UK Kidney Association Clinical Practice Guideline:

Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease

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See appendix for list of previous versions/revisions and working group affiliations

Conflicts of Interest Statement
All authors made declarations of interest in line with the policy in the Association's Clinical Practice Guidelines Development Manual. Further details can be obtained on request from the UK Kidney Association.

Executive summary
UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors were initially developed to treat hyperglycaemia in people with type 2 diabetes mellitus (DM). Results from large placebo-controlled clinical outcome trials have shifted the focus to SGLT-2 inhibition's potential to manage cardio-renal risk rather than hyperglycaemia. In people with type 2 DM at high risk of atherosclerotic cardiovascular disease, SGLT-2 inhibition reduces cardiovascular risk, particularly from heart failure. In people with chronic kidney disease (CKD), the CREDENCE and DAPA-CKD trials have demonstrated SGLT-2 inhibition's particular efficacy at also reducing risk of kidney disease progression in people with type 2 DM and albuminuric diabetic kidney disease. Subgroup analyses from DAPA-CKD also suggest these benefits extend to certain types of albuminuric CKD, irrespective of the presence of diabetes mellitus. The effectiveness of SGLT-2 inhibitors at glucose lowering diminishes as the kidney function falls, however, the relative effects of SGLT-2 inhibition on kidney disease progression and cardiovascular risk appear preserved in people with type 2 DM and CKD, at least within the range of kidney function represented in the reported trials.

SGLT-2 inhibition therefore represents a paradigm shift in the management of people with CKD. The aim of these UK Kidney Association Guidelines are to facilitate rapid and safe use of SGLT-2 inhibitors in the context of CKD. Specifically we aim to:

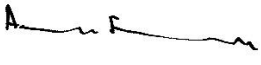
(i) Provide guidance on use of SGLT-2 inhibitors in people with CKD, focusing on the potential to modify risk of kidney disease progression; and
(ii) Support safe implementation of SGLT-2 inhibitors into clinical practice.

We offer evidence-based graded practice guidelines covering the appropriate use of SGLT-2 inhibition in different populations with CKD, accompanied by recommendations for implementation, clinical research and audit, together with template Patient Information Leaflets to facilitate safe prescribing. We also summarize current licensing of different SGLT-2 inhibitors with respect to kidney disease and cross-reference relevant parts of the 2021 Association of British Clinical Diabetologists - Renal Association (ABCD-RA) Clinical Practice Guidelines for the Management of Hyperglycaemia in Adults with Diabetic Kidney Disease.

At the time of writing further trials of SGLT-2 inhibition in CKD and heart failure populations are ongoing, the results from which may necessitate important updates to the present recommendations. This document is structured into individual modular sections to facilitate efficient revisions as the evidence-based expands.

We are enormously grateful to all the members of the Guideline Working Group for their time and effort developing this guideline.

Associate Prof. Will Herrington



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Summary of recommendations

RECOMMENDATIONS FOR USE		
Section 2	**PEOPLE WITH TYPE 2 DM**	**Grade**
1.	In people with type 2 DM and an eGFR ≥25 mL/min/1.73m^2, we recommend initiating SGLT-2 inhibition* in those with: (a) uACR of ≥25 mg/mmol attributed to diabetic nephropathy (b) Established coronary disease, prior heart failure hospitalisation, or known symptomatic reduced ejection fraction heart failure.§	**1A**
2.	In people with type 2 DM and an eGFR ≥25 mL/min/1.73m^2: (a) We suggest initiating SGLT-2 inhibition in those with a uACR of ≥25 mg/mmol attributable to a non-diabetic cause‡ (b) We suggest initiating SGLT-2 inhibition to modify cardiovascular risk in those with an eGFR 25-60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognising effects on glycaemic control will be limited.	**2B**
Section 3	**PEOPLE WITHOUT DM**	
1.	We recommend initiating SGLT-2 inhibition* in those with symptomatic reduced ejection fraction heart failure.§	**1A**
2.	We recommend initiating SGLT-2 inhibition* in those with a uACR of ≥25 mg/mmol, excluding people with polycystic kidney disease or on immunological therapy for renal disease.‡	**1B**
** See section 4 for summary of indications/licenced uses* *§ Left ventricular ejection fraction of ≤40%* *‡ DAPA-CKD provides the key clinical evidence and excluded people with a kidney transplant, polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, and those receiving immunological therapy for renal disease in the last 6 months.*		

