

## Initiation of Empagliflozin in Adults with Heart Failure

### Key Points

- This advice applies to monitoring of pharmacotherapy in clinically stable patients; **it does NOT apply to patients with intercurrent acute illness.**
- Empagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection in adults, only if it used as an add-on to optimised standard care.
- It should only be started on advice from a heart failure specialist.
- Increased risk of diabetic ketoacidosis (counsel patient).
- If prognostic medication is stopped due to AKI/ acutely unwell patient, please consider restarting if renal function recovers.
- Empagliflozin has a NICE technological evaluation for use in patients with HFpEF/HFmrEF with a publication date of 01 November 2023.

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**Key words:** HFrEF, HFmrEF, HFpEF, Empagliflozin

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### Abbreviations

|        |                                                |
|--------|------------------------------------------------|
| ARR    | Absolute Risk Reduction                        |
| DKA    | Diabetic Ketoacidosis                          |
| eGFr   | Estimated glomerular filtration rate           |
| HbA1c  | Glycated Haemoglobin                           |
| HF     | Heart Failure                                  |
| HFrEF  | Heart Failure reduced ejection fraction        |
| HFmrEF | Heart Failure mildly reduced ejection fraction |
| HFpEF  | Heart Failure preserved ejection fraction      |
| LVEF   | Left ventricular ejection fraction             |
| IV     | Intravenous                                    |
| NNT    | Number needed to treat                         |
| NYHA   | New York Heart Association                     |
| SGLT1  | Sodium-glucose transport protein 1             |
| SGLT2  | Sodium-glucose transport protein 2             |

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### Purpose of guideline

To support the prescribing of empagliflozin in patients with symptomatic chronic heart failure.

### Guideline rationale

Empagliflozin is a sodium-glucose transport protein 2 (SGLT2) inhibitor licensed for the treatment of adults (with or without type 2 diabetes) with symptomatic heart failure (NYHA class II-IV).

SGLT2 inhibition leads to reduced reabsorption of glucose in the kidneys with a resultant increased excretion of glucose and an osmotic diuresis. SGLT2 inhibitors were initially licensed for use in diabetics.

The EMPEROR-Reduced trial evaluated dapagliflozin versus placebo in patients with heart failure and reduced ejection fraction ( $\leq 40\%$ ) in patients with or without type 2 diabetes. The primary end-points of cardiovascular death and heart failure hospitalisation were significantly reduced (ARR 5.2%, NNT =19) in the treatment group regardless of diabetic status.

The EMPEROR-Preserved trial evaluated empagliflozin versus placebo in patients with chronic heart failure (NYHA II-IV) with preserved ejection fraction (LVEF  $>40\%$ ) as adjunct to standard care therapy with and without T2DM. The primary endpoint was the time to adjudicated first event of either cardiovascular death or hospitalisation for heart failure. Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo (HR 0.79, 95%CI 0.69-0.90, P=0.0003).

## Mechanism of Action

Inhibition of SGLT2 by empagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis.

Empagliflozin therefore increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure.

This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling.

The cardiac benefits of empagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the EMPEROR-Reduced and EMPEROR-Preserved studies.

The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and eGFR. Thus, in subjects with normal blood glucose, empagliflozin has a low propensity to cause hypoglycaemia.

Empagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. It acts independently of insulin secretion and insulin action.

SGLT2 is selectively expressed in the kidney and empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues. It is 5000 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

## Place in Therapy

Empagliflozin is recommended as an option for treating symptomatic (NYHA class II to IV) HF in adults, with or without type 2 diabetes and eGFR  $>20\text{mls/min/1.73m}^2$ . For HFpEF, it may only be prescribed as an add-on to optimised standard care. This is currently:

- Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Neprilysin Inhibitor (ARNI)
- Plus Beta blockers
- Plus Mineralocorticoid receptor antagonists (MRAs)

It is important to document when empagliflozin is being used for HF to ensure it is not stopped when diabetes medication is reviewed. Empagliflozin is not effective as a glucose lowering agent if eGFR  $< 30\text{mls/min}$  but it still has benefits in HF. The trials for HFpEF showed efficacy in patients with EF of  $<55\%$ .

Patients with type 2 diabetes and HF may also be prescribed empagliflozin for management of their diabetes.

In patients with HF who are already prescribed an alternative SGLT2 inhibitor (e.g., canagliflozin) for the management of type 2 diabetes this may be continued.

Empagliflozin has a NICE technological evaluation for use in patients with HFpEF/HFmrEF with a publication date of 01 November 2023.

## Initiation

### Use in HF

Initiation must be by specialist review only, as per NICE Technology appraisal guidance [TA773 and TA929] Published 9 March 2022 and 01 November 2023 respectively.

At FHFT this will mean:

- Recommendation via the Heart Failure MDTs at Frimley Park and Wexham Park Hospitals.
- Recommendation following an outpatient appointment with a Cardiologist.
- Recommendation during Cardiologist led ward round while an inpatient.

### Diabetes and HF (see cautions)

Consider referring for specialist diabetes advice.

