NHS County Durham CCG
NHS Tees Valley CCG
NHS North Yorkshire CCG (for those patients seen by STHFT)
County Durham & Darlington NHS Foundation Trust
North Tees & Hartlepool NHS Foundation Trust
South Tees Hospitals NHS Foundation Trust

NHS
County Durham & Tees Valley
Area Prescribing Committee

Prescribing guidance – dapagliflozin in heart failure with or without type 2 diabetes mellitus

Drug	**Dapagliflozin**
Specialty	**Cardiology**
Background	Dapagliflozin belongs to a group of medicines called sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), sometimes referred to as "gliflozins". They reduce blood glucose levels by acting on the kidneys to excrete more glucose in the urine. It is indicated for the treatment of symptomatic chronic heart failure with reduced ejection fraction (EF). It is effective at reducing cardiovascular morbidity and mortality in patients with heart failure and reduced ejection fraction with or without type 2 diabetes.
Patient criteria	Patients initiated on dapagliflozin should fulfil all the following criteria: • Persistent moderate or severe left ventricular impairment (EF < 40%). • Symptomatic heart failure (NYHA II to IV)(Limited data in NYHA IV). • Recent (within the last 4 weeks) eGFR > 15 ml/min/1.73m^2. • Systolic blood pressure > 95mmHg.
Place in therapy	It should be commenced after ACE inhibitor, beta-blocker and mineralocorticoid antagonists are established. This will take into account the patient's clinical status and their response to the introduction of these agents.
Contra-indications to use	• **Type 1 diabetes.** • **Past history of diabetic ketoacidosis** • If someone is suspected as having LADA (latent autoimmune diabetes), other genetic forms of diabetes, known pancreatic insufficiency, those who have progressed rapidly from diagnosis to insulin therapy in less than 1 year). • eGFR < 15 mL/min/1.73m^2 – do not initiate - see additional information in "before initiation" section. • Systolic blood pressure < 95 mmHg. • Pregnancy/breast feeding/females of childbearing age who are sexually active without contraception. • Severe liver impairment. • BMI < 20.
Caution advised	• Volume depletion. Increased diuresis may lead to modest decrease in blood pressure. This may be more pronounced in those with very high blood glucose. • Previous history of orthostatic hypotension. • Previous history of severe hypoglycaemia. • **Temporary interruption is recommended in cases of intercurrent conditions that lead to volume depletion (medicine sick day rules) – see page 2**. • **Treatment should also be interrupted in patients hospitalised for major surgical procedures or acute serious medical illnesses**. • Active genital fungal infection. • HbA1c > 86 mmol/mol
Before initiation	Check renal function prior to initiation. The glycaemic efficacy of dapagliflozin is dependent on renal function. Whilst there is increasing evidence for benefit in CKD, it is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate < 15 mL/min/1.73m^2. A modest decline in eGFR (approximately 3

	to 4 ml/min) is expected after initiation, but SGLT2 inhibitors result in long-term renoprotection and reduced albuminuria. SGLT2 inhibitors are being actively studied in established CKD (albuminuria), and dedicated trials in HF are enrolling patients with eGFR down to 20 ml/min. Dapagliflozin 10mg once daily can be started if eGFR >15 mL/min/1.73m^2.
Initiation & titration	The recommended starting dose is 10mg once daily. No titration is necessary. See flow chart (page 4).
Monitoring	**Blood pressure** Treatment with SGLT2 inhibitors is associated with sustained but minimal lowering of systolic blood pressure (2 to 3 mmHg) stemming from reductions in plasma volume and direct effects on vascular function. Educate patient about potential for orthostatic hypotension and necessity to monitor daily weights and blood pressure, particularly in the first week of therapy. Encourage patient to call healthcare providers if home weight decreases in the setting of symptomatic hypotension. Increased risk with concomitant diuretic use; consider diuretic dose adjustment. **Renal** Baseline and periodic monitoring of renal function is recommended, especially if used in chronic kidney disease. The latter should be performed at 4 weeks and repeated every 6 months, in line with standard monitoring for such patients. A modest decrease in eGFR (3 to 4 ml/min) is expected with initiation. **Blood glucose** This only needs to be monitored in diabetics. The insulin-independent mechanism of action means that hypoglycaemia is uncommon but there is increased risk with concomitant use of sulfonylureas and insulin. If HbA1c is well controlled at baseline or there is a history of hypoglycaemic events, reduce or stop the sulphonylurea and consider reducing basal insulin by 20%. Educate patient to monitor for signs of hypoglycaemia.
Patient education	Ensure that the patient has the patient information leaflet and education about Dapagliflozin. Educate patient about potential for orthostatic hypotension **Medicine sick day rules**:Patient should be reminded that if they become unwell and are unable to maintain adequate fluid intake they should stop taking the following medicines: **S** Sacubitril Valsartan and Sulfonylureas, e.g. gliclazide. **A** ACE inhibitors, e.g. perindopril and lisinopril. **D** Diuretics, e.g. furosemide, bumetanide, bendroflumethiazide and Direct Renin Inhibitors, e.g. aliskiren. **M** Metformin. **A** Angiotensin Receptor Blockers e.g. candesartan and losartan. **N** Non-steroidal anti-inflammatory drugs, e.g. ibuprofen. **S** SGLT2 inhibitors, e.g. dapagliflozin, empagliflozin, canagliflozin and ertugliflozin. Once the person is feeling better and able to eat and drink for 24–48 hours, these medications should be restarted. **Diabetic ketoacidosis** – educate patient regarding signs and symptoms – see patient information leaflet.