RECOMMENDATIONS FOR IMPLEMENTATION		
Sections 2 & 3	**PEOPLE WITH OR WITHOUT DM (excluding TYPE 1)**	**Grade**
1.	We recommend using SGLT-2 inhibitors with demonstrated efficacy for their given indications.*	**1A**
2.	We recommend using clinically appropriate single agent RAS blockade in combination with SGLT-2 inhibition, wherever RAS blockade is indicated and tolerated.	**1A**
3.	We suggest following NICE guidelines on screening for albuminuria (NICE CG182): a single uACR of ≥70 mg/mmol or a confirmed measurement between 25-69 mg/mmol fulfil recommendations for use of SGLT-2 inhibition based on albuminuria.	**2C**
4.	We suggest using uACR to assess for sufficient proteinuria to guide SGLT-2 inhibitor use: reagent strips and protein:creatinine ratio should not be used (NICE CG182).	**2C**
5.	We suggest that when used to slow kidney disease progression or heart failure risk, SGLT-2 inhibition can be continued until the need for dialysis or kidney transplantation arises.	**2B**
6.	We suggest that co-prescription of SGLT-2 inhibition with MRA can be considered, where each are individually indicated.	**2B**
7.	We suggest the beneficial effects of SGLT-2 inhibition on renal outcomes in people with type 2 DM are likely to be a class effect, but there is insufficient data in people without DM to be conclusive.	**2B**
8.	We suggest the beneficial effects of SGLT-2 inhibition on heart failure hospitalisation in people with reduced ejection fraction heart failure§ are likely to be a class effect, irrespective of the presence or absence of DM.	**2B**
Section 5a	**DIABETIC KETOACIDOSIS**	

