

Protocol for the use of dapagliflozin for the treatment of heart failure with reduced ejection fraction.

This protocol provides prescribing and monitoring guidance for dapagliflozin therapy for the treatment of heart failure.

Background for Use

Dapagliflozin (Forxiga®) is an SGLT2 inhibitor (sodium-glucose cotransporter-2 inhibitor; SGLT2i) which has an important role in the management of heart failure. DAPA-HF, a large randomised controlled trial, showed that dapagliflozin had a significant benefit for patients with heart failure with reduced ejection fraction (HFREF) when added to optimal medical therapy^{1,2}. This benefit is seen in patients with and without diabetes and is independent of its effect on diabetes outcomes such as glycaemic control.

The core disease modifying medications in HFREF are a RAAS inhibitor (ACE inhibitor, or Angiotensin receptor blocker (ARB), or sacubitril / valsartan the combination of an ARB and neprilysin inhibitor), a beta-blocker, and aldosterone receptor antagonist. SGLT 2 inhibitors are a fourth core disease modifying medication, available evidence suggests the magnitude of benefit is similar to the above agents. NICE have approved use of dapagliflozin in patients on therapy with the above medications who remain symptomatic³.

Indications for use of dapagliflozin in heart failure, as per NICE technology approval 679

- Adults >18 years with
 - Heart failure with a reduced left ventricular ejection fraction of 40% or less
 - Persistent symptoms despite optimised medications as below (i.e. New York Heart Association (NYHA) class II to IV symptoms)
 - With or without type 2 diabetes
- Patients should be on optimised medications for heart failure with all tolerated / indicated of:
 - Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs) or sacubitril/ valsartan (but dapagliflozin can be used before sacubitril/ valsartan if wished)
 - Beta blockers
 - Mineralocorticoid receptor antagonists (MRAs)

Who can recommend dapagliflozin for heart failure:

- The NICE TA suggests that dapagliflozin should be recommended by a specialist, ie:
 - Cardiology consultant, specialist, or registrar
 - Heart failure specialist nurse
 - GP with a specialist interest in heart failure or GP cardiologist
 - General physician with heart failure expertise
 - Renal physician

Who can prescribe dapagliflozin:

- Specialists as above, but note caveats below about who is best to prescribe in some patients with diabetes on hypoglycaemic medications.
- General practitioners or prescribing members of the primary care team, on the advice of a specialist.

Contraindications

- Type 1 diabetes
- Recurrent or particularly problematic hypoglycaemia
- Pregnancy or breast feeding
- Hypersensitivity to dapagliflozin or lactose intolerant (excipient)
- Previous history of diabetic ketoacidosis

Precautions

- Volume depletion or hypotension: Caution if systolic blood pressure less than 95 mmHg, consider reduction in diuretics when starting, particularly in patients with very high blood glucose.
- Severe hepatic impairment: Reduce to 5 mg starting dose.

Dosing and initiation

- Prior to initiation the following should be monitored:
 - Blood pressure
 - Bloods: Renal function, Electrolytes, Liver function
- Start at 10 mg once daily; no dose titration.
- Trade name is Forxiga. Cost to NHS is ~£35 per month.
- The beneficial effect of dapagliflozin has been shown in studies to start within days to weeks and is independent of dose of other therapies for heart failure^{1,2}.
- Blood tests are not routinely needed in the immediate months after initiation (see later paragraph).
- The indication (“to treat heart failure”) should be recorded on the primary care prescription.

