SGLT2 inhibitor treatment protocols - Heart Failure (HF) and Chronic Kidney Disease (CKD) indications

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SGLT2 inhibitor treatment protocols - Heart Failure (HF) and Chronic Kidney Disease (CKD) indications

SGLT2 inhibitors (sodium-glucose cotransporter-2 inhibitor; SGLT2i) have an important role in the management of HF and in reducing progression of CKD. Use of SGLT2i for HF or CKD is different to their use for diabetes, but hypoglycaemic effects and their side effect profile (including risk of diabetic ketoacidosis (DKA) in diabetes) must be taken into account when prescribing. SGLT2i indications for HF, CKD and diabetes overlap - for example, in one HF trial, half of the patients had a GFR < 60, and half had diabetes. Patients may therefore have multiple indications.

The below summary hopefully provides enough information on starting the medications in the majority of cases. The rest of this document aims to provide further detail on prescribing and monitoring for SGLT2i therapy for the treatment of HF or CKD, taking into account safety considerations in patients with and without diabetes.

Contents:

Contact details for information and advice

	Berkshire West	Buckinghamshire	Oxfordshire
HF	*Hospital HF nursing team* • 0118 322 6638 • cardiacsupport@nhs.net *Community Heart Failure Nurses* • 0118 467 2891 - option 3 • heartfailure@berkshire.nhs.uk	*Heart failure nurses:* • 0781 685 7077 • buc.tr-commHF@nhs.net	*Hospital HF nursing team* • 01865 223067 • heartfailure.nurse@nhs.net *Community Heart Failure Nurses* • 01865 904808 • communityheartfailureteam@oxfordhealth.nhs.uk
CKD	*Nephrology team* • Rbb-tr.renal.enquiries@nhs.net • 0118322-7969 / 7513	*Renal email advice Oxon and Bucks* • orh-tr.renaladvice@nhs.net *Renal Pharmacy Team:* • 01865 226105 • orh-tr.oxfordrenalpharmacy@nhs.net	
DM	*Community Diabetes Specialist Nurse Team* • 07879814922 Mon-Fri 10-4 • diabetesnursereferrals@berkshire.nhs.uk	*Community Diabetes Nurse Team* Advice and Guidance. • 01494 323030	*Oxfordshire community diabetes team* • 01869 604089 • diabetesdialogue@nhs.net • via the unified diabetes referral form on EMIS

SGLT2 inhibitors for heart failure and kidney disease - in people *without diabetes*

Heart Failure & CKD

Indications

HF

- **Any persistent symptoms** despite optimised medications for heart failure
- **If reduced ejection fraction (EF under 40%) should be on 3 other classes**
  - Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-2 receptor blocker (ARB) or sacubitril/valsartan,
  - Beta blocker
  - Mineralocorticoid receptor antagonist
- If ejection fraction > 40%, can be used alone or added to diuretics.
- Recommended by heart failure specialist or GP if confident to do so
- Can be initiated by specialist or GP

CKD

- **eGFR over 25 and**
- urine albumin: creatinine ratio (uACR) over 22.6mg/mmol
- (urine protein:creatinine ratio (uPCR) over 35 is equivalent)
- **Started by GP** (ask specialist renal team if concerns)

Which SGLT2i

HF

- **Dapagliflozin** 10mg once daily down to eGFR 15 (discuss with renal/cardiac team if lower)
  - Any ejection fraction
- **Empagliflozin** 10mg once daily down to eGFR 20 (discuss with renal/cardiac team if lower)
  - Ejection fraction under 40%

CKD

- **Dapagliflozin** 10mg once daily down to eGFR 15 (discuss with renal team if lower)

Starting SGLT2i

Contraindications

- Pregnancy or breastfeeding
- Type 1 diabetes. See next page for type 2 diabetes

Cautions

- Caution if blood pressure less than 95 mmHg
- Consider reducing diuretic doses transiently when starting
- No additional bloods / checks required, monitor renal function as per normal for condition

Side-effects

- Advise patient not to take if not eating and drinking
- Marginally increased risk of urinary tract infection (7% increased risk)
  - Caution with recurrent urinary tract infection (UTI), kidney transplant patients and renal immunosuppression patients

SGLT2 inhibitors for heart failure and kidney disease - in people *with diabetes*

Heart Failure & CKD

Indications in type 2 diabetes

Heart failure and type 2 diabetes

- **All should be on SGLT2i**

- **Any cause of heart failure, any ejection fraction**
- Independent of other treatments
- **Started by GP** (heart failure advice if concerns) or specialist
- See starting advice below

CKD and type 2 diabetes

- **Should be on: eGFR over 25 and uACR over 22.6 mmol/l** (or uPCR over 35)

- **Consider:** eGFR over 25 and uACR over 3 mmol/l (or uPCR over 3)
- For minimal or no proteinuria still consider if eGFR greater than 45 for glycaemic and renoprotective benefit.
- **Started by GP or service managing diabetes** (renal advice if concerns)