1.	We recommend that people with type 1 DM should only have SGLT-2 inhibitors initiated under the strict direction of the diabetes team.	**1C**
2.	We recommend that people with type 2 DM at greater risk of DKA (defined in Table 5a.1) should have SGLT-2 inhibitors initiated with caution after discussion with the diabetes team.	**1C**
3.	We recommend SGLT-2 inhibitors are discontinued when a patient develops DKA.	**1A**
4.	We suggest that after an episode of DKA and where a clear contributing factor has been identified, there should be discussion with the person and clinical team to establish whether the benefits of re-introducing an SGLT-2 inhibitor outweigh the risks.	**2D**
5.	When initiating SGLT-2 inhibitors, we suggest that individuals should be advised on the signs and symptoms of DKA and be instructed to temporarily withhold SGLT-2 inhibitors and to seek immediate medical advice if symptoms develop.	**1C**
6.	We recommend always offering advice on sick day guidance when initiating SGLT-2 inhibitors and reminding them of this at every medication review.	**1C**
7.	We suggest that individuals taking SGLT-2 inhibitors should be advised against following a ketogenic diet.	**2C**
8.	We suggest that for people who choose to intermittently fast (e.g. for Ramadan), ketone testing should be undertaken if unwell.	**2D**
Section 5b	**HYPOGLYCAEMIA**	
1.	We recommend considering reducing the dose of insulin/SUs/meglitinides when initiating SGLT-2 inhibitors to reduce the risk of hypoglycaemia.	**1C**
2.	We recommend that when initiating SGLT-2 inhibitors in people taking SUs (e.g. gliclazide) or meglitinides (e.g. repaglinide) when the HbA1c <58 mmol/mol AND eGFR >45 mL/min/1.73m^2, consider reducing dose of SU or meglitinide by 50% to reduce risk of hypoglycaemia.	**1C**
3.	We recommend that when starting SGLT-2 inhibitors in people taking insulin when the HbA1c <58 mmol/mol AND eGFR >45 mL/min/1.73m^2, consider reducing the insulin dose by 20% to avoid hypoglycaemia.	**1C**
4.	We recommend that when starting SGLT-2 inhibitors in people taking only metformin ± pioglitazone ± DPP-4i/gliptins or GLP-1RA therapy, no dosage adjustment is necessary.	**1C**
Section 5c	**ACUTE KIDNEY INJURY, HYPOVOLAEMIA AND POTASSIUM**	
1.	We recommend that individuals initiated on an SGLT-2 inhibitor do not routinely require an early assessment of renal function or potassium following initiation of treatment.	**1C**
2.	We suggest that if an individual has a renal function assessment within the first few weeks post initiation of an SGLT-2 inhibitor, a decline in eGFR needs to be interpreted with caution and in the context of an expected drug effect to avoid unwarranted discontinuation of treatment.	**2B**
3.	We suggest that individuals on diuretics are counselled on the symptoms of hypovolaemia and advised to seek medical attention if they develop any such symptoms.	**2B**
4.	We suggest that clinicians consider an early clinical review and if appropriate a diuretic or antihypertensive dose reduction in individuals they consider at high risk of hypovolaemia.	**2C**
5.	We recommend that SGLT-2 inhibitors are temporarily withheld during acute illness (see sick-day guidance in section 5a.1.2).	**1C**
6.	We suggest that for people who choose to fast, and particularly those who are elderly, on diuretics or have CKD, consider withholding SGLT-2 inhibitors during the duration of the fasting period.	**2D**
Section 5d	**PERIPHERAL VASCULAR DISEASE AND AMPUTATION RISK**	

1.	We suggest avoiding initiation of SGLT-2 inhibitors in the presence of active foot disease (infection, ulceration and ischaemia) and withholding treatment in those who develop foot complications whilst taking an SGLT-2 inhibitor.	**2B**
2.	We suggest a shared decision-making approach, with appropriate counselling on risks and benefits of treatment and the importance of routine preventative foot care measures for: • Individuals at high risk of amputation (previous amputations, existing PVD, peripheral neuropathy) • Re-initiation of SGLT-2 inhibitors after treatment and full resolution of a foot complication that occurred whist taking SGLT-2 inhibitors.	**2B**
Section 5e	**FRACTURE RISK**	
1.	In people with CKD treated with SGLT-2 inhibitors, we suggest monitoring of bone parameters including calcium, phosphate and PTH should be performed as appropriate for CKD stage (see NICE CG182).	**2D**
Section 5f	**MULTIMORBIDITY AND FRAILTY**	
1.	We suggest an approach to care that takes account of frailty and multimorbidity where these apply. This can include: • Establishing the person's goals, values and priorities • Consideration of the balance of disease and treatment burden (for example, prognostic benefits in people with limited life expectancy or frailty) • Agreeing an individualised management plan.	**2D**
Section 5g	**MYCOTIC GENITAL INFECTIONS AND FOURNIER'S GANGRENE**	
1.	We recommend that all people are counselled on the risks of mycotic genital infections prior to initiation of SGLT-2 inhibitors.	**1D**
2.	We recommend that all people are counselled on self-care to maintain good genital hygiene.	**1C**
3.	We recommend that all people are counselled on the symptoms of mycotic genital infections and how to seek help including self-management.	**1D**
4.	We suggest that for those individuals with a history of recurrent mycotic genital infections on SGLT-2 inhibition, consideration is given to offering prophylactic anti-fungal treatment, which should be reviewed after 6 months of therapy or earlier if clinically indicated.	**2D**
5.	We suggest that SGLT-2 inhibitor therapy can be continued during the treatment of mycotic genital infections.	**2D**
6.	We highlight the specific MHRA warning and suggest that all people are counselled on the symptoms of Fournier's gangrene and advised to stop SGLT-2 inhibitors and to seek urgent help if they develop such symptoms.	**2D**
7.	We highlight the specific MHRA warning and suggest that SGLT-2 inhibitors are discontinued if Fournier's gangrene is diagnosed or suspected.	**2D**
Section 5h	**URINARY TRACT INFECTION**	
1.	We recommend temporary discontinuation of SGLT-2 inhibitors when treating pyelonephritis or urosepsis (see sick-day guidance in Section 5a.1.2).	**1C**
Section 5i	**CHILDREN, PREGNANCY AND BREASTFEEDING**	
1.	We suggest SGLT-2 inhibitors are not used in children under 18 years of age.	**2D**
2.	We suggest that all women of child-bearing potential are counselled, prior to conception, on the risks of SGLT-2 inhibitors during pregnancy.	**2D**
3.	We suggest SGLT-2 inhibitor therapy is discontinued upon planning, suspicion or confirmation of pregnancy.	**2D**

