Guideline for the use of dapagliflozin and empagliflozin for treating patients with chronic heart failure with preserved ejection fraction (HFpEF) or heart failure with mildly reduced ejection fraction (HFmrEF) without diabetes

NICE approved SGLT2 inhibitors dapagliflozin and empagliflozin may be prescribed in patients with symptomatic chronic heart failure with preserved or mildly reduced ejection fraction with or without type 2 diabetes mellitus. NICE have approved both SGLT2i for this indication as they have a similar cost, work in a similar way and have benefits in similar populations. For patients with renal impairment dapagliflozin may be the preferred option as may be prescribed to CrCl ≥15ml/min. This guideline focuses on patients without diabetes. For further information see NICE TA902 and NICE TA929. This guidance is for patients without diabetes: For patients with diabetes please discuss with the diabetes team- *SEL guidance for use of SGLT2i in heart failure and diabetes is in development*

Heart Failure Definitions [6 (ESC)]:

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	**1**	Symptoms +/- signs	Symptoms +/- signs	Symptoms +/- signs
	2	LVEF ≤ 40%	LVEF 41 – 49%	LVEF ≥ 50%
	3	N/A	The presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis of HFmrEF more likely	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures including raised natriuretic peptides. For the diagnosis of HFpEF, the greater the number of abnormalities present the higher the likelihood of HFpEF

LVEF= left ventricular ejection fraction, HFrEF = heart failure with reduced ejection fraction (*not covered by this guidance*)

Initiation Guidance: Follow the flowchart below when initiating dapagliflozin or empagliflozin for patients with HFpEF or HFmrEF. Please see SEL guidance on the pharmacological management of chronic heart failure in adults and SGLT2i in HFrEF guidance for more information on the management of all types of heart failure.

Dapagliflozin 10mg OD or empagliflozin 10mg OD may be initiated for patients with symptomatic HFpEF or HFmrEF by a specialist in secondary care or community setting or in primary care (amber 1 on RAGG list) on the advice of an appropriate specialist e.g. nurse, doctor or pharmacist (NICE TA902 and NICE TA929). Refer to initiation guidance and patient information (*see pages 3 & 4*)

↓

Check this is a suitable choice for the patient based on the relative **cautions** and **contraindications** (*see table on page 2*) and ensure a documented shared decision with the patient (*think overprescribing*)

↓

If dapagliflozin or empagliflozin is initiated by a specialist in secondary care or community settings, each patient must have a clear management plan to allow primary care to take over prescribing. **Communication to primary care must include**: 1. Clear indication for dapagliflozin or empagliflozin therapy 2. Documentation of baseline checks (*see page 3*) 3. Confirmation that the patient has been counselled on this therapy (*see page 4*)

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

Use with CAUTION in the following circumstances

Full list: *Dapagliflozin SPC* or *Empagliflozin SPC*

Patient Characteristics

- Body mass index <25kg/m² (<23kg/m² in South Asian people)
- Person adhering to a ketogenic/low calorie/low carbohydrate diet/intermittent fasting
- Recent weight loss
- Potential for pregnancy- dapagliflozin is to be avoided in pregnancy
- People at risk of hypotension/volume depletion (e.g. frail, elderly)
- Cognitive impairment or use of medicine compliance aids (may imply inadequate understanding or ability to follow sick day rules and act to prevent and identify DKA)
- On high dose diuretics/metolazone – contact heart failure team for advice as may need dose adjustment

Other past medical history

- On long term or recurrent courses of steroids (IV or oral) e.g. 3 or more per year
- Raised haematocrit
- Severe hepatic impairment (dose reduction required at initiation for dapagliflozin; avoid empagliflozin)
- Recurrent urinary tract or genital tract infections
- Pancreatitis (these patients may be at higher risk of DKA)

