SGLT2i for Heart Failure with Reduced Ejection Fraction for adults with or without Type 2 Diabetes

- Dapagliflozin is the first sodium glucose co-transporter-2 inhibitor (SGLT2i) to be licensed & recommended by NICE (TA679) as an option for symptomatic heart failure with reduced ejection fraction (HFrEF) in adults with and without type 2 diabetes, as an add-on to optimised standard care.

- Basingstoke, Southampton and Winchester District Prescribing Committee (DPC) support this new indication. Initiation of dapagliflozin will be on the advice of heart failure (HF) MDT led by a specialist.

- Dapagliflozin may still be started in primary care in type 2 diabetes in line with local diabetes guidance without specialist input (green classification on formulary). Dapagliflozin is licensed in type 1 diabetes, although this use is restricted to specialist diabetes team recommendations.

- The attached HFrEF pathway demonstrates where SGLT2i sit with other evidence-based medicines.
    1. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-2 receptor blockers (ARBs), or an angiotensin receptor neprilysin inhibitor (ARNI) like sacubitril-valsartan
    2. Beta-blockers
    3. Mineralocorticoid receptor antagonists (MRAs), (if remains symptomatic)
    4. Dapagliflozin 10mg once daily

- In the DAPA-HF trial, dapagliflozin in addition to standard care reduced the risk of cardiovascular deaths or worsening HF by 26% compared with placebo. This benefit was seen in people both with and without type 2 diabetes.

- The overall safety profile of dapagliflozin in patients with HF was consistent with its already known safety profile. Additional key points are listed below.

Renal Function & Fluid Balance

- The glucose-lowering efficacy of SGLT2i's decline with glomerular filtration rate (eGFR) ranges, however the cardiovascular benefits are preserved. The eGFR requirement to initiate is specific to the indication. For an HFrEF indication, it is acceptable to initiate in patients with eGFRs down to 30ml/min, and with appropriate monitoring it is safe to continue even if eGFR drops below 30ml/min.

- Patients should be informed of the dual indication for the drug and their specific indication, to minimise the chance that is stopped inappropriately.

- After initiation of SGLT2i, the eGFR can dip by up to 15-20% this is not usually reflective of nephrotoxicity, but rather a reduction in renal blood flow. The long term renoprotective effects are mediated by reducing glomerular hyperfiltration. In DAPA-HF, the peak decline in eGFR (up to 5ml/min/1.73m^2 from baseline) occurred at around day 14 in the active group. In the event that the decline in eGFR is greater than expected (>30% reduction), it is

important to consider overdiuresis. Dapagliflozin can potentiate the effects of existing diuretic treatment. Clinical review of fluid balance is necessary to differentiate a decline in renal function due to volume depletion and the expected reduction in eGFR.

- If the patient is clinically dehydrated, then it would be preferable to reduce the loop diuretic dose in the first instance as they offer no long-term prognostic benefit. Withdrawal of the SGLT2i is necessary, if the decline in eGFR remains >30% and there is no improvement with correcting fluid balance, although this should be discussed with a member of the heart failure team.

- Volume status re-assessment and concomitant diuretic dose review is recommended at follow-up within 2-4 weeks of SGLT2i initiation, especially in those with renal impairment at baseline. If there are concerns regarding fluid status/renal profile, then the HF Specialist Nurses (HFSN) can be contacted for further advice.

- In the longer term, recent studies of SGLT2i, such as CREDENCE and DAPA-CKD confirm SGLT2i such as dapagliflozin and canagliflozin slow the rate of decline in renal function compared to placebo.

Counselling – Key Points

On prescribing dapaglifozin, patients require counselling on the indication, potential benefits, Sick Day Rules and possible adverse drug reactions. Only patients with diabetes require counselling on the risk of potential diabetic ketoacidosis (DKA). DKA has not been observed in patients without diabetes, ideally a recent HbA1C will be known to confirm the presence or absence of diabetes.

Sick Day Rules

When patients are acutely unwell for any reason and oral intake is reduced:

- Temporarily discontinue SGLT2i, ACEi/ARB/ARNI/MRA, loop diuretics. Restart when illness resolved.
- Maintain a low threshold to seek medical advice.

DKA

- SGLT2i have been associated with DKA (affecting around 1in 10,000 people. DKA may present in the absence of significant hyperglycaemia. DKA was rare in DAPA-HF and no more common than placebo, but caution is required in particular patients with diabetes. There is inadvertent risk of ketosis if SGLT2 inhibitors are used in those who are likely to be insulin deficient. This includes type 1 diabetes, those with type 2 diabetes with age related pancreatic dysfunction rather than insulin resistance (low BMI, frailty) and Type 3c diabetes (previous pancreatic damage, those on pancreatic enzyme replacement, alcohol dependency) or previous Diabetic Ketoacidosis (DKA). In these clinical situations, individuals should not be treated with SGLT2 inhibitors without a clear exploration of risk and benefits. This is a life threatening metabolic emergency that requires prompt recognition and treatment.

DKA Signs & Symptoms

Including excessive thirst, nausea or vomiting, abdominal pain, fast/deep breathing, drowsiness, sweet or metallic taste in mouth or different odour to urine or sweat. Discontinue dapagliflozin and seek immediate medical attention.

Diabetes medication adjustment

Those patients in insulin or sulfonylureas are likely to need an adjustment to their medication to reduce the risk of hypoglycaemia. This is more likely to be necessary for those patients with an eGFR >60ml/min/1.73m^2 as below this, the glucose-lowering effects of SGLT2i are significantly reduced and <45 ml/min/1.73m^2 glucose-lowering effects are negligible. Any dose adjustments required are based on several factors, including current glycaemic control. Any uncertainty about dose reductions should be discussed with a member of the specialist diabetes team locally.

Dietary restriction

Patients with diabetes prescribed SGLT2i such as dapagliflozin should be advised not to commence a ketogenic diet (less than 50g of carbohydrate per day) as this can increase the risk for the development of diabetic ketoacidosis. Low carbohydrate diets (60-150g carbohydrate per day) are considered to be safe, as there is enough carbohydrate to suppress significant ketone generation.

Side Effects

Common or very common: dizziness, hypoglycaemia (in conjunction with insulin or sulfonylurea) increased risk of infection, urinary disorders, and genital mycotic infections.
Good genital hygiene should always be emphasised to reduce the risk of genital mycotic infections.
Warn patients that adding an SGLT2i may potentiate concomitant diuretics and require a dose reduction to avoid dehydration.