4.	We suggest SGLT-2 inhibitors are not used in women who are breastfeeding.	**2D**
Section 7a	**PEOPLE WITH TYPE 1 DM**	
1.	We recommend that SGLT-2 inhibitors be initiated in people with type 1 DM, only under the strict direction of the diabetes team.	**1C**
2.	We suggest considering referring people with type 1 DM to the specialist diabetes team, for consideration of an SGLT-2 inhibitor, if they have an eGFR ≥25 mL/min/1.73m^2 and an uACR ≥25 mg/mmol attributable to diabetic nephropathy despite being on maximum tolerated ACEi/ARB.	**2D**
3.	We recommend all people with type 1 DM started on SGLT-2 inhibitors be provided with ketone monitoring, be advised on the signs and symptoms of DKA and to seek immediate medical advice if any of these symptoms develop or ketone levels are >0.6 mmol/L.	**1B**
SUMMARY STATEMENTS		
Section 7b	**KIDNEY TRANSPLANT RECIPIENTS**	**Grade**
1.	There is currently insufficient evidence on safety and efficacy to provide recommendations for use of SGLT-2 inhibition in people with a functioning kidney transplant.	**-**
2.	Any use of SGLT-2 inhibition to treat diabetes mellitus in a kidney transplant recipient should be evaluated by multi-disciplinary discussion.	**2D**
Section 7c	**HEART FAILURE WITH PRESERVE EJECTION FRACTION and ACUTELY DECOMPENSATED HEART FAILURE**	
1.	There is currently insufficient evidence to provide further recommendations for use of SGLT-2 inhibition in people with CKD with co-existent HFpEF or acutely decompensated heart failure.	-

- NICE CKD guidance is available at www.nice.org.uk/guidance/cg182.
- For sick day rules also see Section 6's template Patient Information Leaflets.

Table abbreviations:

ACEi	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin-II Receptor Blocker
CKD	Chronic Kidney Disease
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DPP-4i	Dipeptidyl Peptidase-4 inhibitors
eGFR	Estimated Glomerular Filtration Rate (mL/min/1.73m^2)
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
HbA1c	Glycosylated Haemoglobin
HFpEF	Heart Failure with Preserved Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid Receptor Antagonist
NICE	National Institute for Health and Care Excellence
RAS	Renin Angiotensin System
SGLT-2	Sodium-Glucose Co-transporter-2
SU	Sulphonylurea
uACR	Urinary Albumin:Creatinine Ratio