Atherosclerotic cardiovascular disease and type 2 diabetes

- **Should be on: if any vascular disease:**
  - Established coronary artery disease,
  - Acute coronary syndrome, myocardial infarction
  - Angina, coronary revascularisation,
  - Cerebrovascular disease, peripheral arterial disease

- **Consider: age more than 40 and QRISK2 more than 10%**
- **Consider: age less than 40 and one or more risk factor**
  - Hypertension
  - Dyslipidaemia
  - Smoking
  - Obesity
  - Family history (in a first-degree relative) of premature CVD cardiovascular disease

Which SGLT2i

HF (any ejection fraction) and type 2 diabetes

- **Dapagliflozin** 10mg once daily down to eGFR 15 (discuss with renal/cardiac team if lower)
- **Empagliflozin** 10mg once daily down to eGFR 20

CKD and type 2 diabetes

- **Canagliflozin** 100mg once daily down to eGFR 30
- **Dapagliflozin** 10mg once daily down to eGFR 15 (discuss with renal team if lower)
- **Empagliflozin** 10mg once daily down to eGFR 30

Type 2 diabetes with atherosclerotic CV disease or for glucose control

- **Canagliflozin** start 100mg if eGFR 30 or more; (can increase to 300mg if needed & eGFR 60 or more.)
- **Dapagliflozin** start 10mg if eGFR 30 or more.
- **Empagliflozin** start 10mg once daily if eGFR 30 or more; (can increase to 25mg if needed & eGFR 60 or more)

- If eGFR falls below 45, glucose lowering is reduced but cardiovascular disease, renal and HF benefits are maintained. Only stop if no other indication i.e. no albuminuria, no CVD, low risk, no HF.

Starting SGLT2i in diabetes

Not taking insulin or gliclazide:
(or glipizide, repaglinide, nateglinide)
Low risk of hypoglycaemia or DKA

- Specialist or GP to add SGLT2i to current medications
- Usual diabetes team to review diabetes medications non-urgently

Taking insulin or gliclazide:
(or glipizide, repaglinide, nateglinide)
Some risk of hypoglycaemia or DKA

- SGLT2i to be added by GP with community diabetes team input if needed
- Insulin dosing will generally need adjusting (except when eGFR<45)

Contraindications in people with diabetes:

- Type 1 diabetes
- Insulin deficiency: pancreatitis, total pancreatectomy, Latent Autoimmune Diabetes of Adulthood (LADA)
- Pregnancy or breastfeeding
- Any history of diabetic ketoacidosis
- Recurrent or particularly problematic hypoglycaemia
- Any ketogenic diet (eg very low carbohydrate)

Cautions in people with type 2 diabetes:

- Caution if systolic blood pressure less than 95 mmHg
- Consider reducing diuretic dose when starting
- No additional bloods / checks required, monitor renal function as per normal for condition
- Overall evidence does not suggest an increased risk of lower limb amputation with SGLT2is other than Canagliflozin (in one trial only). Preventive foot care is important for all patients with diabetes.

Side effects in people with type 2 diabetes:

- Increased risk of hypoglycaemia
- Increased risk of diabetic ketoacidosis (DKA; although still very rare; can be euglycaemic)
- Marginally increased risk of urinary tract infection
  - Particular caution with kidney transplant patients and renal immunosuppression patients
- Increased risk of genital tract mycotic infections
- Possible association with Fournier's gangrene (necrotising fasciitis of genitalia or perineum): advise to stop and seek medical advice if develops groin pain, tenderness, erythema, or swelling in the genital or perineal area associated with fever or malaise. Report via Yellow Card scheme.

"Sick day rules" - advise patients of these:

- If a patient becomes ill and is unable to maintain an adequate fluid intake, discontinue SGLT2i until eating and drinking normally again. Discuss signs and symptoms of DKA.
- Consider need to see health care professional to check blood ketone concentrations. Seek specialist help if capillary ketone concentrations 1 mmol/l or higher.

- Stop SGLT2i 24 hours prior to surgery or other procedures requiring a period of reduced oral intake.
- Restart 7 days after operation or procedure (when eating and drinking normally again)

Abbreviations used on this page and previous:

SGLT2i: SGLT2 inhibitor.
uPCR: urine protein-to-creatinine ratio in mg/mmol
ACEi: Angiotensin-converting enzyme inhibitor
eGFR: estimated glomerular filtration rate in ml/min/1.73 m^2
uACR: urine albumin-to-creatinine ratio in mg/mmol
ARB: angiotensin-2 receptor blockers

Heart Failure

Background for Use

Large randomised controlled trials have shown showed that dapagliflozin and empagliflozin have a significant benefit for patients with heart failure (independent of left-ventricular ejection fraction), when added to optimal medical therapy. This benefit is seen in patients with and without diabetes and is independent of its effect on diabetes outcomes such as glycaemic control. In people with heart failure SGLT2 inhibitors improve symptoms, reduce hospital admissions/ readmissions, and reduce mortality[1–5].