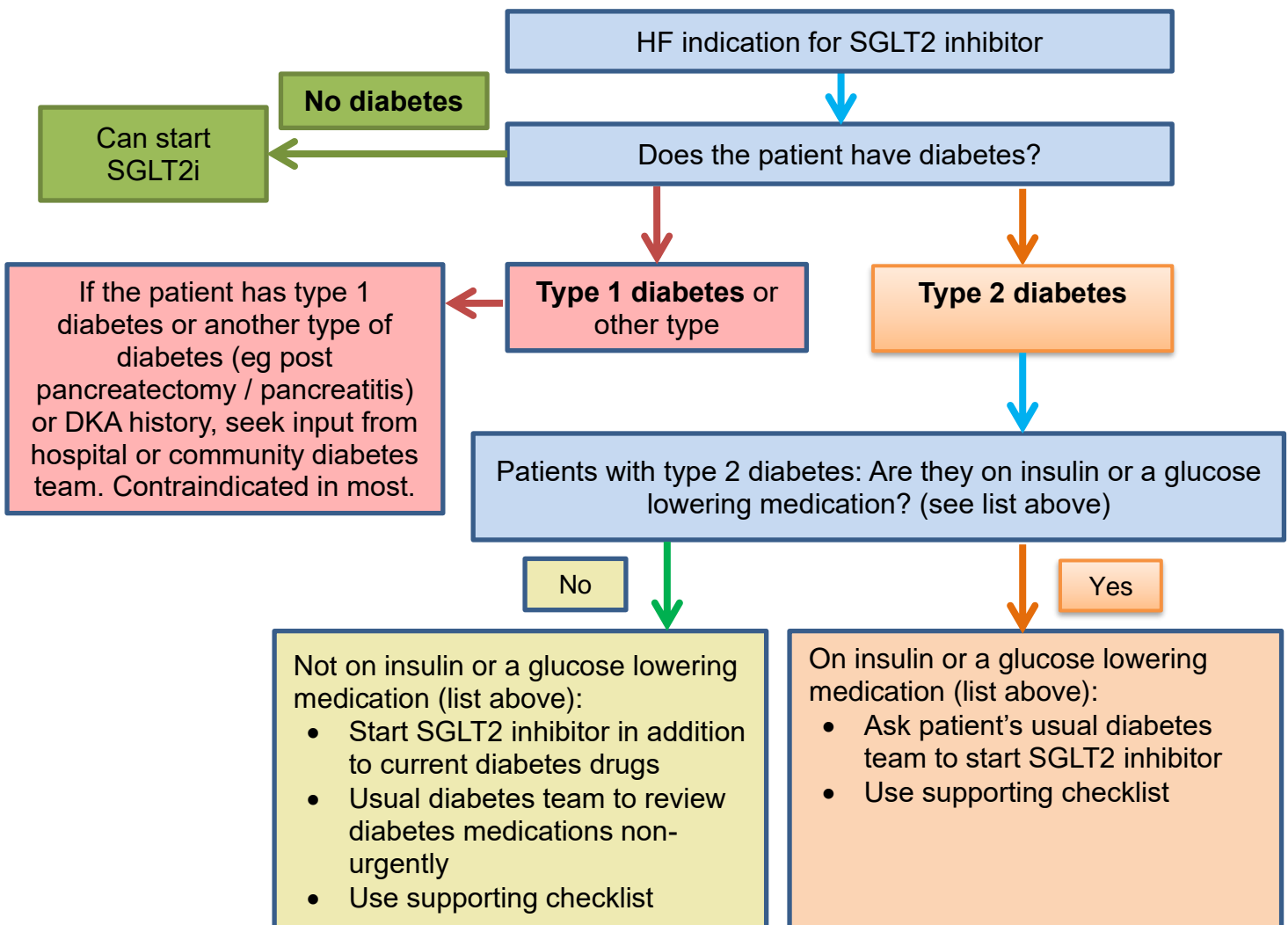
Renal impairment

- Dapagliflozin is licensed for use in heart failure in patients with reduced eGFR – note that this is different to the diabetes licence.
- In heart failure there is limited experience with eGFR below 30 (mL/min/1.73m²), but the licence now supports use to eGFR 15^{4,5}, continuing beyond this if felt appropriate by renal team. No dose adjustment need be made.
- For use in patients with diabetes alone, in the absence of heart failure, dapagliflozin is currently not licensed with an EGFR below 45. There is little effect on blood glucose and HbA1c in patients with diabetes if eGFR is <45 but the cardiac and renal benefits are still present.
- eGFR may be observed to drop by up to 5 when starting an SGLT2 inhibitor; this is part of the drug effect and is usually not concerning.
- In a large trial including patients with eGFR 25-75 and urinary albumin to creatinine ratio 23-566 mg/mmol, dapagliflozin reduced progression of renal dysfunction as well as death and admissions with heart failure⁵. The licence now includes use in this indication, and NICE have recently suggested the use of SGLT2 inhibitors in patients with diabetes and urine ACR>30mg/mmol⁶.