Section listing/contents

List of abbreviations

Abbreviation	Definition
ABCD-RA	Association of British Clinical Diabetologists - Renal Association
ACEi	Angiotensin-Converting Enzyme Inhibitor
ADA	American Diabetes Association
AF	Atrial Fibrillation
AKI	Acute Kidney Injury
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ARB	Angiotensin-II Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease- Mineral Bone Disease
95%CI	95% Confidence Interval
CV	Cardiovascular
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DPP-4i	Dipeptidyl Peptidase-4 inhibitors
eGFR	Estimated Glomerular Filtration Rate (mL/min/1.73m^2)
EASD	European Association for the Study of Diabetes
ESKD	End-Stage Kidney Disease
EU	European Union
FDA	US Food and Drug Administration
FGF-23	Fibroblast Growth Factor-23
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-Like Peptide-1
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
HbA1c	Glycosylated Haemoglobin
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HHF	Hospiltalisation for Heart Failure
HR	Hazard Ratio
KDIGO	Kidney Disease Improving Global Outcomes
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse/Atherosclerotic Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid Receptor Antagonist
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NODAT	New Onset Diabetes After Transplantation
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
OR	Odds Ratio
PADP	Pulmonary Artery Diastolic Pressure
PTH	Parathyroid Hormone
Q1-Q3	Quartile 1-Quartile 3 (i.e. the interquartile cutoffs)
QALY	Quality-Adjusted Life Years
RAS	Renin Angiotensin System
RCT	Randomised Controlled Trials
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error
SGLT-2	Sodium-Glucose Co-transporter-2
SmPC	Summary of Product Characteristics
SU	Sulphonylurea
uACR	Urinary Albumin:Creatinine Ratio
UK	United Kingdom
UTI	Urinary Tract infection

Section 1: Background, aims and concise methods

1.1 SUMMARY

Prevention of kidney disease progression and reducing cardiovascular risk are unmet clinical needs among people with chronic kidney disease (CKD). Large-scale placebo-controlled trials have demonstrated that sodium-glucose co-transporter-2 (SGLT-2) inhibition favourably modifies both such risks in a range of different studied populations. In people with CKD, the CREDENCE and DAPA-CKD trials have demonstrated SGLT-2 inhibition's particular efficacy at reducing risk of kidney disease progression in people with type 2 diabetes mellitus (DM) and albuminuric diabetic kidney disease. Subgroup analyses from DAPA-CKD also suggest these benefits extend to certain types of albuminuric CKD, irrespective of the presence of DM. This section provides the background to this guideline by introducing: (i) CKD and the concept of intraglomerular hypertension; (ii) the molecular mechanisms of SGLT-2 inhibition; and (iii) the large placebo-controlled trials that have informed us of its cardio-renal beneficial effects.

1.2 INTRODUCTION

1.2.1 CKD is common and associated with risk of progression to renal replacement therapy

The age-standardized prevalence of CKD in adults in the UK is estimated to be about 6-11% (1). In the absence of effective new interventions, this proportion is predicted to rise as the population ages, premature mortality from cardiovascular and other causes declines further, and type 2 DM becomes more prevalent (2). Worldwide, diabetic kidney disease accounts for 30-50% of advanced CKD (i.e. stages 4-5) (3, 4). In the UK, currently about 30% of those starting maintenance renal replacement therapy have diabetic nephropathy as their primary renal disease, peaking at 38% among those starting at the ages of 55-64 years (5).

CKD can be a progressive condition, with albuminuria representing a significant risk factor for more rapid kidney function decline both in people with and without diabetes (6). The avoidance of progressive CKD is important as end-stage kidney disease (ESKD) has adverse effects on morbidity and quality of life, dialysis or transplantation incur substantial societal costs (7, 8), and low levels of kidney function increase cardiovascular risk (9).