The core disease modifying medications in heart failure with reduced ejection fraction (HFrEF) are a beta-blocker, an aldosterone receptor antagonist, and a RAAS inhibitor (ACE inhibitor, or Angiotensin receptor blocker (ARB), or sacubitril / valsartan which is the combination of an ARB and neprilysin inhibitor. SGLT2i 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 and empagliflozin in patients on therapy with the above medications who remain symptomatic [TA679,773][6,7].

In people with diabetes and heart failure, there is benefit from SGLT2 inhibitors at any ejection fraction and NICE suggest they should be a first-line therapy for diabetes for this group [NG28][8,9].

In people with heart failure and ejection fraction over 40%, there is a benefit of empagliflozin and dapagliflozin[3,4], and both dapagliflozin and empagliflozin have a licence for the treatment of heart failure at any ejection fraction, but NICE have only to date approved dapagliflozin for this indication [TA902][10].

The beneficial effect of SGLT2i in HF has been shown in studies to start within days to weeks and is independent of dose of other therapies for HF[1,11].

Indications for use of dapagliflozin and empagliflozin in heart failure with reduced ejection fraction, as per NICE technology approvals 679 and 773

- 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 generally 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 SGLTi can be used before sacubitril/ valsartan if wished)
  - Beta blockers
  - Mineralocorticoid receptor antagonists (MRAs)
  - Although it should be appreciated that the order of initiation of these medications should be personalised to patients depending on comorbidities and clinical status

Indications for use of dapagliflozin in heart failure with ejection fraction >40%, as per NICE technology approval 902

- Adults >18 years with
  - Heart failure with left ventricular ejection fraction of more than 40%
  - Symptoms of this (i.e. New York Heart Association (NYHA) class II to IV symptoms)
  - With or without type 2 diabetes
  - Can be used alone or added to other appropriate medications (for example, diuretics) and alongside treatment of other comorbidities

Indication for use of dapagliflozin, empagliflozin and canaglflozin in people with diabetes and heart failure with any ejection fraction, as per NICE guideline NG28

- Adults >18 years with type 2 diabetes and heart failure, with any ejection fraction
  - In this cohort, SGLT2i should be used as first-line therapy for diabetes alongside metformin
  - Use is not dependent on symptoms, and is appropriate in asymptomatic people
  - Dapagliflozin, empagliflozin or canagliflozin can be used

Who can recommend SGLT2i for heart failure:

- In people with diabetes specialist recommendation is not required but advice may need to be sought regarding adjustment of other diabetes drugs (see Diabetes section 4 below).
- In people without diabetes, GP initiation is appropriate if the clinician is confident in doing so, with advice as required from Cardiology specialist

Who can initiate (start prescribing) an SGLT2i for heart failure

- GPs or prescribing members of the primary care team, with input where appropriate from the Diabetes team – see Diabetes section 4 below.
- Heart failure specialist (as listed above) **UNLESS the patient has type 2 diabetes** AND is taking medicines which can cause hypoglycaemia (see Diabetes section 4 below). For these patients, the GP (or prescribing member of the Primary care team) prescribes on the advice of the HF team (and where appropriate the Diabetes team)

Renal impairment

- Dapagliflozin and empagliflozin are licensed for use in heart failure in patients with reduced eGFR – note that this is different to the diabetes licence.
- The licence supports use to eGFR 15 for dapagliflozin and eGFR 20 for empagliflozin, continuing beyond this if felt appropriate by renal team[2,12]. No dose adjustment need be made.

People with type 2 diabetes

- See 0 below for advice about safe use in people with diabetes.
- Pioglitazone may worsen heart failure and should be stopped in HF patients.

Chronic Kidney Disease – indications

Background for Use

See latest NICE guidelines on CKD [NG203]. CKD is under-diagnosed and under-coded. Diagnosis requires both eGFR and urine ACR. Failure to assess for urine ACR can under-estimate the presence of CKD and the severity of disease. Albuminuria is an independent risk factor for admission, CVD mortality and accelerated end stage renal failure.

Renal protective effects of SGLT2i were first seen in diabetes trials set up to investigate cardiac safety. The first SGLT2i trial designed to investigate renal outcomes (CREDENCE) looked at Canagliflozin in patients with diabetes and CKD down to eGFR 30ml/min/1.73m^2 - reduction in the risk of the composite outcome of CKD progression or cardiovascular death was demonstrated[13].

Dapagliflozin has since been evaluated in DAPA-CKD - a large randomised double blind in patients with CKD and without diabetes. DAPA-CKD included patients with eGFR 25-75 and urinary albumin to creatinine ratio (ACR) 23-566 mg/mmol, where dapagliflozin reduced risk of progression of CKD as well as death and admissions with heart failure[12]. The licence now includes use of dapagliflozin in CKD (irrespective of diabetes status and level of albuminuria), but the best evidence for efficacy is in patient with albuminuria. NICE advises use of this SGLT2i in patients with CKD with or and without diabetes.[14,15]

Indications for use of dapagliflozin for treating CKD, as per NICE technology approval 775 and guideline NG28

- Adults >18 years with:
    - CKD: an estimated glomerular filtration rate (eGFR in ml/min/1.73 m^2) of 25 to 75 at the start of treatment and:
        - type 2 diabetes or
        - a urine protein-to-creatinine ratio (uPCR) of greater than or equal to 35mg/mmol or
        - a urine albumin-to-creatinine ratio (uACR) greater than or equal to 22.6 mg/mmol.
- Patients should also be on optimised on the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless contraindicated.
- Note that patients with a functioning kidney transplant or polycystic kidney disease have not been studied in these trials, and licences do NOT extend to type 1 diabetes mellitus.
- Empagliflozin is not licensed for this indication, but the EMPA-KIDNEY trial showed a similar benefit[16].