Diabetes history

- Long duration of diabetes (generally over 10 years since diagnosis)
- Person with very high HbA1c i.e. 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 or foot ulceration
- Existing diabetic foot ulcers/infection
- Previous lower limb amputation
- History of peripheral arterial disease (PAD)
- Taking sulfonylureas and/or insulin – increased risk of hypoglycaemia if started on SGLT2-inhibitor and eGFR >45ml/min
- Recurrent problematic hypoglycaemia
- Those with risk factors for DKA e.g. low reserve of insulin secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or increased requirement for insulin due to illness or surgery

AVOID in the following circumstances

Full list: *Dapagliflozin SPC* or *Empagliflozin SPC*

Patient Characteristics

- Age <18 years
- Pregnancy, breastfeeding, planning pregnancy, female in their child-bearing years and sexually active without contraception
- Person with excess alcohol consumption or intravenous drug user
- Hypersensitivity to active substance or excipients. The tablets contain lactose therefore do not give in galactose intolerance or total lactase deficiency

Current medical history

- Acutely unwell (acute illness including COVID-19, surgery or planned medical procedure)
- Active foot disease or acute ischaemic limb event
- Inpatient with vascular event who is not stable
- Eating disorder
- eGFR lower than allowed in the up-to-date licensing of the medication being considered (see SPC - *Dapagliflozin SPC*)
- Multiple pre-disposing risks for Fournier's gangrene e.g. weight loss, symptoms of hyperglycaemia
- Organ transplant (contact transplant team for advice)

Diabetes history

- T1DM or suspected or possible T1DM
- Current/past history of DKA including ketone prone T2DM
- Any diagnosis- or suspicion of latent autoimmune diabetes (LADA), other genetic causes of diabetes, known pancreatic disease or injury
- Rapid progression to insulin (within 1 year of diagnosis)
- Recent major surgery

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

Initiation Guidance

Check baseline renal function

- Dapagliflozin is not recommended in eGFR <15 ml/min; empagliflozin is not recommended in eGFR <20ml/min
- Please note that: 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 (chronic kidney disease)
- If patients have a diabetes co-morbidity then glycaemic control may be reduced with eGFR <45ml/min (seek advice from DM specialists as these patients are excluded from this guidance)
- **Monitor at baseline, within 3 months and as clinically indicated thereafter, at least annually**

Note:

- eGFR can fall approx. 4 to 6 ml/min after starting therapy. Seek renal specialist advice if eGFR drop >10ml/min within a 6-month period or >15ml/min within a 12-month period
- If eGFR becomes <30ml/min during treatment, refer to specialist (HF/renal team). Continue therapy unless an urgent clinical need to stop. NICE approved SGLT2i have been shown to slow progression of CKD alongside CV risk reduction benefits and should only be stopped following a discussion with a specialist.

Check baseline blood pressure

- Caution when initiating if SBP <95mmHg for patients ≥65 years and if symptomatic hypotension
- **Monitor at baseline, within 3 months and as clinically indicated thereafter, at least annually**

Note:

- SGLT2i increase diuresis which may lead to a modest decrease in blood pressure (approximately 3 to 5mmHg SBP and 2mmHg DPB observed in clinical studies)
- Monitor for any signs of dizziness or hypotension. A review of existing antihypertensives or diuretics may be required. Refer to heart failure specialist for advice if required.

Assess fluid balance/volume status

- SGLT2i have a diuretic effect which may lead to dehydration
- Review of existing diuretic or antihypertensive therapy may be required when starting SGLT2i. Refer to heart failure specialist for advice if required.
- **Monitor fluid balance, BP and laboratory tests (e.g. haematocrit, urea & electrolytes) at baseline, within 3 months and as clinically indicated thereafter**
- General assessment of patient – check for volume depletion/dehydration alongside a review of diuretic therapy
- Recommend caution in patients with intercurrent conditions which may lead to volume depletion (e.g. gastrointestinal illness)

Check baseline liver function

- No dose adjustment is required for dapagliflozin or empagliflozin in mild hepatic impairment
- In severe hepatic impairment (Childs-Pugh score C, AST/ALT >3 x ULN or Bilirubin 2 x ULN), initiate dapagliflozin at lower dose of 5mg daily. Dose may then be increased to 10mg if well tolerated. Avoid empagliflozin in severe liver impairment as no data is available (BNF)
- **Monitor liver function at baseline and as clinically indicated thereafter**

