Dapagliflozin▼ in Heart Failure with Reduced Ejection Fraction (HFrEF) in patients without Diabetes Mellitus

July 2021

Dapagliflozin is a sodium glucose co-transporter 2 inhibitor (SGLT2i) traditionally prescribed for diabetes, but this guidance focuses on patients with HFrEF defined by left ventricular ejection fraction (LVEF) ≤40% ***without diabetes mellitus*** *(DM).*

Evidence from clinical trial data suggests that, when added to optimised medical therapy, dapagliflozin lowers the risk of dying from cardiovascular causes and reduces the likelihood of hospitalisation or urgent outpatient visit due to heart failure (HF). In South East London, dapagliflozin is recommended, within its marketing authorisation (unless contra-indicated), as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, as an add-on to optimised standard medicines for chronic heart failure (See: *SEL guidance on the pharmacological management of heart failure HF in adults*):

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
With a beta-blocker (BB)
And, if tolerated, a mineralocorticoid receptor antagonist (MRA)

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Use of dapagliflozin in HFrEF is "Amber 2" in SEL – initiation and initial supply by specialist.
HF specialist (nurse, doctor or pharmacist) will initiate dapagliflozin (if eGFR is ≥ 30ml/min):
Dapagliflozin 10mg once daily (*see initiation checklist below*)
(5mg daily initial dose if severe hepatic impairment: *see cautions on page 2*)

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Initiation checklist:

1. **A shared decision** to initiate dapagliflozin for each patient, follows a discussion of the benefits and risks, current co-morbidities (*including a check for diabetes where possible*) and contra-indications to this therapy (*see page 2*). See page 3 for side effects to consider in the consultation.
2. **Check baseline renal function**: do not start therapy if eGFR <30ml/min as there is limited experience in HF patients with severe renal impairment.
3. **Check baseline blood pressure (BP)**- caution if SBP <95mmHg for elderly ≥65 years and if symptomatic hypotension. Dapagliflozin can lead to a reduction in BP- 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 dapagliflozin to exclude undiagnosed type 2 diabetes mellitus (T2DM). Refer to DM team if HbA1c is above 48 mmol/mol. See NICE guidance for T2DM.
5. **Check baseline liver function:** For severe hepatic impairment (Childs-Pugh score C, AST/ALT > 3x ULN or Bilirubin > 2x ULN) initiate dapagliflozin at 5mg daily- dose may then increase to 10mg if well-tolerated.
6. **Communication to primary care** (heart failure management plan)**:** Prescribing of dapagliflozin will transfer to primary care following hospital discharge. If initiated in hospital, patients will be reviewed by the initiating HF team or referred to the community HF team. Patients initiated on dapagliflozin in outpatient clinics will be followed up by primary care (*see roles and responsibilities on page 3*).
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 by email to their local pharmacy for further counselling/adherence support through the discharge medicines service (NHS DMS).

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Patient information: An information leaflet is under development for patients without diabetes, as currently all product information refers to dapagliflozin 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 below*).

Good Prescribing Practice: Ensure the indication for dapagliflozin is added to the prescription eg "for the heart" and that this is added to the dispensing label in pharmacy and the patient's clinical record.

Cautions and contra-indications (full list: *BNF* and *SPC*)

Contra-indications	Cautions
Pregnancy and breastfeeding	Limited experience in HF indication in severe renal impairment (eGFR <30ml/min)
Hypersensitivity to active substance or excipients	Anti-hypertensive therapy in hypotensive or elderly/frail patients if at risk from BP drop due to dapagliflozin: caution SBP below 95mmHg at initiation or symptomatic hypotension
	Lactose intolerance
	Severe hepatic impairment: Childs-Pugh score C, AST/ALT > 3x ULN or Bilirubin > 2x ULN except in Gilbert's: use 5mg initial dose but may increase to 10mg if well tolerated
	Limited experience in NYHA class IV
	History of urinary tract infections or recurrent thrush
	Low weight/ weight loss
	Patients undergoing surgical procedures- risk of DKA in the peri-operative period: temporarily withhold and monitor ketone levels – see MHRA guidance for further information

Interactions (link: Dapagliflozin | Interactions | BNF content published by NICE)
Documented 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.