May be prescribed as part of the treatment for glycaemic control as per national and local guidelines.

| Contra-indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Cautions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Hypersensitivity to the active substance or to any of the excipients</li> <li>• Unacceptable side effects associated with a SGLT2 inhibitor</li> <li>• Type 1 diabetes</li> <li>• History of diabetic ketoacidosis (DKA)</li> <li>• Pregnancy and breastfeeding</li> <li>• Age under 18 years old</li> <li>• Systolic blood pressure of less than 95 mm Hg</li> <li>• Patients with <math>eGFR &lt; 20 \text{ ml/min/1.73m}^2</math></li> <li>• Patients on dialysis</li> </ul> | <ul style="list-style-type: none"> <li>• Severe hepatic impairment (Child-Pugh class C) – consider 5mg starting dose.</li> <li>• HF with NYHA IV symptoms</li> <li>• Patients at risk of Fournier's Gangrene</li> <li>• Patients at increased risk of urinary tract infections</li> <li>• Complicated urinary tract infections. (Consider temporary interruption)</li> <li>• Elevated haematocrit</li> <li>• Patients with infiltrative disease or Takotsubo cardiomyopathy. (Efficacy has not been established)</li> <li>• Patients at increased risk of DKA (discuss sick day rules)</li> <li>• Severe peripheral vascular disease</li> <li>• Patients with type 2 diabetes who are already at target HbA1c and currently taking hypoglycaemic agents, e.g., insulin and sulphonylureas (Consider reducing dose of current hypoglycaemic agent)</li> <li>• Patients with type 2 diabetes who are not at target HbA1c level and <math>eGFR &lt; 30 \text{ ml/min/1.73m}^2</math> (Empagliflozin is still indicated and effective to treat HF and has been shown to be reno-protective, but it may not be effective as a hypoglycaemic agent)</li> <li>• HbA1c <math>&gt; 85</math> as this increases risk of DKA</li> <li>• Surgical procedure (see <a href="#">Adult patients with Diabetes undergoing surgery and elective procedures</a>)</li> <li>• Tertiary centres may request stopping 72 hours before prolonged surgery</li> </ul> |

## Important drug reactions

Diuretics - Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues - Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of 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 empagliflozin in patients with type 2 diabetes mellitus.

## Dose

The recommended dose is 10 mg empagliflozin once daily.  
It can be taken with or without food.

| Side Effects          |                                                                                                                                                                                                                                              |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Common or very common | Constipation<br>Dyslipidaemia<br>Genital infections<br>Hypoglycaemia (in combination with insulin or sulphonylurea)<br>Increased risk of infection<br>Polyurea<br>Pruritus<br>Rash<br>Thirst<br>Urinary tract infections<br>Volume depletion |
| Uncommon              | Angioedema<br>Blood creatinine increased/ glomerular filtration rate decreased<br>Diabetic ketoacidosis<br>Dysuria<br>Haematocrit increased<br>Urticaria                                                                                     |
| Rare or very rare     | Fournier's gangrene<br>Tubulo-interstitial nephritis                                                                                                                                                                                         |

## Counselling

Risk of diabetic ketoacidosis (DKA).

Inform patients of the signs and symptoms of DKA, (nausea or vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or 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. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

Risk of genital infections.

Remind patients of the importance of good genital hygiene.

**With Intercurrent illness: Temporarily withhold empagliflozin (or any other SGLT2 inhibitor) in patients who**

- are hospitalised for major surgery or acute serious illnesses: blood ketone levels should be monitored (and be normal before restarting)
- are not eating and drinking
- have vomiting or diarrhoea
- have major infection

Treatment may be restarted once the patient's condition has stabilised and they are eating.

**Monitoring**

Baseline renal function and blood pressure

Minimum of six-monthly review of renal function and blood pressure

**References**

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**Full version control record**

|                                                                          |                                                                                   |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Version:</b>                                                          | 1                                                                                 |
| <b>Guidelines Lead(s):</b>                                               | Dr Lydia Sturridge, Consultant Cardiologist                                       |
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| <b>Lead Director / Chief of Service:</b>                                 | Dr Peter Clarkson, CoS for Cardiology                                             |
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| <b>Review Date:</b>                                                      | March 2027                                                                        |
| <b>Pharmaceutical dosing advice and formulary compliance checked by:</b> | Alexandra Kirke, 12 December 2023                                                 |
| <b>Key words:</b>                                                        | HFrEF, HFpEF, Empagliflozin                                                       |

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Caution is advised when using guidelines after the review date.

This guideline is for use in Frimley Health Trust hospitals only. Any use outside this location will not be supported by the Trust and will be at the risk of the individual using it.

**Version History**

| Version | Date                | Guideline Lead(s)                   | Status | Comment |
|---------|---------------------|-------------------------------------|--------|---------|
| 1       | Jan 2023 - Dec 2023 | Dr Lydia Sturridge, Alexandra Kirke | Final  |         |

**Related Documents**

| Document Type | Document Name                                                                           |
|---------------|-----------------------------------------------------------------------------------------|
| Guideline     | <a href="#">Adult patients with Diabetes undergoing surgery and elective procedures</a> |