Check HbA1c

- Check baseline 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 48mmol/mol (6.5%). See NICE T2DM

Check Interactions

- See manufacturers summary of product characteristics or British National Formulary for full details: *Dapagliflozin SPC; Dapagliflozin BNF; Empagliflozin SPC; Empagliflozin BNF*

Information for the patient

- Ensure patient understands the indication for treatment and provide them with an appropriate patient information leaflet (PIL) clarifying that they do not have diabetes but this treatment is for their heart
- Ensure the patient is counselled on the individualised benefits of taking SGLT2i i.e. reduced mortality, improved HF symptoms and reduced risk of hospitalisation for heart failure
- Ensure the patient is counselled on **side effects** and **sick day rules** (see detailed below)
- Ensure the patient is counselled on appropriate foot care and management
- Advise the patient to not start a very low carbohydrate or ketogenic diet without discussing with an appropriate healthcare professional first

- Documented drug interactions are related to the potential effects of synergistic hypotension, hypovolaemia or hypoglycaemia with medications that lower BP and blood glucose. These parameters should therefore be monitored in these patients.
- **Loop and thiazide diuretics:** SGLT2i can potentiate the diuretic effect and increase the risk of hypotension or dehydration. Consider discussing with the patient's HF team to amend doses of co-prescribed diuretics.

Patient Education:

SICK DAY RULES

There are certain circumstances in which SGLT2i should be **temporarily withheld** to reduce the likelihood of further deterioration or developing diabetic ketoacidosis (DKA). These include:

- If you are unwell with diarrhoea, vomiting, fever, dehydration or unusual drowsiness
- If you are unable to eat and drink normally
- If you are unwell with infection or illness or if symptoms have not resolved within 24 hours
- Prior to surgery – as advised by pre-op team (see MHRA alert for more information including advice on stopping if hospitalised)
- Consider in any other hospital admission until patient is well/stable. If you are unsure, withhold, and seek advice from senior team member

Ensure monitoring of blood glucose levels more frequently during period of acute illness (where applicable).

Patients can restart SGLT2i once they are no longer acutely unwell and are eating and drinking normally for at least 24 hours (providing no new contraindications exist)

Patient Education: ADVERSE EFFECTS

For full side effect profile see drug monograph: Dapagliflozin SPC; Empagliflozin SPC

Common:

- **Increased risk of UTI and mycotic genital infections**: Reinforce adequate genital hygiene, can be managed with antimicrobial treatment but may require cessation if recurrent or problematic infections. Stop therapy if significant UTIs such as pyelonephritis, urosepsis.
- **Increased urinary frequency:** Due to excretion of glucose in the urine. Consider stopping if problematic.
- **Volume depletion effects (thirst, postural dizziness, hypotension):** Monitor fluid balance. Counsel patients on the risk of dehydration and importance of adequate hydration.
- **Hypoglycaemia:** Most likely to occur in combination with insulin/sulfonylurea. Counsel on prevention, identification and management of hypoglycaemia and follow initiation flowchart on page 3 to reduce risk. Advise to report all episodes of hypoglycaemia to GP practice or specialist diabetes team.

Uncommon, serious

- **Diabetic ketoacidosis (DKA):** *this has not yet been reported in patients without diabetes, but it is important to be aware of and to inform patients of the signs and symptoms of metabolic acidosis, as this may be an issue for undiagnosed T2DM*
  DKA can also occur when glucose levels are normal (see MHRA recommendations). The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, SGLT2i treatment should be stopped immediately.
- **Fournier's Gangrene:** Necrotising fasciitis of the perineum is rare and treatment should be stopped immediately. Advise patients to seek urgent medical attention if they experience severe pain, tenderness, erythema or swelling in the genital or perineal area, accompanied by fever or malaise. Report all suspected cases via Yellow Card Scheme. See MHRA alert for more information.
- **Lower limb amputation risk (MHRA footcare advice):** Advise on importance of routine preventative footcare and reporting issues in a timely manner.
- **Rash:** Eliminate other possible causes first, if persists, consider stopping
- **Angioedema:** Treatment should be discontinued immediately
- **Cases of hepatic injury:** have been reported with empagliflozin in clinical trials. A causal relationship has not been established