Who can recommend dapagliflozin for treating CKD:

- Any suitably trained clinician including:
    - General practitioner
    - Diabetes specialist team
    - Renal physician including junior renal doctor under supervision of Consultant Nephrologist
    - Renal Specialist Nurse
    - Renal Pharmacist

People with type 2 diabetes

- See 0 below for advice about safe use in people with diabetes.

Degree of renal impairment and proteinuria

- There is limited experience with eGFR below 25 (mL/min/1.73m^2), but the licence supports initiation of dapagliflozin down to eGFR 15, continuing beyond this if felt appropriate by renal team. No dose adjustment need be made.
- There is currently a lack of evidence to demonstrate renal benefit in patients with low levels of proteinuria (ACR less than 22.6mg/mmol or PCR less than 35mg/mmol) and the NICE TA does not currently support prescribing in CKD patients without diabetes who have these lower levels of proteinuria[15].
- The renal unit do not routinely monitor ACR – it is reasonable to use a PCR of more than 35mg/mmol as being roughly equivalent to an ACR of 22.6 for the purpose of prescribing dapagliflozin.
- There is a reduced effect on blood glucose and HbA1c in patients with diabetes if eGFR is less than 45 but the renal and cardiac benefits are still present.

Initiation of SGLT2i for HF or CKD

Summary of drug doses and indications

Approved indications	***Heart failure***		***Chronic kidney disease***	***Type 2 diabetes***
• Dose • eGFR limit in mL/min/1.73m2	*Reduced ejection fraction <40%*	*Preserved ejection fraction >40%*	• *eGFR 25-75 and* ○ *Type II diabetes or* ○ *uPCR > 35 / uACR > 22.6*	*SGLT2 inhibitors should be first line in those with* • *HF* • *Cardiovascular disease* • *At high risk of these*
Dapagliflozin	• Licensed ✓ • NICE ✓ • 10mg once daily • eGFR down to 15	• Licensed ✓ • NICE ✓ • 10mg once daily • eGFR down to 15	• Licenced ✓ • NICE ✓ • 10mg once daily • eGFR down to 15	• Licenced ✓ • NICE ✓ • 5-10mg once daily • eGFR down to 15
Empagliflozin	• Licensed ✓ • NICE ✓ • 10mg once daily • eGFR down to 20	• Licenced ✓ • No NICE approval ✕ • 10mg once daily • eGFR down to 20	• No licence ✕ • No NICE ✕	• Licenced ✓ • NICE ✓ • 10-25mg once daily • eGFR down to 30
Canagliflozin	• No licence ✕ • No NICE ✕	• No licence ✕ • No NICE ✕	• No licence ✕ • No NICE ✕	• Licenced ✓ NICE ✓ • 100-300mg once daily • eGFR down to 30
Ertugliflozin	• No licence ✕ • No NICE ✕	• No licence ✕ • No NICE ✕	• No licence ✕ • No NICE ✕	• Licenced ✓ NICE ✓ • 5-15mg once daily • eGFR down to 60

Who can initiate (start prescribing) an SGLT2i for HF or CKD:

- Clinicians as defined above in HF / CKD sections but note caveats with regards to diabetes as per section 4 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, with advice of a specialist as needed.

Use of checklists, Patient Information Leaflet (PIL) and Sick Day Rules

Clinicians recommending or initiating dapagliflozin or empagliflozin for HF or CKD must, as far as possible, ensure:

- Patient is eligible for treatment as per above criteria.
- Review and verify / exclude contraindications and precautions etc using the appropriate checklist

- Patient is given counselling and information on indication, need for monitoring, risks and benefits, adverse effects. Written patient information leaflet and Sick Day rules electronic card (the links may be texted to the patient)
- The clinic / discharge letter clearly specifies the indication, criteria for use and confirms that the patient has been counselled (as above) and has received the written PIL and Sick Day rules electronic card.

Contraindications

- Previous history of diabetic ketoacidosis (DKA). If you think there would still be reasons to still consider an SGLT2i, please discuss with local Diabetes team (contact details below).
- Patients on very low calorie/very low carbohydrate diets (VLCD) should seek diabetic specialist advice before initiation
- Type 1 diabetes
- Recurrent or particularly problematic hypoglycaemia
- Pregnancy or breast feeding
- Hypersensitivity to dapagliflozin/empagliflozin or lactose intolerant (excipient)
- Severe renal impairment (eGFR under 15ml/min for dapagliflozin, eGFR under 20ml/min for empagliflozin) - see 'renal impairment' section and checklists appendices x and y)
- Severe hepatic impairment (empaglifozin).

