/min *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 [b]	Mild and moderate: 10 mg once a day Severe: Start 5 mg once a day and increase to 10mg if tolerated	Mild and moderate: 10 mg once a day Severe: Not recommended for use due to lack of experience
Blood pressure	Cautioned use if SBP < 95mmHg or if symptomatic hypotension especially in elderly/frail patients	
Age	> 18 years	18-85 years *The manufacturers of empagliflozin do not recommend its use in those 85 and over due to limited therapeutic experience*
Patient specific factors (cautions/ contra-indications)	- Hypersensitivity to the active substance or any excipients. The tablets contain **lactose** therefore do not give in galactose intolerance or total lactase deficiency - Pregnancy: not to be initiated and discontinue if pregnant - Breast-feeding: do not use - Type 1 diabetes: SGLT2i are contra-indicated (refer to DM specialist) - History of diabetic ketoacidosis on SGLT2i – do not use (refer to DM specialist) - History of recurrent thrush or urinary-tract infections requires caution - Patients undergoing surgical procedures – increased risk of DKA in the peri-operative period (see 'sick day rules' on page 3) - Limited experience in NYHA class IV	

[a] *glycaemic control likely to be reduced with eGFR <45 mL/min (only of significance for patients with DM)*
[b] *mild and moderate hepatic impairment is defined as Child-Pugh A & B. Severe is Child-Pugh C or if ALT/AST >3x ULN or bilirubin >2x ULN.*

Patient information: An information leaflet (PIL) is available for dapagliflozin and empagliflozin for patients without diabetes, as some product information refers to SGLT2i use in diabetes, and this may cause confusion. It is imperative that the patient does not think that they have diabetes and that their healthcare providers know this is therapy for HF and not DM. The patient should have clear information concerning the benefits of therapy (improved quality of life and HF symptoms, and reduced risk of hospitalisation for HF) and potential adverse effects, with monitoring requirements for this medication (*see page 3*). Acute trusts in SEL have PIL for HF including sick day rules.

Documented **drug interactions** are related to the potential effects of synergistic hypotension with medications that lower blood pressure, and these parameters should be monitored in patients without diabetes.

- Loop and thiazide diuretics: NICE approved SGLT2i can potentiate the diuretic effect and increase the risk of hypotension or dehydration, consider discussion with the patient's HF team to amend doses of co-prescribed diuretics. Refer to the BNF or manufacturer's summary of product characteristics for full details.

Monitoring Requirements (by HF specialist/primary care)- *see page 5 for HF team contact details*

Monitoring Requirement	Frequency	Cautions
Renal function	At baseline, as clinically indicated and at least annually thereafter	eGFR can fall after initiation and if eGFR falls below 20ml/min for empagliflozin and 15ml/min for dapagliflozin- consider specialist/renal advice and co-prescribed medications/co-morbidities that may affect eGFR. NICE approved SGLT2i have been shown to slow progression of chronic kidney disease alongside CV risk reduction benefits and should only be stopped following a discussion with a specialist.
Blood Pressure (BP)	Check blood pressure at initiation, within the first 3 months and then at least annually	Caution if SBP <95mmHg for elderly ≥65 years and if symptomatic hypotension NICE approved SGLT2i increase diuresis which may lead to a modest decrease in blood pressure (about 3 to 5mmHg SBP and 2mmHg DBP) observed in studies. Caution should be exercised in patients for whom a drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly/frail patients. Patients who have experienced or are at risk of hypotension and/or dehydration may require additional monitoring if prescribed diuretics - may require diuretic dose reductions. Refer to HF specialist if there are any BP concerns.
Patient tolerance to therapy	Within the first 3 months, as indicated and at least annually	Check adherence to therapy and side effects (*see page 4*). Discuss any concerns with HF specialist team as required.
Monitoring of volume status	Physical examination, BP and laboratory tests: haematocrit, electrolytes, urea	Recommended if intercurrent conditions that may lead to volume depletion (eg gastrointestinal illness)
Heart failure review	6 to 12 monthly	NICE HF guidance: The frequency of monitoring should depend on the clinical status and stability of the person. The monitoring interval should be short (days to 2 weeks) if the clinical condition or medication has changed, but is needed at least 6-monthly for stable people with proven HF. It is good practice to also monitor cardiovascular (CV) risk with an annual lipid profile and HbA1c. Review of these blood results, medication optimisation and lifestyle may require agreed actions to reduce CV risk as necessary. HF teams are available to support and advise as required.