Adverse events

Fournier's gangrene – advise good perineal hygiene.

Adverse event	Incidence	Comment
UTIs	Common (1 in 10 to 1 in 100)	Most infections were mild to moderate. Subjects responded to standard therapy and rarely required discontinuation. Temporary interruption of therapy should be considered when treating pyelonephritis or urosepsis.
Diabetic Ketoacidosis	Rare (1 in 1000 to 1 in 10,000)	The risk of DKA must be considered in the event of nonspecific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients may develop euglycaemic ketoacidosis. Measurement of blood ketone levels is preferred to urine. Therapy can be restarted when ketone levels are normal and the patient's condition stabilised. However, this is not recommended unless a clear precipitating factor is identified and resolved. DKA occurred in 3 patients with Type II DM in DAPA-HF.
Necrotising fasciitis of the perineum (Fournier's gangrene)	Rare (1 in 1000 to 1 in 10,000)	There are rare cases of necrotising fasciitis of the perineum. Patients should seek urgent medical attention if they experience severe pain, tenderness, redness, or swelling in the genital or perineal area accompanied by fever or malaise. Urogenital infection or perineal abscess may precede more serious infections (such as necrotising fasciitis).

Clinically important interactions

Consider and review any concomitant medications which are likely to increase risk of volume depletion (e.g. diuretics), orthostatic hypotension (e.g. antihypertensive therapy) and blood glucose (see flow chart).

See BNF or SPC for full details.

Other information

Note that therapy will result in positive urine glucose tests.

Diabetics:

If the eGFR < 60mL/min, the glycaemic effect of Dapagliflozin is reduced. However, it may still be initiated for the indication of HF unless eGFR <15 mL/min/1.73m^2.

If not previously diagnosed, refer patient to primary care for further assessment.

Type 1 diabetes: **do not commence** Dapaglifozin

Type 2 diabetes: consider dose reduction of insulin and sulfonylureas (as outlined below in the flow chart). Refer to diabetes team for advice if:

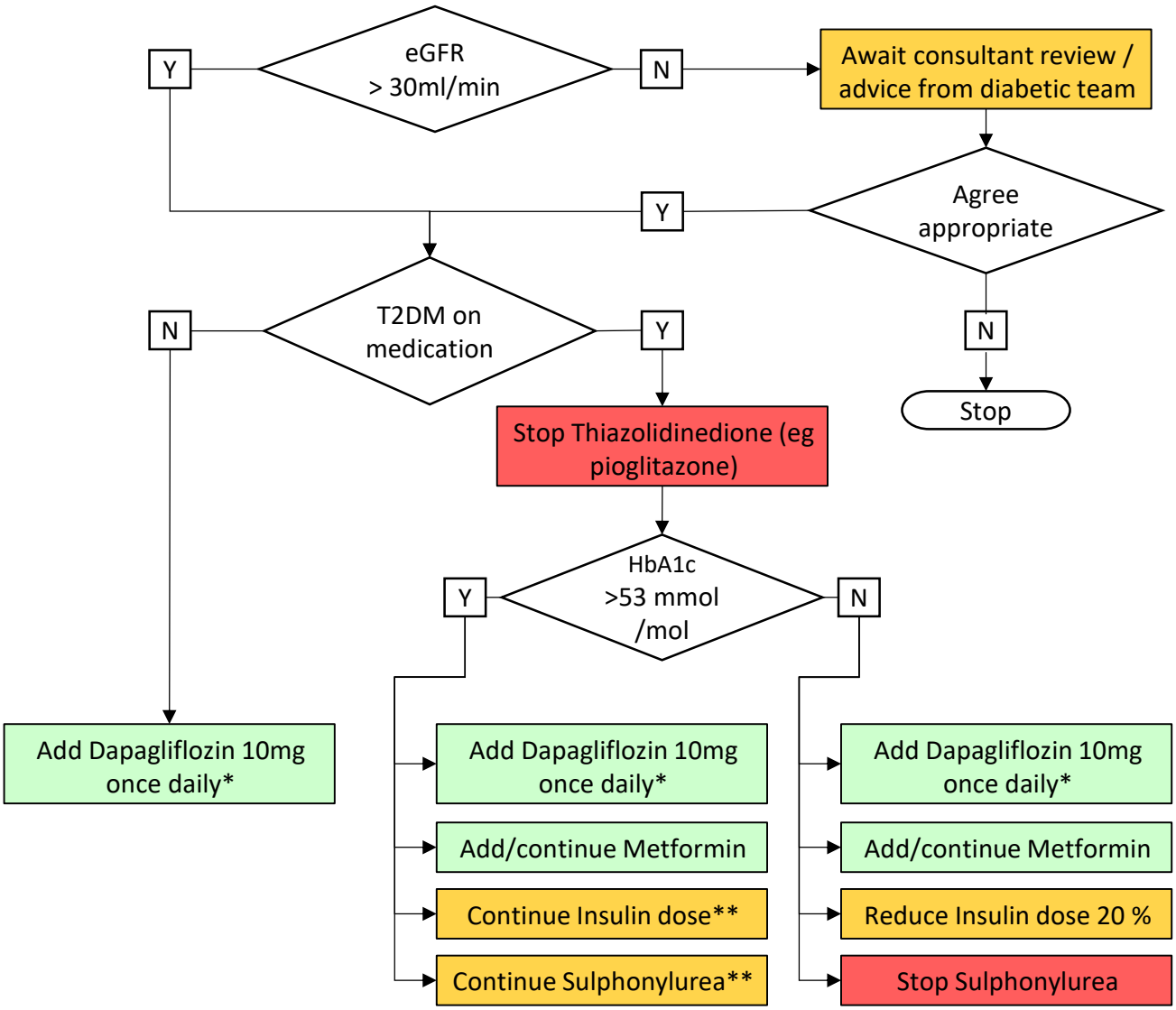
· There is a history of previous/frequent hypoglycemia.

· Impaired renal function: The glycaemic effect is dependent on renal function. Additional glucose-lowering treatment may need to be considered if eGFR persistently < 45mL/min.

HbA1c > 86	Caution as increased risk of genital mycotic infection
HbA1c > 65	Start SGLT2 inhibitor and refer to Diabetic Specialist Nurse to consider intensification of glycaemic control
HbA1c 53-65	Start SGLT2 inhibitor
HbA1c < 53	If diabetic but good control may need other agents adjusting (as outlined

	below in the flow chart)
Further reading	DAPA HF study: McMurray JJV et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019; 381:1995-2008. DOI: 10.1056/NEJMoa1911303 Manufacturer's SPC: https://www.medicines.org.uk/emc/product/7607/smpc#gref

How to commence dapagliflozin (SGLT-2 inhibitor) in patients with moderate or severe LVSD with or without T2DM (renal and diabetic considerations)



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ONLY USE SGLT2 inhibitors in patients with type 2 DM DO NOT use in type 1 DM
Avoid in patients with a history of DKA or severe hypoglycaemia.
Avoid initiation in patients who are clinically unstable or hypotensive (SBP < 95mmHg)
Avoid hypovolaemia: consider reducing diuretic (thiazide/loop) when initiating in patients stabilised on diuretic dose.
Caution in cachectic or malnourished patients, or history of alcohol excess.
SGLT2 inhibitors increase the risk of genital infections.

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If HbA1c well-controlled at baseline or history of frequent hypoglycaemic events, reduce Sulphonylurea by 50% or basal insulin by 20% when commencing dapagliflozin.
Educate patient to monitor for signs of hypoglycaemia.

Give patient information leaflet and ensure understanding (especially regarding DKA)