Albuminuria is a marker of intraglomerular hypertension and has been used as a means to select participants at high risk of kidney disease progression into CKD trials. Such trials have often studied diabetic nephropathy separately from other causes of CKD. For example, pharmacological inhibition of the renin-angiotensin system (RAS) reduces efferent arteriolar tone and hence intraglomerular pressure, and large trials have shown this reduces albuminuria and the risk of overt diabetic nephropathy progressing to ESKD (10, 11). However, intraglomerular hypertension is also considered to be a common pathway for kidney disease progression shared by some non-diabetic forms of CKD (12). The concept centres on the idea that reduced nephron numbers induces hyperfiltration in the remaining glomeruli. Support for this concept includes the observations that: (i) for a given level of urinary albumin excretion, the risk of ESKD is relatively independent of the primary renal diagnosis (13); and (ii) trial meta-analyses show that RAS-inhibition slows progression of a range of proteinuric non-diabetic kidney diseases (14, 15). Single agent RAS-inhibition is therefore the standard of care for proteinuric CKD, with clinician judgement used to estimate clinically appropriate dosage. Nevertheless, despite use of appropriate RAS-inhibition alongside suitably intensive glycaemic (16-18) and blood pressure (19-22) control, substantial residual risk of ESKD remains in people with proteinuric CKD (10, 11).

1.2.2 People with CKD are at high risk of structural heart disease and heart failure

In cohorts with appropriate cardiac imaging, structural heart disease is identified in about one-half of patients with CKD stage 4-5 (23). CKD often co-exists with heart failure, due to a combination of shared risk factors and integrated pathophysiology (24). This may more commonly present as heart failure with preserved ejection fraction, and so we have provided special consideration of this condition in section 7 of this guideline document. Many people with CKD consequently die from cardiovascular disease before progression to ESKD. Management of CKD therefore includes modification of risk of both kidney disease progression and associated cardiovascular risk (24, 25). SGLT-2 inhibitors have emerged as a potential therapy to address both the cardiac complications of CKD and risk of kidney disease progression (26-36).

1.3 MOLECULAR MECHANISMS OF ACTION OF SGLT-2 INHIBITION

Everyone has a threshold of renal tubular glucose concentration above which glucose appears in the urine (37). It was recognized that this threshold could be reduced with an apple tree bark extract called phlorizin (38, 39). Following the cloning of the SGLT-1 and SGLT-2 genes, phlorizin was characterized as a non-specific SGLT inhibitor. SGLT-1 is a low-capacity, high-affinity transporter located primarily in the gastrointestinal tract. It functions to absorb dietary glucose and is also expressed in the later renal proximal tubule segment (S3), where it is responsible for reabsorbing only ~3% of filtered glucose under normal physiological conditions. By contrast, SGLT-2 is a high-capacity, low-affinity transporter located mainly in the early renal proximal tubule segments. SGLT-2 is responsible for reabsorbing ~97% of filtered glucose. Inhibition of SGLT-2 therefore has a much larger effect on the glucose threshold than SGLT-1 inhibition. Dual SGLT-1/2 inhibitors have also been developed with the aim of increasing urinary glucose-lowering excretion because SGLT-1 has significant reserve capacity to reabsorb glucose if SGLT-2 is inhibited (40-42), but gut effects include a potential to cause diarrhoea (34, 36).

For each SGLT-2 reabsorbed molecule of glucose, a sodium ion is co-transported. SGLT-2 inhibition therefore increases sodium delivery through the renal tubules to each nephron's macula densa, and subsequently into the urine. The macula densa is the structural area of the early distal convoluted tubule which lies between the afferent and efferent arteriole of the mother glomerulus to that distal tubule. Sodium delivery to the macula densa results in changes to intraglomerular blood flow and pressure by means of changes to the calibre of the afferent arteriole, a homeostatic process referred to as tubuloglomerular feedback. High sodium delivery to the macula densa results in constriction of the afferent arteriole, which results in a decrease in glomerular blood flow and glomerular capillary pressure, whilst decreased sodium delivery has the opposite effect. Therefore, SGLT-2 inhibition augments macula densa tubuloglomerular feedback as well as generating a natriuresis to combine with the glycosuric osmotic diuresis. These sodium effects appear to be central to both the renal and cardiovascular physiological effects of SGLT-2 inhibition.

