Guideline for Dapagliflozin in Heart Failure
With Reduced Ejection Fraction (HFrEF)

Key points

- Dapagliflozin is licensed for the treatment of adults (with or without type 2 diabetes) with symptomatic chronic heart failure with reduced ejection fraction (≤40%).

- For the management of heart failure dapagliflozin may be used in patients with renal impairment.

- In patients with type 2 diabetes refer for specialist advice where the patient is taking insulin or advice needed on diabetes management prior to initiation/during treatment.

Background
Dapagliflozin is one of a number of a sodium-glucose transport protein 2 (SGLT2) inhibitors, initially developed for the glycaemic management of patients with type 2 diabetes (and more recently type 1 diabetes). Blood glucose is lowered as SGLT2 inhibition leads to reduced reabsorption of glucose in the kidney with resultant increased excretion of glucose and an osmotic diuresis.

The DAPA–HF trial evaluated dapagliflozin versus placebo in patients with heart failure and reduced ejection fraction (≤40%) in patients with or without type 2 diabetes. The primary end-point of cardiovascular death, worsening heart failure (unplanned hospital admission for heart failure or urgent HF visit requiring IV therapy) was significantly reduced (ARR 4.9%, NNT =21) in the treatment group regardless of diabetic status. Patients could be enrolled in the trial if the baseline eGFR was above 30ml/min/1.73m².

Licensed indication
Dapagliflozin is now licensed for the treatment of adults (with or without diabetes) with symptomatic chronic heart failure with reduced ejection fraction (≤40%). The recommended dose is dapagliflozin 10mg once a day.

Place in therapy for management of heart failure (HFrEF)

- Patients with symptomatic (NYHA II-IV) HFrEF (ejection fraction ≤40%) with or without type 2 diabetes. Dapagliflozin may be prescribed in addition to the standard heart failure treatment of diuretics (if required for congestion) a renin-angiotensin-system inhibitor (which may be an ACE inhibitor or an angiotensin receptor blocker (ARB) or sacubitril+valsartan (an ARNI)) and a beta-blocker +/- mineralocorticoid receptor antagonist (MRA).

- In patients with HFrEF and type 2 diabetes dapagliflozin may be prescribed as part of the regimen for glycaemic control in line with national and local guidelines for the management of type 2 diabetes.
Who can prescribe
Secondary care specialist teams – e.g. heart failure, cardiology, diabetes, renal
Primary care specialist teams – e.g. heart failure, diabetes
Primary care clinicians on the recommendation of above teams

(NB dapagliflozin may still be started in primary care for patients with type 2 diabetes in line with local diabetes guidelines without specialist input – green classification on local formulary)

Contra-indications for initiation dapagliflozin in heart failure (HFrEF)

- Type 1 diabetes (known or suspected) *
- History of diabetic ketoacidosis (DKA)
- History of allergic reaction to dapagliflozin
- Severe renal impairment with an eGFR < 20 ml/minute/1.73m² or end stage renal disease or dialysis patients
- Pregnancy or breastfeeding
- Patients on very Low calorie / low carbohydrate diets

*Dapagliflozin is licensed in patients with type I diabetes - use is restricted to specialist diabetes team recommendation.

Cautions

- Heart failure (HFrEF) with NHYA IV symptoms (limited clinical experience)
- Patients at increased risk of DKA (including a low beta cell reserve, conditions leading to restricted food intake or severe dehydration, sudden reduction in insulin, increased insulin requirements due to acute illness, surgery or alcohol abuse)
- History of recurrent urinary tract infections or candida
- Patients at risk of necrotising fasciitis (Fournier’s gangrene)
- There is limited experience in patients with an eGFR < 30 ml/minute/1.73m²
- If euvoalaemic consider dose reduction of diuretic to reduce risk of dehydration
- SBP < 95 mmHg
- Severe hepatic impairment (5mg starting dose recommended)
- Cognitive impairment

Monitoring

Baseline renal function and blood pressure.
Recheck renal function and blood pressure 4 weeks after initiation.
Re-check renal function prior to, and after, initiation of concomitant medicinal products that may reduce renal function.

As a minimum renal function should be checked annually.
If the eGFR is <60 ml/minute/1.73m² monitor more frequently (e.g. every 3-6 months).

In case of inter-current conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Dapagliflozin should be temporarily withheld (see ‘intercurrent illness’ section below).
Management of medication in patients with type 2 diabetes

Although SGLT2 inhibitors have a low risk of hypoglycaemic events, reducing blood glucose levels via this mechanism could potentially predispose patients taking other anti-glycaemic medication (particularly insulin or sulphonylureas) to hypoglycaemia.

Medication prescribed for glycaemic control must be reviewed in line with the patient’s HbA1c target.

In patients with type 2 diabetes refer for specialist diabetes team advice prior to initiation/during treatment if for example:
- The patient is taking insulin
- There is a history of previous/frequent hypoglycaemia
- Any advice is needed on diabetes management or suitability of an SGLT2 inhibitor for your patient

In patients with HFrEF who are already prescribed an alternative SGLT2 inhibitor (e.g. empagliflozin, canagliflozin) for the management of type 2 diabetes this may be continued in line with the licence for the prescribed product (or may be switched to dapagliflozin – clinical decision between clinician and patient).

As part of holistic healthcare planning glucose lowering therapies that have not provided adequate glucose lowering should be stopped. It is important to highlight the indication for dapagliflozin as heart failure (HFrEF) to ensure this medication is not stopped at routine diabetes review.

In patients treated with dapagliflozin for both heart failure and type 2 diabetes mellitus, additional glucose-lowering treatment may need to be considered if eGFR falls persistently below 45 ml/minute/1.73m² (as SGLT2 inhibitors have minimal effect on glycaemic control with reduced renal function).

Side effects

Common or very common - back pain; balanoposthitis; dizziness; dyslipidaemia; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of urinary tract infection; rash; urinary disorders

Uncommon - Constipation; dry mouth; genital pruritus; hypovolaemia; thirst; vulvovaginal pruritus; weight decreased

Rare or very rare - Angioedema; Fournier’s gangrene (discontinue and initiate treatment promptly, diabetic ketoacidosis when used in type 2 diabetes (discontinue immediately and DO NOT restart).
**Patient Counselling /Advice**

**Patient information booklet** - dapagliflozin in patients with HFrEF (produced by Astra Zeneca)

**Risk of diabetic ketoacidosis (DKA)**
Inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), and advise them to seek immediate medical advice if they develop any of these.

GP/hospital to test for raised ketones in patients with signs and symptoms of DKA, even if plasma glucose levels are near-normal or normal.

**With Intercurrent illness:**

Temporarily withhold dapagliflozin (or any other SGLT2 inhibitor) in patients who
- are hospitalised for major surgery or acute serious illnesses
- are not eating or drinking
- with inter-current conditions that may lead to volume depletion (e.g. vomiting /diarrhoea)
- have 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 -see above)

**Association of British Clinical Diabetologists**
SGLT-2 inhibitors in people with type 2 diabetes: An educational resource for health professionals

Diabetes UK advice for patients on ‘diabetes when you are unwell’

**Fournier’s gangrene**

Fournier’s gangrene is a rare but potentially life-threatening infection that requires urgent medical attention.

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