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 (dapagliflozin). Reduce starting dose as per BNF / SPC medicines.org.uk/emc
- Renal impairment (see section on CKD)
- Type 2 diabetes at risk of ketoacidosis (e.g. on insulin, sulfonylurea, 'glinide' medicines) – see section 4
- Immunosuppression, particularly in transplant patients (see below)

Pre-treatment assessment

- Prior to initiation the following should be monitored:
  - Blood pressure
  - Renal function, electrolytes,
  - Liver function
  - HbA1c in people with diabetes
  - Consider blood glucose if person has diabetes

Ongoing monitoring by the GP

- Blood tests are not routinely needed in the immediate months after initiation (see later paragraph).
- No routine blood tests are needed in the first 6 months after initiation in patients with eGFR over 30ml/min/m^2 (see 'renal impairment' paragraph).
- Thereafter eGFR and blood pressure (BP) are monitored every 6 months.
- If eGFR falls below 30 monitoring should be more frequent as per NICE guidelines. Dapagliflozin should be stopped if eGFR is consistently below 15. Empagliflozin should be stopped if eGFR is consistently below 20.
- eGFR may be observed to temporarily drop by up to 5 when starting an SGTL2 inhibitor. This is part of the renal protective drug effect and it may be sensible to counsel patients who closely follow their eGFR to expect this.
- If raised at baseline, repeat HbA1c at 3 months. Consider capillary glucose monitoring if risk of hypoglycaemia.

Dose

- Dapagliflozin 10 mg once daily (CKD or HF) Empagliflozin 10mg once daily (HF). No dose titration needed.
- The indication ("to treat heart failure / CKD") should be recorded on the primary care prescription and in clinical notes/ clinic letters / discharge letters.

Immunosuppression

- There is a 4-fold increased risk of fungal genital infection and a very small increased risk of UTI in patients taking SGLT2i (see 0).
- Fungal genital infections are self-limiting and can be treated with standard anti-fungal treatments – e.g. topical creams. A single dose of fluconazole is considered to be safe, but not a course.
- UTIs are a particular concern in kidney transplant patients and renal immunosuppression patients. Risk of pyelonephritis and resulting damage must be carefully considered and treatment offered only after discussion with nephrology or transplant team.

Patients with type 2 diabetes - initiating SGLT2I for HF or CKD

- 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 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 the dose of this medication at the time of initiation of SGLT2i, 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 and so changes to insulin dose should be done cautiously. If unfamiliar with this process, please contact the community diabetes team (contact details below).
- 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 local specialist diabetes teams: Community Diabetes Service or hospital diabetes service (contact details below).
- In type 2 diabetes, although glucose lowering efficacy is reduced with **eGFR < 45 mL/min (for dapagliflozin) and <60ml/min (for empagliflozin),** the renal and cardiac benefits are maintained[4]