Sick day rules: temporarily withhold SGLT2i (and also other HF medications in acute illness) in patients who:

- Are hospitalised for major surgery or acute serious illnesses (see MHRA 2020): blood ketone levels may be monitored (and be normal before restarting)
- Also consider stopping in any other hospital admission, if the patient is acutely unwell, until the patient is well/stable -if unsure, withhold and seek advice from senior member of the team
- Develop volume depletion until the depletion is corrected
- Are not eating or drinking
- With inter-current conditions that may lead to volume depletion (e.g. vomiting /diarrhoea)
- Have a major infection
  - **Treatment should be restarted once the patient's condition has stabilised and they are eating normally for at least 24 hours (providing no new contra-indications exist)**

Side effects refer to SPC for dapagliflozin or empagliflozin for a full list of side effects:

Side effect	Recommended action
Urinary frequency, polyuria, dysuria, glucose in urine	Common side effects
Dehydration, volume depletion, dizziness, hypotension	Monitor and encourage patient to report any symptoms
Mycotic genital infections can commonly occur (particularly at the start of therapy)	Manage with antifungals - reassure patient and ensure adequate genital hygiene - **if problematic/recurrent, stop therapy***
Urinary tract infections (UTIs): SGLT2i cause glucose to be excreted in the urine	**Stop therapy* if significant UTIs** such as pyelonephritis or urosepsis
Fournier's gangrene	Advise patients to seek medical attention if onset of genital pain, tenderness or swelling with fever or malaise **Necrotising fasciitis of the perineum is rare and therapy should be stopped***
Rash	Investigate possible other causes and, **if persists, consider stopping therapy***
Angioedema	Rare, **requires cessation of therapy***
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 this may be an issue for undiagnosed T2DM	Symptoms may include rapid weight loss, excessive thirst, nausea, vomiting, anorexia, abdominal pain, excessive thirst, 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 the patient to stop therapy and immediately seek medical advice if signs and symptoms occur.** If patients present with symptoms of metabolic acidosis, GP/hospital to test for raised ketones in patients, even if plasma glucose levels are near-normal or normal and stop therapy without restarting.

**** Always discuss stopping therapy with a HF specialist, unless there is an urgent clinical need to stop immediately***
(contact details for SEL HF community teams on page 5)

Roles and Responsibilities

Initiation information to be communicated via clinic or discharge letter and to be recorded in primary care:
• Indication for therapy, including an updated HF management/medicines optimisation plan, and details of the shared decision-making process/counselling with the patient (see initiation checklist- *page 1*)
• Baseline renal function assessment and BP reading (include baseline HbA1c if checked)
• Details of HF specialist and/or community HF team for follow up/support (contact details on *page 5*)

For primary care: Initiate on the advice of a HF specialist and continue prescribing of NICE approved SGLT2i, ensure the indication for therapy is linked to the patient record, monitor as indicated and review the patient 6 to 12 monthly in line with NICE HF guidance *(see monitoring and side effects on pages 3 to 4)*. Support patient adherence unless adverse effects necessitate cessation of therapy (discuss with the HF team before stopping any prognostic medicines for heart failure, unless there is a clear clinical reason to stop immediately). As this is a new indication for established medicines, report any adverse effects via the MHRA yellow card system.

When to refer from primary to secondary care?
Seek advice and guidance from the initiating team or appropriate specialist team for: renal function decline (eGFR below 20ml/min for empagliflozin and 15ml/min for dapagliflozin), patient tolerability issues and frailty concerns that may lead to cessation of therapy.

Contact details for South East London Community HF teams: see SEL guidance on the pharmacological management of heart failure in adults: page 23:

Borough	Heart Failure Community Team
Bexley	Email: oxl-tr.cardiac@nhs.net; Tel: 020 7188 8952 or 0208 3197060
Bromley	kch-tr.PRUHheartfailurenurses@nhs.net 01689866097 and Bleep number is 739 kch-tr.br-bromleyintegratedheartfailurenurses@nhs.net 0797 1484 508
Greenwich	oxl-tr.cardiac@nhs.net 0208 3197060
Lambeth & Southwark	Gst-tr.KHPcommunityHF@nhs.net 020 3049 4652
Lewisham	LH.commuhfreferrals@nhs.net 0203 049 3473

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. If dapagliflozin or empagliflozin are prescribed for non-approved/unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation

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