Report any suspected side effects here: www.mhra.gov.uk/yellowcard

Always discuss stopping SGLT2i therapy with a HF or diabetes specialist, unless there is an urgent clinical need to stop immediately

Roles and Responsibilities

Specialist team – 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
- Details of the shared decision-making process/counselling with the patient (*Think Overprescribing*)
- Baseline renal function and BP reading (include baseline HbA1c if checked and liver function test if severe hepatic impairment requiring dose adjustment at initiation for dapagliflozin- *see page 3*)
- Details of upcoming specialist and/or community HF team follow up/support

Refer to the patient's local community pharmacy (via email) for the Discharge medicines service (NHS DMS) if possible, which will assist understanding of and adherence to therapy and ensure accurate medicines reconciliation. All new initiations for **medicines compliance aid** patients must be discussed with their community pharmacy to safeguard the patient and reduce risk of medication errors.

Primary care:

- Initiate on the advice of secondary care (these patients may be seen by specialists in medicine, renal, diabetes, respiratory and cardiology for example), heart failure community team or continue ongoing prescribing of dapagliflozin or empagliflozin once initiated by relevant team
- Ensure the indication for therapy is clearly linked to the patient record (SNOMED codes)
- Monitor as indicated and review the patient every 6 to 12 months in line with NICE HF guidance (see monitoring and side effects on pages 2-3)
    - *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*
- Support patient adherence unless adverse effects necessitate cessation of therapy (discuss with HF team before stopping any prognostic medications for heart failure unless there is a clear clinical reason to stop immediately)
- 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 in any of the following circumstances: • Patient tolerability issues and frailty concerns which may lead to cessation of therapy • If eGFR drops >10ml/min within a 6-month period or >15ml/min within a 12-month period • If eGFR becomes <30ml/min during therapy or is <15ml/min at initiation • If concerns re hypoglycaemia in patients with diabetes- refer to DM specialists (*this guidance focuses on patients without diabetes)*

Contact details for South East London Community HF teams: see SEL guidance on the pharmacological management of heart failure in adults: page 25. *Please note that not all patients with HFpEF and HFmrEF will be under HF teams*

Borough	Heart Failure Community Team
Bexley	Email: oxl-tr.cardiac@nhs.net Tel: 0207 188 8952 or 0208 319 7060
Bromley	Email: kch-tr.PRUHheartfailurenurses@nhs.net Tel: 01689866097 (bleep #739) Email: kch-tr.br-bromleyintegratedheartfailurenurses@nhs.net Tel: 07971484508
Greenwich	Email: oxl-tr.cardiac@nhs.net Tel: 0208 319 7060
Lambeth & Southwark	Email: Gst-tr.KHPcommunityHF@nhs.net Tel: 0203 049 4652
Lewisham	Email: LH.commuhfreferrals@nhs.net Tel: 0203 049 3473

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

References:

1. Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction TA929 Nov. 2023: https://www.nice.org.uk/guidance/ta929
2. Empagliflozin 10mg summary of product characteristics: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
3. Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction TA902 June 2023: https://www.nice.org.uk/guidance/ta902/chapter/1-Recommendations
4. Heart failure- SGLT2i in HFrEF non-DM guidance: SEL IMOC - Cardiovascular disease guidance - NHS South East London (selondonics.org)
5. Dapagliflozin 10mg summary of product characteristics: Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
6. NICE CHF guidance NG106: Recommendations | Chronic heart failure in adults: diagnosis and management | Guidance | NICE
7. SEL IMOC Heart failure- adult treatment guideline: SEL IMOC - Cardiovascular disease guidance - NHS South East London (selondonics.org)
8. EuHeartJ ESC HF guidelines: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure | European Heart Journal | Oxford Academic (oup.com) [accessed 30/05/23]