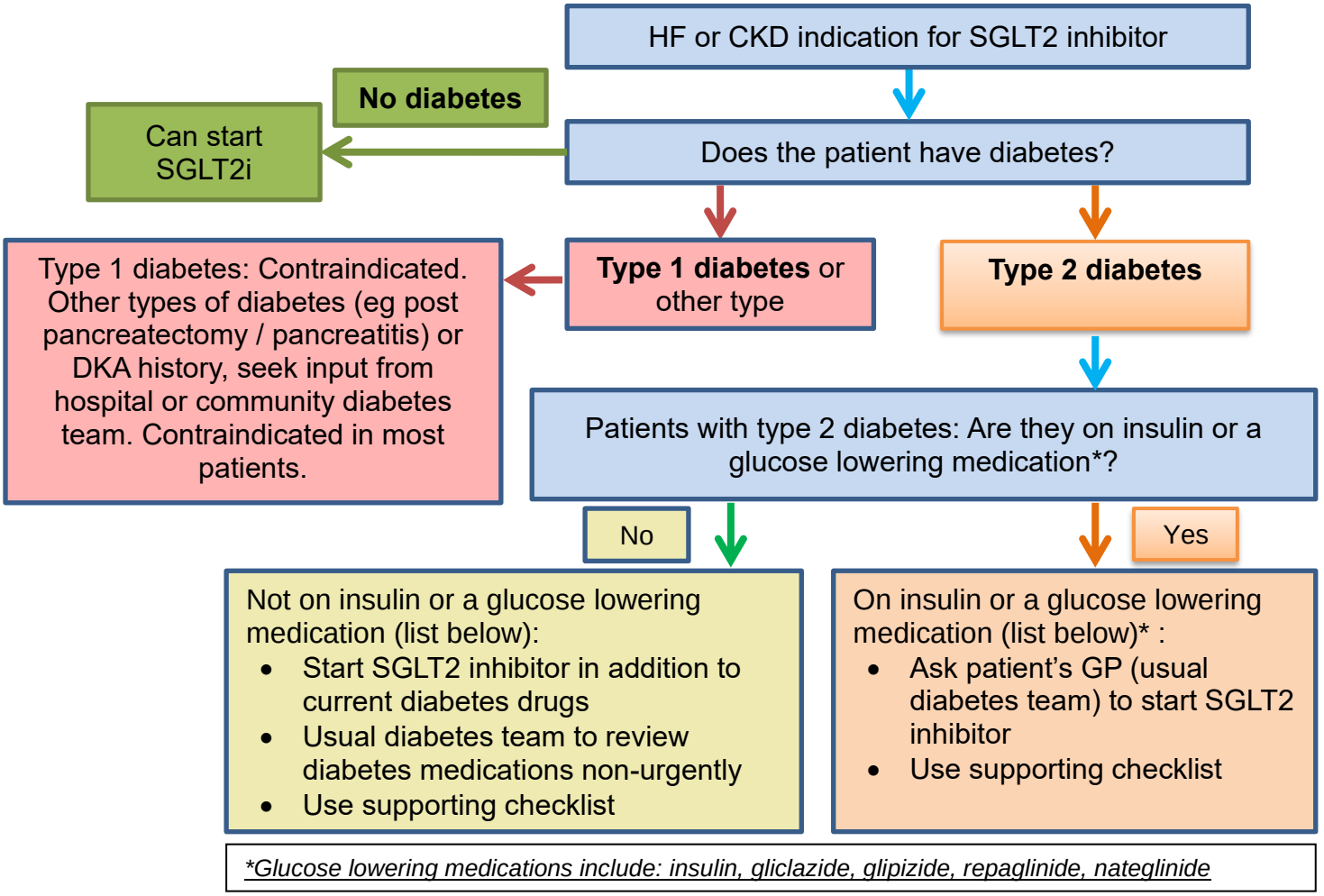
Starting SGTL2i for renal / cardiac indications in people with type 2 diabetes – risk stratification

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 of insulin deficiency** **(eg pancreatitis, total pancreatectomy)**
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 or CKD	GP, Cardiology or Renal	GP, Cardiology or Renal	GP *(input from specialist diabetes as required)*	**Contraindicated.-** *see flow chart. Input from local Diabetes team needed*

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 only 0.3 additional events per 1000 patient years , versus preventing about 33 heart failure hospitalisations or deaths per 1000 patient years, although DKA risk can be higher in particular patients[9].
- 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 community diabetes team if you need advice about this (contact details below).
- 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.

Starting SGTL2i in patients with type 2 diabetes – flow chart



Other risks and contraindications

"Sick day" rules

- Electronic copies of sick day rules can be found at https://ihub.scot/improvement-programmes/scottish-patient-safety-programme-spsp/spsp-programmes-of-work/spsp-medicines-collaborative/high-risk-situations-involving-medicines/medicines-sick-day-rules-card/
- We should advise people with diabetes of "sick day" rules and provide them with the link to the Sick Day rules electronic card (which may be texted to them).
- 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. Although the risk of ketosis is very low in people without diabetes, we would still advise this precaution.
- SGLT2 inhibitors should be stopped 24 hours prior to surgery or other procedures requiring a period of reduced oral intake.
- Restart 7 days after operation or procedure.
- These rules do not apply if heart failure symptoms have deteriorated, but they are still eating and drinking normally - the patient should continue the SGLT2 inhibitor.

Genital infections, UTI, foot ulcers

- All SGLT2 inhibitors increase the risk of genital tract mycotic infections (relative risk about 4x) as well as marginally increasing risk of urinary tract infections (relative risk 1.07)[9].
- 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.
- Overall evidence does not suggest an increased risk of lower limb amputation with SGLT2is other than Canagliflozin (in one trial only)[9]. Preventive foot care is important for all patients with diabetes.

Hospital admissions

- Stop SGLT2 inhibitor at hospital admission if patient is not eating and drinking normally, or if a procedure requiring interruption of normal diet is planned.
- 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 may be best avoided for about 24 hours after administration of a SGLT2 inhibitor.
- Use of SGLT2 inhibitor for inpatients with heart failure:
    - Ensure stable patient before initiating.
    - Consider adjusting diuretic dosing when starting.
    - 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 clinical team if there is concern about this, as many heart failure and renal patients may tolerate relative hypotension without symptoms.
- As discussed above, the concurrent use of SGLT 2 inhibitors and insulin or insulin secretagogues (e.g. sulphonlyureas 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.
- Risk of interactions with anti-fungals such as tacrolimus or ciclosporin in patients on renal immunosuppression.