1.3.1 SGLT-2 inhibitors' glycaemic effects

SGLT-2 inhibitors (also known as "gliflozins") were initially assessed and licensed for their glucose-lowering potential (43). However, the glycosuric effect of SGLT-2 inhibition linearly attenuates as kidney function declines, and so such licences were initially restricted to people with generally preserved kidney function. These preclusions for use in people with CKD have been progressively relaxed following the results of several large trials (section 4 of this guideline provides a summary of current licensing in CKD). Large FDA-mandated trials in type 2 DM populations were initiated in order to assess their cardiovascular safety (44). These trials demonstrated that SGLT-2 inhibitors are non-inferior to placebo with respect to effects on

major atherosclerotic (or adverse) cardiovascular events (MACE) with some trials also demonstrating superiority (26-28). Subsequently, the CREDENCE and DAPA-CKD trials have demonstrated SGLT-2 inhibition's particular efficacy at reducing risk of kidney disease progression and heart failure hospitalisation in people with type 2 DM and CKD down to an estimated glomerular filtration (eGFR) rate of 25 ml/min/1.73m^2 (29, 45). The realisation from these trials that SGLT-2 inhibition confers cardiac and renal protection independent of glycaemic effects and kidney function, with substantial benefits also evident in people without DM, has led to a shift in focus from purely lowering glycosylated haemoglobin (HbA1c) to disease risk modification. At the time of writing, there are ten reported and three ongoing large placebo-controlled trials in different settings, including trials in populations with type 2 DM, heart failure and CKD (see Table 1.1 for a listing, including key eligibility criteria and outcomes).

1.3.2 SGLT-2 inhibitors' effects on kidney physiology

In people with CKD, the CREDENCE and DAPA-CKD trials have demonstrated SGLT-2 inhibition's particular efficacy in reducing risk of kidney disease progression in people with type 2 DM and albuminuric diabetic kidney disease (29, 45). Subgroup analyses from DAPA-CKD also suggest these benefits extend to certain types of albuminuric CKD, irrespective of the presence of DM (45). Despite the attenuated ability of SGLT-2 inhibitors to lower glucose at reduced levels of kidney function, the relative benefits of SGLT-2 inhibition on kidney disease progression appear preserved in people with type 2 DM and CKD, at least within the range of kidney function represented in the reported trials (29, 45).

As described above, the key mechanism for renoprotection is considered to be through SGLT-2 inhibitor's modulation of tubuloglomerular feedback; increased delivery of sodium to the macula densa and the enhancement of glomerular afferent arteriolar vasoconstriction (46, 47). The consequent reduction in renal glomerular blood flow is believed to be responsible for the acute, reversible dip in kidney function, reductions in albuminuria and slowing of kidney function decline following initiation of SGLT-2 inhibition (46). This modulation of renal haemodynamics appears to persist in people with normoglycaemia (although it may be attenuated). Acute dips in eGFR on initiation of SGLT-2 inhibition are apparent in people without DM (48-50). Consequently, SGLT-2 inhibition is hypothesized to reduce intraglomerular hypertension and target the proposed final common pathway for kidney disease progression in people with or without DM (51).

SGLT-2 inhibition also appears to reduce the risk of adverse events attributed to AKI (52), with a protective effect evident in the trials of people with type 2 DM (32, 52), heart failure (30, 34, 53) and CKD populations alike (29, 35, 36). The proposed protective mechanisms are reduced risk of ischaemic-reperfusion injury or renal tubular hypoxia from the lowered metabolic demand of inhibited co-transporters (54). Conceivably, a reduction in AKI risk may also translate into benefits on CKD progression, providing a mechanistic explanation for suggested beneficial effect of SGLT-2 inhibition on estimated glomerular filtration rate slopes in individuals with heart failure and without albuminuria (33, 53, 55, 56).