Patients with type 2 diabetes

- For patients who are not on a glucose lowering medication or insulin, the risk of hypoglycaemia or ketoacidosis is very low (ketoacidosis <0.5% of patients per year).
 - Glucose lowering medications include: insulin, gliclazide, glipizide, repaglinide, nateglinide.
 - There are many different medications containing insulin, which are often prescribed by brand name, if in doubt check in British National Formulary (bnf.nice.org.uk)
- In patients who are on one of the above medications, consideration should be given to reducing these at the time of initiation of dapagliflozin, to reduce the risk of hypoglycaemia. This should be done by the patient's GP or diabetes specialist. In this context hypoglycaemia is a common side-effect. Note rapid or large reductions of insulin dose may precipitate diabetic ketoacidosis.
- Only start SGLT2 inhibitors for insulin treated patients if you are confident and competent to do so. For advice on how much to reduce oral hypoglycaemics or insulin by – contact the specialist diabetes teams: Community Diabetes Service or hospital diabetes service (contact details below).
- Pioglitazone may worsen heart failure and should be stopped in HF patients.

Patient's diabetes Status	No diabetes	Type 2 not on insulin or other glucose lowering medication	Type 2 on insulin or other glucose lowering medication	Type 1, history of DKA or other cause (eg pancreatitis, pancreatectomy, genetic conditions)
Risk of hypoglycaemia	None	Low	Moderate	High
Risk of diabetic ketoacidosis	None	Low <0.5% per year	Low ~0.5-1% per year	Moderate up to 5% per year
Who should prescribe SGLT2 inhibitor for HF	GP or Cardiology	GP or Cardiology	GP <i>(input from specialist diabetes as required)</i>	Contraindicated in most people <i>(input needed from specialist diabetes team)</i>



Diabetic ketoacidosis

- Diabetic ketoacidosis (DKA) can occur in patients with diabetes on SGLT2 inhibitors but is not expected in people without diabetes.
- It is worth stressing that the increased risk of DKA with these medications is small, with an odds ratio probably in the order of about 1.8. Overall, the number needed to treat to cause a DKA is about 700, versus about 40 to prevent hospitalisation with heart failure, and 80 to prevent a death of any cause.
- Patients at higher risk of DKA include those with
 - a low beta-cell function reserve (e.g. type 1 diabetes patients, type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA))
 - a history of pancreatitis or pancreatectomy),
 - conditions that lead to restricted food intake or severe dehydration,
 - insulin doses reduced too fast at the time of SGLT2 inhibitor initiation
 - increased insulin requirements due to acute medical illness, surgery or alcohol abuse.
- Signs and symptoms of DKA are nausea or vomiting, as well as 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.
- Inform patients with diabetes of the signs and symptoms of DKA, and advise them to seek immediate medical advice if they develop any of these.
- Check blood ketone levels as well as blood sugar if any concern about possible diabetic ketoacidosis; note that DKA can be euglycaemic (i.e. normal blood sugar levels, but raised ketones).
- Ketone meters should be available in all GP surgeries. Contact the diabetes team if you need advice about this.
- Patients on SGLT2 inhibitors should not undertake a “ketogenic” diet (eg low carb, Paleo diets).
- If patients do develop DKA, they should not use SGLT2 inhibitors again in the future.

“Sick day” rules

- We should advise the patient of “sick day” rules: If they become ill for any reason and are unable to maintain an adequate fluid intake or become dehydrated, SGLT2 inhibitors should be discontinued and restarted when the patient is eating and drinking normally again.
- SGLT2 inhibitors should be stopped 3 days prior to surgery or other procedures requiring a period of reduced oral intake.
- These rules do not apply if their heart failure symptoms have deteriorated, but they are still eating and drinking normally - the patient should continue the SGLT2 inhibitor.

Future monitoring by GPs

- NICE clinical guideline (106) recommends at least 6 monthly review of patients with heart failure which should include monitoring BP and renal function. If eGFR falls below 30 mL/min/1.73m² renal function monitoring should be closer. If eGFR falls below 20 mL/min/1.73m², monitoring should be closer and continuing should be discussed with the renal or cardiac teams, and consideration should be given to stopping if eGFR is consistently below 15 mL/min/1.73m².
- The effect on blood glucose levels is attenuated if eGFR is less than 45 mL/min/1.73m², so additional diabetes treatments may be needed. Note that these guidelines are when SGLT2i are used for heart failure; the SPC for their use in the treatment of diabetes is different.