Section 6: Other SGLT2 inhibitors

- Canagliflozin has not been shown directly to benefit patients with heart failure alone, although it has been shown to reduce the incidence of heart failure in patients with diabetes[17]. Unless there is a particular concern about the patient, we would not recommend switching patients to dapagliflozin/empagliflozin.
- Canagliflozin has been shown to reduce risk of progression of CKD in patients with diabetes down to eGFR 30.
- Ertugliflozin appears to have less cardiovascular benefit[18], and we would suggest switching patients with heart failure or CKD onto dapagliflozin 10mg or empagliflozin 10mg once daily.
- [Sotagliflozin has benefits in heart failure[19]; not yet licensed in the UK.]

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BOB Buckinghamshire, Oxfordshire and Berkshire West Integrated Care System

SGLT2 Inhibitor Therapy Checklist for HF and CKD

For use in patients WITHOUT diabetes only

Please see separate checklist for patients with diabetes

Dapagliflozin and empagliflozin are the SGLT2 inhibitors (SGLT2i) currently licensed for use in heart failure.

Date seen:	**GP name:**
Patient name: **NHS number:**	

Indication for heart failure as per NICE TA679 and TA773:

- Symptomatic heart failure
- Left ventricular ejection fraction <40% and on (or not tolerated/ contraindicated)
  - ACE inhibitor or ARB or sacubitril/valsartan
  - Beta blocker
  - Mineralocorticoid receptor antagonist (MRAs)
- All patients with HF and type 2 diabetes, independent of ejection fraction, other meds, symptoms
- Left ventricular ejection fraction >40% alone or on other treatments as indicated

Indication for CKD as per NICE TA775:

- eGFR over 25 and
  - urine albumin: creatinine ratio (uACR) 22.6 or more
  - urine protein: creatinine ratio (uPCR) 35 or more
- or type 2 diabetes and uACR or uPCR over

Contraindications:

- Please see other document for patients with diabetes
- Pregnancy or breastfeeding . Discuss pregnancy planning and contraception. Stop SGLT2i 2 to 3 months before pregnancy and when pregnant / breastfeeding
- eGFR less than 15ml/min (dapagliflozin) or 20 (empagliflozin)
- Lactose intolerant (excipient)
- STOP if acutely unwell or major pre-operative procedure
- SEEK SPECIALIST advice with extreme diets (e.g. VLCD, pre-op bariatric, Atkins)
- Severe hepatic impairment (empagliflozin).

Cautions:

- Blood pressure less than 95 mmHg systolic
- Consider reducing doses of loop/thiazide diuretics
- Frail, elderly: slightly increased risk of dehydration, hypotension and falls, consider loop diuretic dose reduction.
- Review use if complicated or recurrent UTI's or genital infections
- Severe hepatic impairment: Dapagliflozin starting dose 5 mg daily. Increase to 10mg daily If tolerated.
- Immunosuppression, particularly in transplant patients

Patient Advice / Warnings:

Tick to confirm risks have been discussed	✓		✓
Risk of genital thrush and UTI, and of actions to take. (Common)		STOP SGLT2i if unwell or stop eating and drinking	
Potentiation of diuretics, thus volume depletion (Common)		STOP SGLT2i 24 hrs before surgery, restart 7 days after discharge	
Polyuria (consider incontinence issues)		If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and start treatment urgently	

Monitoring therapy: Renal function should be monitored as per normal advice for the condition. Blood pressure does not need to be monitored unless symptoms change.

BOB Buckinghamshire, Oxfordshire and Berkshire West Integrated Care System

SGLT2 Inhibitor Therapy Checklist for HF and CKD
For use in patients WITH diabetes only
Please see separate checklist for patients without diabetes

Date seen:	**GP name:**
Patient name: **NHS number:**	

Indications for SGLT2i in people WITH type 2 diabetes	
Heart failure	• All people with heart failure and type 2 diabetes should be on SGLT2 inhibitor, independent of type of heart failure or ejection fraction
Chronic kidney disease	• Should be on: eGFR over 25 AND uACR 30 mmol/l or more OR uPCR 35 or more or • Consider: eGFR 25 to 75 AND uACR 3 or more OR uPCR 3 mmol/l or more

Atherosclerotic cardiovascular disease	• Should be on if any vascular disease:
	  ○ Established coronary artery disease,
	  ○ Acute coronary syndrome, myocardial infarction
	  ○ Angina, coronary revascularisation,
	  ○ Cerebrovascular disease, peripheral arterial disease
	• Consider: age more than 40 and QRISK2 more than 10%
	• Consider: age less than 40 and one or more risk factor
	  ○ Hypertension
	  ○ Dyslipidaemia
	  ○ Smoking
	  ○ Obesity
	  ○ Family history (in a first-degree relative) of premature CVD cardiovascular disease

Which SGLT2i and dose in people with type 2 diabetes	
Heart failure	• Dapagliflozin 10mg once daily down to eGFR 15 (discuss with renal/cardiac team if lower), at any ejection fraction • Empagliflozin 10mg once daily down to eGFR 20, if ejection fraction under 40%
Chronic kidney disease	• Canagliflozin 100mg once daily down to eGFR 30 • Dapagliflozin 10mg once daily down to eGFR 15 (discuss with renal team if lower) • Empagliflozin 10mg once daily down to eGFR 30
Atherosclerotic cardiovascular disease or for glucose control	• Canagliflozin start 100mg if eGFR 30 or more; (can increase to 300mg if needed & eGFR 60 or more.) • Dapagliflozin start 10mg if eGFR 15 or more. • Empagliflozin start 10mg once daily if eGFR 30 or more; (can increase to 25mg if needed & eGFR 60 or more) • If eGFR falls below 45, glucose lowering is reduced but cardiovascular disease, renal and HF benefits are maintained. Only stop if no other indication i.e. no albuminuria, no CVD, low risk, no HF.

