Cambridgeshire & Peterborough Integrated Care System

NHS Cambridgeshire & Peterborough

Dapagliflozin & Empagliflozin for Heart Failure in Adults

Prescribing Support Document

Executive summary

- Dapagliflozin and empagliflozin are recommended by NICE as add-on therapy for the treatment of heart failure in patients with or without type 2 diabetes mellitus (T2DM), encompassing:
    - **heart failure with reduced ejection fraction (HFrEF)**.
    - **heart failure with mildly reduced ejection fraction (HFmrEF)**.
    - **heart failure with preserved ejection fraction (HFpEF)**.
- Primary care may initiate dapagliflozin/empagliflozin following recommendation by the Community or Secondary Care Heart Failure Multidisciplinary Team.
- The dose of dapagliflozin and empagliflozin in the treatment of all forms of heart failure is 10mg daily.
- Dapagliflozin should not be started if eGFR below 15ml/min/1.73m^2.
- Empagliflozin should not be started if eGFR below 20ml/min/1.73m^2.
- Patients with type 1 diabetes mellitus (T1DM) or a history of diabetic ketoacidosis (DKA) are not eligible for treatment with dapagliflozin or empagliflozin.
- Rare cases of DKA have been reported in patients treated with SGLT2 inhibitors. Patients may be euglycaemic. In patients where DKA is suspected or diagnosed, dapagliflozin/empagliflozin should be stopped immediately and appropriate management initiated.
- Patients with T2DM with HbA1c below 53mmol/mol using insulin or sulphonylurea and/or recent hypoglycaemia, may need a dose reduction of insulin and/or sulphonylureas.
- Patients with T2DM should be advised on sick day rules.

Background and evidence summary

Dapagliflozin and empagliflozin are sodium-glucose cotransporter 2 inhibitors (SGLT2i). They work by blocking the action of SGLT 2 in the kidneys, and by preventing glucose reabsorption; therefore, increasing glucose excretion in the urine. The additional glucose in the urine osmotically retains water, thus acting as an osmotic diuretic. They are already an approved drug for the management of type 2 diabetes mellitus due to its plasma glucose lowering effects.

Heart failure is a chronic condition that occurs when the heart is unable to pump enough blood to meet the body's needs. Left ventricular ejection fraction (EF), the amount of blood pumped by the left ventricle during each heartbeat, is one measure used to classify the different types of chronic heart failure, with:

- 40% or less defined as heart failure with reduced ejection fraction (HFrEF).
- 41% to 49% defined as heart failure with mildly reduced ejection (HFmrEF).
- 50% or more defined as heart failure with preserved ejection fraction (HFpEF).

Two large, randomised control trials involving dapagliflozin and empagliflozin (DAPA-HF and EMPEROR-Reduced) have shown significant reduction in heart failure (HF) hospitalization and cardiovascular mortality in patients with HFrEF. Further large, randomised control trials (DELIVER and EMPEROR-Preserved) have shown that dapagliflozin and empagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with HFmrEF and HFpEF. The benefits of SGLT2 inhibitors were seen in patients with or without T2DM. The precise mechanism for the beneficial effects of the drug in patients with HF are incompletely understood. Potential theories include reduction of preload by osmotic diuresis, reduction of afterload, alteration of myocardial energetics, reduction of myocardial mass, modulation of renal afferent tone and the inhibition of cardiac fibrosis.

NICE Guidance

Heart failure with reduced ejection fraction

NICE Technology Appraisal Guidance (TA679 for dapagliflozin; published 24 February 2021 and TA773 for empagliflozin; published 9 March 2022) state: dapagliflozin/empagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it used as an add-on to optimised standard care with:

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin 2 receptor blockers (ARBs), with beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or
- Sacubitril valsartan, with beta blockers, and, if tolerated, MRAs.

Heart failure with preserved ejection fraction or heart failure with mildly reduced ejection fraction

NICE Technology Appraisal Guidance (TA902 for dapagliflozin; published 21 June 2023 and TA929 for empagliflozin; published 01 November 2023) states:

- Dapagliflozin and empagliflozin are recommended, within their marketing authorisation, as an option for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults.
- The specialist will consider with the patient, the most appropriate choice of treatment for their individual needs.