Monitoring Requirements (by HF specialist/primary care):

1. **Renal function:** Monitoring of renal function is recommended as follows:
   - At baseline, within the first 3 months of therapy, as clinically indicated and at least annually thereafter (eGFR can fall after initiation and if eGFR falls below 30ml/min- consider specialist/renal advice and co-prescribed medications/co-morbidities that may affect eGFR).
   - Seek advice and guidance from a renal specialist if eGFR drop of >10ml/min in a 6 month period or >15ml/min in a 12 month period.
2. **Blood pressure:** Dapagliflozin increases diuresis which may lead to a modest decrease in blood pressure (about 3-5mmHg SBP and 2mmHg DBP) observed in studies:
   - Caution should be exercised in patients for whom a dapagliflozin-induced 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.
   - Check blood pressure at initiation, within the first 3 months and then at least annually.
3. **Intercurrent conditions that may lead to volume depletion** (eg. gastrointestinal illness):
   - Monitoring of volume status (eg. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes, urea) is recommended.

Sick day rules: Temporarily withhold dapagliflozin (or any other SGLT2 inhibitor) in patients who:
- are hospitalised for major surgery or acute serious illnesses (see MRHA 2020): blood ketone levels may be monitored (and be normal before restarting)
- also consider stopping in any other hospital admission 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 may 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)

4. **Check patient tolerance/adherence and side effects:** See below for side effects to consider.
5. **Urinary frequency, polyuria, dysuria, glucose in urine:** all common side effects- see point 7 concerning UTIs
6. **Dehydration/volume depletion/dizziness/hypotension:** monitor and encourage patient to report any symptoms
7. **Important side effects that may require cessation of therapy:** for full side effect profile see[2] SPC Forxiga 10mg
   - Mycotic genital infections: commonly occur (particularly at the start of therapy) but are managed with antifungals- reassure patient and ensure adequate genital hygiene- if problematic/recurrent, stop therapy*
   - Urinary tract infections (UTIs): dapagliflozin causes glucose to be excreted in the urine, stop therapy* if significant UTIs such as pyelonephritis or urosepsis,
   - Fournier's gangrene: Necrotising fasciitis of the perineum is rare and therapy should be stopped*
   - Rash: eliminate 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 TIIDM. 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
8. **General practice 6 to 12 month HF review:** See HF pathway KHP. 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. 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.

Roles and Responsibilities: Following initiation in hospital 1 month's supply of dapagliflozin will be given to the patient at discharge (unless a medicines compliance aid is required- *local guidance applies*). A discharge letter will be sent to primary care with initiation information and monitoring/follow up requirements.

Following initiation in outpatients, 1 month's supply will be provided to the patient, the primary care healthcare provider (HCP) will be asked to prescribe on receipt of initiation information in the clinic letter and clear follow up/monitoring requirements.

In exceptional circumstances, for example if there is no prescriber in the HF team, this may be initiated in primary care, on the advice of a HF specialist.

Primary care to ensure the indication for therapy is linked to the patient record and to ensure a follow up is scheduled either by a primary care HCP or with community HF support. Check patient

adherence/tolerance to therapy and heart failure management (eg. BP, U&Es, fluid balance) within the first three months of therapy.

Initiation information to be completed by the prescriber:

- 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 within the first month (*if required*)

It is recommended that patients are referred (via email) to their **local community pharmacy** for the Discharge Medicines Service (NHS DMS), which will assist understanding of and adherence to therapy, and ensure accurate medicines reconciliation. All **medicines compliance aid patients** must be discussed with their community pharmacy for new initiations to safeguard the patient and reduce the risk of medication errors.

For primary care, continue prescribing dapagliflozin, monitor as indicated and review the patient 6 to 12 monthly in line with NICE HF guidance (*see monitoring and side effects on pages 2 to 3*). 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 an established medicine, 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 and eGFR<30ml/min, patient tolerability issues and frailty concerns, that may lead to cessation of therapy.

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

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 is prescribed for non-approved/unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation.

References: *accessed 24/3/21*

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