Contraindications:

- Type 1 diabetes
- Diabetic ketoacidosis (DKA) or any history of DKA
- Insulin deficiency: pancreatitis, total pancreatectomy, Latent Autoimmune Diabetes of Adulthood (LADA)
- Any ketogenic diet (e.g very low carbohydrate)
- Pregnancy or breastfeeding. Discuss pregnancy planning and contraception. Stop 2-3 months before pregnancy and when pregnant / breastfeeding
- eGFR less than limit for drug as above
- Recurrent or particularly problematic hypoglycaemia
- Lactose intolerance (excipient)
- Severe hepatic impairment (empagliflozin).

Cautions:

- Patient on insulin, sulfonylurea, repaglinide, nateglinide, consider adjusting dose; see below.
- Severe insulin deficiency suspected or confirmed.
- Systolic blood pressure less than 95 mmHg
- Consider reducing diuretic dose when starting
- Frail / elderly: Slightly increased risk of dehydration, hypotension, falls. See SPCs for specific guidance. Consider transient reduction in loop diuretic when starting.
- Overall evidence does not suggest an increased risk of lower limb amputation with SGLT2is other than canagliflozin (in one trial only). Preventive foot care is important for all patients with diabetes.
- Marginally increased risk of urinary tract and genital infection
- Particular caution with kidney transplant patients and renal immunosuppression patients
- Severe hepatic impairment - dapagliflozin starting dose 5 mg daily, increased to 10mg daily if tolerated.
- Monitor carefully if BMI<25kg/m^2

DKA Risk Assessment:

At risk if not enough insulin or increased demand for insulin

- Any history of ketone production or DKA
- History of pancreatitis or pancreatectomy
- Increased insulin requirements (acutely unwell, surgery)
- Restricted carbohydrate / calorie intake
- Dehydration
- Reduced insulin doses

If patient is at risk of DKA, seek specialist advice before initiating an SGLT2i or consider an alternative option.

Adjustment of Insulin, sulfonylurea (SU), repaglinide or nateglinide doses

- Starting SGLT2i in patients on insulin or the above glucose lowering drugs risks euglycemic DKA and hypoglycaemia.
- On starting an SGLT2i, the dose of insulin and the above glucose lowering drugs is often reduced to avoid hypoglycaemia. However, large/sudden reduction in insulin doses increases DKA risk.
- Only start SGLT2i for patients on insulin and the above glucose lowering drugs if you are confident and competent to do so.
  If unsure about how much to decrease (or subsequently increase) doses in individual patients or would like to improve your confidence in starting SGLT2i, please contact the Specialist Diabetes team

"Sick day rules" - advise patients of these:

- If a patient becomes ill and are unable to maintain an adequate fluid intake, discontinue SGLT2i until eating and drinking normally again. Discuss signs and symptoms of DKA.
- Consider need to see health care professional to check blood ketone concentrations. Seek specialist help if capillary ketone concentrations 1 mmol/l or higher.
- Stop SGLT2i 24 hours prior to surgery or other procedures requiring a period of reduced oral intake.
- Restart 7 days after operation or procedure (when eating and drinking normally again)

Patient Advice / Warnings:			
Tick to confirm risks have been discussed	✓		✓
Patient warned of risk of DKA (Rare) and sick day rules and given patient leaflet		Instructions given to seek prompt advice if experiencing abdominal pain, nausea, vomiting, breathing difficulties, confusion (symptoms of DKA)	
Risk of genital thrush and UTI, and of what actions to take. (Common)		STOP SGLT2i if unwell or stop eating and drinking	
Potentiation of diuretics, thus volume depletion (Common)		STOP SGLT2i 24 hrs before surgery, restart 7 days after discharge	
Polyuria (consider incontinence issues)		If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and start treatment urgently	

Monitoring therapy:
No additional bloods / checks required Monitor renal function and BP as per normal for condition
Monitoring for Heart Failure with type 2 diabetes:

	Baseline	**6 months**
Date:		
HbA1c - If raised at baseline, repeat at 3 months.		**3 months:**
Capillary blood glucose (Consider if there is risk of hypoglycaemia)		**3 months:**
Weight (kg)		
BMI (kg/m^2)		
eGFR (mL/min - STOP if eGFR persistently below 15mL/min (dapagliflozin) or if eGFR is persistently below 20 mL/min (empagliflozin)		
Tolerability		

NOTE: It is important to record the indication for the SGLT2i as heart failure in order to ensure that it is not stopped at a routine diabetes review

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