Start dapagliflozin/ empagliflozin for treating symptomatic heart failure on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.

These recommendations are not intended to affect treatment with dapagliflozin/ empagliflozin that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Please refer to the Cambridgeshire and Peterborough system-wide formulary for links to local and national guidance.

ADVICE **SPECIALIST ADVICE -** Primary care may initiate dapagliflozin/ empagliflozin following recommendation by the Community or Secondary Care Heart Failure Multidisciplinary Team.

Licensed indications and prescribing good practice

When will primary care clinicians be asked to prescribe?

Primary care clinicians will only be asked to prescribe dapagliflozin or empagliflozin for HF patients on the advice of a heart failure specialist. Eligible patients will be identified through cardiology and heart failure clinics, through hospital admission and in the community via the heart failure specialist nursing teams. Eligible patients will meet inclusion criteria in keeping with NICE TA 679 or TA 902 (dapagliflozin), or TA 773 or TA 929 (empagliflozin).

Medication information

For further information, please consult the latest edition of the British National Formulary (BNF) or Summary of Product Characteristics (SPC) for full details.

Preparations and Dosage

Preparation

Dapagliflozin 10mg and 5mg tablets.
Empagliflozin 10 mg and 25mg tablets.

Dosage and Administration

For all forms of HF:

Dapagliflozin and empagliflozin: 10mg once daily. This can be taken with or without food. There is no fixed time, but it should be taken at the same time each day.

In patients with severe hepatic impairment: start at dose of dapagliflozin 5mg daily and increase if tolerated to 10mg daily.

Otherwise, there is no indication for using the lower dose of dapagliflozin (5mg daily) or the higher dose of empagliflozin (25mg daily) in the treatment of HF.

Contraindications and cautions

Contraindications

- Type 1 Diabetes Mellitus.
- History of diabetic ketoacidosis.
- Renal impairment.
  - Dapagliflozin: Do not start treatment if eGFR below 15mL/min/ 1.73m^2.
  - Empagliflozin: Do not start treatment if eGFR below 20mL/min/1.73m^2.
- Pregnancy or breastfeeding.
- Hypersensitivity to dapagliflozin/ empagliflozin or excipients.

Cautions

- Frail patients
- Patients where there is a risk of volume depletion
- Hypotension (Systolic blood pressure less than 95mmHg at 2 out of 3 measurements).
- Hepatic impairment.
  - Dapagliflozin: start at dose of 5mg daily in severe hepatic impairment, increased if tolerated to 10mg daily.
  - Empagliflozin: avoid in severe hepatic impairment.

Drug interactions

Below are some general drug interactions but prescribers must consult the Summary of Product characteristics for more detailed information on each specific drug. This is not an exhaustive list.

Drug/Therapeutic group	**Interaction**
Insulin and insulin secretagogues	Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin or empagliflozin in patients with type 2 diabetes mellitus.
Diuretics	Dapagliflozin or empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

There are no significant interactions with heart failure medications, such as ACE inhibitors, ARB, beta-blockers and MRA.

Adverse effects

Type	**Adverse effect**
Side-effects at 'therapeutic' levels	Most common adverse effects are thrush, back pain, feeling dizzy, skin rash and increased urinary frequency.
Longer term effects	Very common: hypoglycaemia (only in combination with insulin or sulphonylureas) Common: urogenital infections, rash and back pain. Uncommon: volume depletion. Rare: diabetic ketoacidosis (when used in patients with T2DM). Very rare: necrotising fasciitis of perineum (Fournier's gangrene).

Frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Pregnancy and contraception

Pregnancy

There are no data from the use of dapagliflozin or empagliflozin in pregnant women. For dapagliflozin, animal studies have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. For empagliflozin, animal studies have shown adverse effects on postnatal development. Therefore, the use of dapagliflozin and empagliflozin are not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin and empagliflozin should be discontinued.

Breast-feeding

It is unknown whether dapagliflozin and empagliflozin and/or their metabolites are excreted in human milk. Available data in animals have shown excretion of dapagliflozin and empagliflozin and/or their metabolites in milk, as well as pharmacologically mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Dapagliflozin and empagliflozin should not be used while breast-feeding.

Fertility

The effect of dapagliflozin and empagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin and empagliflozin showed no effects on fertility at any dose tested.