Genital infections

- All SGLT2 inhibitors including dapagliflozin increase the risk of genital tract mycotic infections as well as possibly urinary tract infections.
- Patients should be warned to practice good personal hygiene, and to discuss with their GP if they develop symptoms.
- SGLT2 inhibitors can be stopped transiently in the context of such infections to assist recovery. If they are recurrent the drug may need to be stopped.

- Rare incidences of Fournier's gangrene have been described - advise the patient to seek medical attention if genital pain, tenderness or swelling.

Hospital admissions

- Current advice remains to stop all SGLT2 inhibitor medications at hospital admission.
- Ensure patient is well hydrated particularly for the first 48 hours after stopping SGLT2 inhibitor
- Check blood ketone levels as well as blood sugar if any concern about possible diabetic ketoacidosis; note that DKA can be euglycaemic (i.e. normal blood sugar levels, but raised ketones).
- Nonurgent surgery or other procedures requiring a period of reduced oral intake are best avoided for 48 hours after administration of a SGLT2 inhibitor.
- Use of SGLT2 inhibitor for inpatients with heart failure:
 - Ensure stable patient before initiating.
 - Initiate at discharge or soon after, with consideration of adjusting diuretic dosing.
 - If used as an inpatient, stop if patient deteriorates or is unable to eat and drink normally.

Notable Drug Interactions (Refer to BNF and SPC for full details)

- As mentioned above, SGLT2 inhibitors can potentiate the effects of loop and thiazide diuretics and increase the risk of hypotension or dehydration. In this case review medication and consider reducing doses of diuretics. We suggest discussion with the heart failure team if there is concern about this, as many heart failure patients may tolerate relative hypotension without symptoms.
- As discussed above, the concurrent use of SGLT 2 inhibitors and insulin or insulin secretagogues (e.g. sulphonyureas such as gliclazide) can increase the risk of hypoglycaemia and the dose of insulin or insulin secretagogues may need be to reduced.
- Other side effects include: rash, polyuria, back pain.

Contact details for information and advice

The HF team may be contacted for advice regarding tolerability, side effects or potential complications of dapagliflozin therapy any time during treatment. Patients may also be referred back to the HF team if necessary. Hospital HF nursing team 01865 223067, or heartfailure.nurse@nhs.net, or Community Heart Failure Nurses 01865 904808 or communityheartfailureteam@oxfordhealth.nhs.uk

The Oxfordshire community diabetes team can also be contacted for advice about initiation of SGLT2 inhibitors in patients with diabetes. Tel 01869 604089, Email diabetesdialogue@nhs.net, or via the [unified diabetes referral form on EMIS](#).

Other SGLT2 inhibitors

- At the time of writing, only dapagliflozin is approved in Oxfordshire for use in heart failure.
- Empagliflozin has been shown to have an identical benefit in patients with heart failure⁴, and has a UK licence for this indication. It is not yet approved for this use by NICE or in Oxfordshire. There is no need to switch patients with heart failure already on empagliflozin to dapagliflozin.
- Canagliflozin has not been shown directly to benefit patients with heart failure, although it has been shown to reduce the incidence of heart failure in patients with diabetes⁷. Unless there is a particular concern about the patient, we would not recommend switching patients to dapagliflozin.
- Ertugliflozin appears to have less cardiovascular benefit⁸, and we would suggest switching patients with heart failure onto dapagliflozin.
- [Sotagliflozin has benefits in heart failure⁹; not yet licensed in the UK.]

Patients with heart failure and a preserved ejection fraction

- No SGLT inhibitors are licensed to treat heart failure with preserved ejection fraction.
- Evidence suggests that in patients with diabetes, the benefit of SGLT2 inhibitors is not limited to those with reduced left ventricular ejection fraction, and so SGLT2 inhibitors could be considered in these patients^{5,7,9} (but use would have to be within the diabetes licence).

References

Dapagliflozin Summary of Product Characteristics: <https://www.medicines.org.uk/emc/product/7607/smpc>
Forxiga patient booklet available at <https://www.forxiga.co.uk/heart-failure.html>

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