

Initiation of Dapagliflozin 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**
- Dapagliflozin is recommended as an option for treating symptomatic (NYHA class II to IV) heart failure in adults, with or without type 2 diabetes and eGFr >15mls/min/1.73m²
- Contra-indicated if systolic blood pressure less than 95 mm Hg
- 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
- Dapagliflozin has NICE TA902 for use in patients with HFpEF/HFmrEF published on 21st June 2023.

Version: 4
Date Issued: 17 April 2024
Review Date: March 2027
Key words: Heart failure, Dapagliflozin

This is a controlled document. If you are using a printed copy, check it against the guidelines site to ensure you are using the latest edition.

Print copies must be destroyed after use.

Abbreviations

ARR	Absolute Risk Reduction
DKA	Diabetic Ketoacidosis
eGFr	Estimated glomerular filtration rate
HbA1c	Glycated Haemoglobin
HF	Heart Failure
HFReEF	Heart Failure reduced ejection fraction
HFmrEF	Heart Failure mildly reduced ejection fraction
HFpEF	Heart Failure preserved 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

Contents

Purpose of guideline	2
Guideline rationale	2
Mechanism of Action	2
Place in Therapy	3
Initiation	3
Use in HF	3
Diabetes and HF (see cautions)	3
Important drug reactions	4
Dose	5
Counselling	5
Monitoring	6
References	6
Full version control record	7

Purpose of guideline

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

Guideline rationale

Dapagliflozin is the first sodium-glucose transport protein 2 (SGLT2) inhibitor licensed for the treatment of adults (with or without type 2 diabetes) with symptomatic heart failure with preserved and (> 40%) and reduced ejection fraction ($\leq 40\%$).

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 DAPA –HF 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 endpoint 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.

The DELIVER study has evaluated the use of dapagliflozin in patients with HFpEF and HFmrEF (symptomatic heart failure (NYHA class II-IV) with a left ventricular ejection fraction $\geq 40\%$ and evidence of structural heart disease). The primary outcome, cardiovascular death or worsening HF for dapagliflozin vs. placebo, was: 16.4% vs. 19.5% (HR 0.82, 95% CI 0.73-0.92, $p < 0.001$). Dapagliflozin was found to be superior to placebo irrespective of diabetes status.

Mechanism of Action

Inhibition of SGLT2 by dapagliflozin 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.

Dapagliflozin 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 dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF, DELIVER and DAPA-CKD 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, dapagliflozin has a low propensity to cause hypoglycaemia.

Dapagliflozin 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 dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is >1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Place in Therapy

Dapagliflozin is recommended as an option for treating symptomatic (NYHA class II to IV) HF in adults, with or without type 2 diabetes and eGFR >15mls/min/1.73m². For HFrEF it may 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 dapagliflozin is being used for HF to ensure it is not stopped when diabetes medication is reviewed. Dapagliflozin is not effective as a glucose lowering agent if eGFR < 45mls/min but it still has benefits in HF.

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

Initiation

Use in HF

For HFrEF, initiation must be by specialist review only, as per NICE Technology appraisal guidance [TA679] published 24 February 2021. Similarly, for use in HFmrEF and HFpEF, dapagliflozin should only be started on advice from a heart failure specialist.

If dapagliflozin is not tolerated empagliflozin can be considered as an alternative.

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
- Hypersensitivity to the active substance or to any of the excipients - Unacceptable side effects associated with, an SGLT2 inhibitor - Type 1 diabetes - History of diabetic ketoacidosis (DKA) - Pregnancy and breastfeeding - Age under 18 years old - Systolic blood pressure of less than 95 mm Hg - Patients with $eGFR < 15 \text{ mL/min/1.73m}^2$	- Severe hepatic impairment (Child-Pugh class C) – consider 5mg starting dose. - HF with NYHA IV symptoms - Patients at risk of Fournier's Gangrene - Patients at increased risk of urinary tract infections - Patients at increased risk of DKA (discuss sick day rules) - Severe peripheral vascular disease - Patients with type 2 diabetes who are already at target HbA1c and currently taking hypoglycaemic agents, e.g., insulin and sulfonylurea (Consider reducing dose of current hypoglycaemic agent) - Patients with type 2 diabetes who are not at target HbA1c level and $eGFR$ $15\text{--}45 \text{ mL/min/1.73m}^2$ (Dapagliflozin 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) - HbA1c > 85 as this increases risk of DKA - Surgical procedure, see Adults with diabetes undergoing surgery and elective procedures - Tertiary centres may request stopping 72 hours before prolonged surgery $eGFR < 25 \text{ mL/min/1.73m}^2$