Monitoring: Specialist responsibility

No responsibility for routine monitoring.

Monitoring: Primary care responsibility

Renal function should be checked before initiation and then at least annually thereafter. Patients with HF on renin-aldosterone-angiotensin system (RAAS) inhibitors will be having renal function checked on a bi-annual basis at minimum. Therefore, no additional monitoring is required.

Advice and Support

Issue	**Concomitant Diabetes**	**No Concomitant Diabetes**
1. Glycaemic control	If not using insulin or sulphonylurea, no adjustment needed. If using insulin or sulphonylurea but HbA1c above 53mmol/mol and no recent hypoglycaemia, no adjustment needed. If using insulin or sulphonylurea and HbA1c below 53millimole/mol or recent hypoglycaemia, consider up to 25% total daily dose reduction of insulin and/or sulphonylureas. Rapid or large reductions of insulin dose may precipitate diabetic ketoacidosis and should be avoided.	No hypoglycaemic concerns.
2. Diabetic ketoacidosis	"Sick Day" rules. Withhold during concomitant illness or surgery. It is the responsibility of the team performing any planned operation or procedure to advise the patient on whether treatment with SGLT2 inhibitors should be stopped and when for planned procedures as part of their pre-operative instructions. Advise patients to maintain fluid and carbohydrate intake (do not fast). Seek urgent medical advice if unable to keep fluids/food down. High index of suspicion for DKA. Measure blood ketones even if blood sugar in normal range. **Rare cases of DKA have been reported in patients treated with SGLT2 inhibitors. In patients where DKA is suspected or diagnosed, dapagliflozin/empagliflozin should be stopped immediately.**	Not recognised as a risk in non-diabetics. Hold during intercurrent volume depleting illness until oral intake adequate.
3. Diabetic foot care	Increased risk of lower limb amputation with another SGLT2i (canagliflozin), but not observed in dapagliflozin/empagliflozin studies. People with diabetes should check their feet regularly and adhere to usual foot care advice.	No concerns.

Issue	Concomitant Diabetes	No Concomitant Diabetes
4. Renal function	Early eGFR reduction up to 20% is common and acceptable. This will partially rebound within the first few months. Blood glucose lowering effect is diminished at eGFR below 45mL/min/1.73m^2 but cardiac benefits persist. There are no criteria for stopping dapagliflozin or empagliflozin based on renal function.	Same as diabetes.
5. Volume	Consider reduction in dose of diuretics if normovolemic.	Same as diabetes.
6. Urogenital infection	Advise good perineal hygiene, consider single dose of fluconazole for fungal infection.	Same as diabetes.
7. Urinary tract infection	No increased incidence of UTI.	Same as diabetes

Contact local heart failure specialist team if further support is required, particularly if dapagliflozin or empagliflozin are stopped due to adverse effects.

References

1. McMurray JJV, Solomon SD, Inzucchi SE *et al*. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**:1995-2008.
2. Packer M, Anker SD, Butler J *et al*. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**:1413-1424.
3. Solomon SD, McMurray JJV, Claggett B et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med* 2022; **387**:1089-1098.
4. National Institute for Health and Care Excellence. Dapagliflozin for treating chronic heart failure with reduced ejection fraction. Technology appraisal guidance [TA679]. Published: 24 February 2021. Available online (accessed 15/08/2021).
5. National Institute for Health and Care Excellence. Empagliflozin for treating chronic heart failure with reduced ejection fraction. Technology appraisal guidance [TA773]. Published: 09 March 2022. Available online (accessed 26/04/2022).
6. National Institute for Health and Care Excellence. Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction. Technology appraisal guidance [TA902]. Published: 21 June 2023. Available online (accessed 11/07/23).
7. National Institute for Health and Care Excellence. Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction. Technology appraisal guidance [TA929]. Published: 01 November 2023. Available online (accessed 09/12/23).

Document ratification details

Ratification Process	Details
Authored by:	Cambridge University Hospitals NHS Foundation Trust North West Anglia NHS Foundation Trust Royal Papworth Hospital NHS Foundation Trust
Ratified by:	Cambridgeshire and Peterborough Joint Prescribing Group
Date ratified:	July 2024
Review date:	July 2027
Version number:	3