SGLT2 inhibitors in people with heart failure with reduced ejection fraction

Current European Medicines Agency licence for Dapagliflozin or Empagliflozin 10mg od.

Indication: Symptomatic chronic heart failure NYHA II-IV
Reduced ejection fraction
Patients without and with type 2 diabetes

Benefits in addition to standard therapy with B-Blocker, ACEI/ARN/ARNI, MRA:

- Reduced Mortality (dapagliflozin)
- Improved quality of life
- Reduced admission to hospital for decompensated HF
- Preservation of renal function

Caution/Avoid: eGFR <15ml/min for Dapagliflozin (Based on CKD license)
eGFR <20ml/min for Empagliflozin (Based on HFrEF license)
Hypotension BP<90-100 systolic
Dehydration
Empagliflozin not recommended if age over 85yrs

Contraindications: Type 1 Diabetes
History of DKA
Hypersensitivity to SGLT2 inhibitors
Pregnancy and Breast feeding

Special precautions in Type 2 Diabetes:

- Seek diabetes team advice in patients on insulin
- Consider reducing or discontinuing sulfonylureas e.g. Gliclazide in patients with well controlled HbA1C because of the potential risk of hypoglycaemia. No dose reduction is needed at low eGFR because there is no hypoglycaemic action of gliflozins.
- Maintain previous doses of Metformin, GLP-1 agonists (Glutides) or DPP-4 inhibitors (Gliptins) in most patients on initiation of SGLT2 inhibitor – no risk of hypoglycaemia
- Observe Sick Day rules
- Consider risk of: Fungal genital infection – thrush - common
  Euglycaemic DKA - uncommon – stop, check blood ketones if sick
  Fournier's Gangrene - Very rare, if at all

	Diabetes Excluded (HbA1c<49)	New Diagnosis of Type 2 Diabetes	Type 2 Diabetes Diet Controlled	Type 2 Diabetes on Metformin, GLP1 (glutide) or DPP4 (gliptin)	Type 2 Diabetes on Sulphonylurea e.g. Gliclazide	Type 2 Diabetes on Insulin
Refer to Consultant Diabetologist before initiating SGLT2	X	Not usually	Not usually	Not usually	Not usually	✓
Initiate SGLT2 pre discharge	✓	✓	✓	✓	✓	Refer first
Discuss side efffects in diabetes	X	✓	✓	✓	✓	✓
Sick Day Rules	X	✓	✓	✓	✓	✓
Refer to DSN	X	✓*	X	X	Consider	✓
Comments	Mention in summary that SGLT2 is being used to treat heart failure not diabetes	Other diabetes treatment may be necessary – Refer if poorly controlled	Other diabetes treatment may be necessary – Refer if poorly controled	Low risk of hypoglycaemia. SGLT2 usually added on. Consider whether to stop other drugs if very good control	Risk of Hypoglycaemia. Stop Gliclazide if already well controlled. No edjustment needed with low eGFR. Consider replacing with Metformin or GLP-1	Seek Consultant Diabetologist advice

*At NPTH refer to DSN only if a new type 2 diabetes requiring insulin.

Risks of SGLT2s to discuss with people diagnosed with type 2 diabetes

- No evidence for a higher risk of urinary tract infection from multiple studies
- Higher risk of genital thrush well established – advise scrupulous post-micturition hygiene and over-the-counter anti-fungals are usually effective. Use patient leaflets.
- May experience polyuria after initiation in poorly controlled type 2 diabetes
- Rare euglycaemic DKA - stop and assess for ketosis if unwell even if normal glucose
- Exceptionally low risk of Fournier's Gangrene (if at all)
- Discuss Sick Day Rules.

Notes

- Patients with heart failure enrolled in DAPA–HF and Emperor Reduced had LVEF <40%. This specific cut off is not reflected in the license which says 'reduced ejection fraction'.
- A subgroup of SOLOIST (sotagliflozin) had LVEF>50% and showed benefit, further studies are awaited. There is currently no license for HFpEF.
- Emperor preserved showed a benefit of Empagliflozin in HFpEF but this is currently an unlicensed indication.
- In SOLOIST, patients commenced therapy during or shortly after admission with HF, providing some reassurance for early introduction of SGLT2i.

- The benefit is independent of diabetes – consider these as heart failure drugs which have a side-effect of causing glucosuria and improving glucose control in patients with type 2 diabetes. The glucosuric effect is greater when there is hyperglycaemia and absent when eGFR is low.
- Hypoglycaemic and glucosuric efficacy in type 2 diabetes is dependent on renal function and may be reduced or absent if eGFR<45; consider additional hypoglycaemic agents when prescribing for heart failure in type 2 diabetes and eGFR falls to <45mls/min.
- There may be an additional diuretic and hypotensive effect on top of other diuretics or hypotensive drugs but in clinical trials no reduction in diuretic dose was recommended. This is more marked in patients with type 2 diabetes with hyperglycaemia and in the elderly.
- There is a risk of DKA in patients with type 2 diabetes on insulin, those with low ß-cell functional reserve, previous pancreatitis or LADA (treated as type I); have a low threshold for referral to DSN for advice in these cases.
- Consider reducing the dose of sulphonylureas or insulin (10-20%) when commencing SGLT2i due to risk of hypoglycaemia, consider asking DSN for advice. No dose adjustment is needed with low eGFR.
- Temporary cessation may be indicated in patients with type 2 diabetes who develop volume depletion due to another cause e.g. diarrhoea (sick day rules)
- Consider euglycaemic or hyperglycaemic diabetic ketoacidosis in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Assess for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level and withdraw gliflozin if indicated.
- There is an initial dip in eGFR within the first 4 weeks which recovers and stabilises – don't overreact.
- There is limited experience when eGFR <15 ml/min; heart failure trials of SGLT2s allowed entry with eGFR down to 20 or 30ml/min but did not discontinue study drug if eGFR fell lower. DAPA-CKD showed benefit in eGFR as low as 15mls/min. Gliflozins are renoprotective and not nephrotoxic, but there is little evidence for benefit at very low levels of eGFR and on dialysis.
- Dose adjustment to dapagliflozin 5mg in severe hepatic impairment.
- Interrupt treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitor blood ketones in these patients. Treatment with SGLT2i may be restarted when the ketone values are normal and the patient's condition has stabilised.
- Further reading with hyperlinks:

NICE Guideline on Dapagliflozin in chronic heart failure
2021 ACC Consensus Document for optimization of heart failure treatment (in press)
DAPA HF Trial
EMPEROR Reduced Trial
Metanalysis of Empagliflozin and Dapagliflozin in heart failure
DAPA CKD

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