Important drug reactions

Diuretics - Dapagliflozin 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, 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 in patients with type 2 diabetes mellitus.

Dose

The recommended dose is 10 mg dapagliflozin once daily.
Can be taken with or without food.

Side Effects	
Common or very common	Back pain Creatinine renal clearance decreased during initial treatment Dizziness Dyslipidaemia Dysuria Genital infections Hypoglycaemia (in combination with insulin or sulfonylurea) Increased risk of infection Polyurea Rash Urinary tract infections
Uncommon	Constipation Dry mouth Fungal infection Genital pruritus or vulvovaginal pruritus (ensure good hygiene) Nocturia Weight decreased Hypovolaemia Thirst
Rare or very rare	Angioedema Diabetic ketoacidosis (when used in type 2 diabetes) Fournier's gangrene

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.

With Intercurrent illness: Temporarily withhold dapagliflozin (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

1. Forxiga 10mg tablets. Summary of Product Characteristics Accessed 13/01/2023
<https://www.medicines.org.uk/emc/product/7607/smpc>
2. Scottish Medicines Consortium (2021) Dapagliflozin 10mg film-coated tablets (Forxiga). Available at: [dapagliflozin-forxiga.pdf \(scottishmedicines.org.uk\)](#) (Accessed 13/01/2023)
3. National Institute for Health and Care Excellence [NICE] (2021) *Dapagliflozin for treating chronic heart failure with reduced ejection fraction*. TA679. Available at: <https://www.nice.org.uk/guidance/ta679>
4. National Institute for Health and Care Excellence [NICE] (2023) *Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction*. TA902. Available at: <https://www.nice.org.uk/guidance/ta902> (Accessed 13/01/2023)
5. ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2017, Jan 30. Identifier NCT03036124, Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF). Available from: <https://clinicaltrials.gov/ct2/show/NCT03036124> (Accessed 03/02/2023)
6. ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2018, Aug 7 - . Identifier NCT03619213, Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure. (DELIVER). Available from: <https://clinicaltrials.gov/ct2/show/NCT03619213> (Accessed 03/02/2023)
7. ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2017, Jan 30 - . Identifier NCT03036150, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD). Available from: <https://clinicaltrials.gov/ct2/show/NCT03036150> (Accessed 03/02/2022)

Full version control record

Version:	4
Guidelines Lead(s):	Dr Lydia Sturridge, Consultant Cardiologist
Contributor(s):	Ann Parker, Pharmacist, Farkhanda Majidy, Pharmacist
Lead Director / Chief of Service:	Dr Peter Clarkson, CoS for Cardiology
Library check completed:	3 February 2023
Ratified at:	FPH Cardiology CG Jan 2024 and DTC Feb 2024
Date Issued:	17 April 2024
Review Date:	March 2027
Pharmaceutical dosing advice and formulary compliance checked by:	Preya Fakira 7/12/2023
Key words:	Heart failure, Dapagliflozin

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
2	June 2021	Dr Lydia Sturridge, Ann Parker	Final	Ratified at Frimley Health Drug & Therapeutics Committee April 2021 Cardiology Clinical Governance May 2021
3	February 2022	Dr Lydia Sturridge, Ann Parker	Final	Approved at FPH Cardiology CG Nov 2021 & FPH Cardiology CG Feb 2022
4	November 2023	Adapted by Farkhanda Majidy	Final	Approved at FPH Cardiology CG Jan 2024 and DTC Feb 2024

Related Documents

Document Type	Document Name
Guideline	Adult patients with Diabetes undergoing surgery and elective procedures