Establishing definitively whether or not albuminuria is a pre-requisite for renal benefits of SGLT-2 inhibition is an important question to address as: (i) the majority of individuals with CKD do not have albuminuria, and (ii) if mechanistic theories about intraglomerular hypertension are correct, renal benefits may be substantially different in the absence of albuminuria. The ongoing EMPA-KIDNEY trial has the widest eligibility criteria of the four SGLT-2 inhibitor trials in CKD populations (Table 1.1) and will help assess more precisely which individuals with non-diabetic causes of albuminuric CKD obtain renal benefits from SGLT-2 inhibition (51).

Section 2 and 3 of this guideline will provide a more detailed appraisal of the completed and ongoing trials assessing the effects of SGLT-2 inhibition on kidney disease, with section 7 also providing special consideration for people with a functioning kidney transplant.

1.3.3 SGLT-2 inhibitors' effects on cardiovascular physiology

The totality of the trial evidence shows that relative benefits of SGLT-2 inhibition on heart failure outcomes are both larger and more consistent than on MACE. Meta-analyses estimated that the risk of hospitalisation for heart failure was reduced by about one-third compared to placebo and MACE risk is reduced by about 10% (57). This suggests that the natriuretic, osmotic diuretic and renoprotective effects of SGLT-2 inhibition are more effective at targeting heart failure pathophysiology than atherothrombotic risk. The effects of SGLT-2 inhibition on MACE risk may result from the more modest lowering effects of SGLT-2 inhibition on blood pressure, HbA1c and adiposity. For a more detailed review of the cardiac effects of SGLT-2 inhibition, see a recent update from the European Society of Cardiology ad-hoc task force (58).

1.3.4 SGLT-2 inhibitors effects on metabolism

SGLT-2 inhibitors have broad metabolic effects beyond lowering blood glucose. Glycosuria leads to increased plasma glucagon, which in turn increases hepatic glucose production in part by glycogenolysis (59, 60). Depletion of liver glycogen creates a fasting-like state initiating ketone generation from the liver as an alternative energy source (48). Randomized trials consistently show a dose-dependent reduction in weight (61). Whereas the early weight loss may be due to intra- and extra-vascular volume depletion (62), loss of adipose tissue does occur with longer-term treatment (63).

In addition to inducing a state of ketosis, SGLT-2 inhibition also reduces renal ammoniagenesis. This – in combination with ketosis – leads to urinary loss of bicarbonate which, combined with ketosis, may lower the threshold required to induce ketoacidosis in the presence of an additional insult (e.g. fasting or infection) (64). This accounts for both the increased risk of ketoacidosis in individuals taking SGLT-2 inhibitors and explains presentations of "euglycaemic ketoacidosis". Ketoacidosis is a particular risk in individuals who have limited endogenous insulin production, and particularly those with type 1 DM (65). The benefit-risk ratio is therefore more finely balanced in people with type 1 DM, with use of certain SGLT-2 inhibitors granted by regulators at lower doses and under specialist supervision in this population. (66, 67). Section 7 of this guideline document introduces special consideration for people with type 1 DM.

The risk of severe hypoglycaemia caused by SGLT-2 inhibition is small (26-36). Mechanistically, hypoglycaemia would not be expected because of the compensatory effects of intact SGLT-1 activity and hepatic gluconeogenesis (68). Hypoglycaemia on SGLT-2 inhibitors is therefore largely limited to individuals who are on concomitant hypoglycaemia-inducing medication (i.e. insulin or insulin secretagogues).

1.3.5 Potential adverse effects of SGLT-2 inhibitors

Mycotic genital infections are common in individuals with DM, but there is an increased risk associated with SGLT-2 inhibitor-induced glycosuria. The effect of SGLT-2 inhibition on these infections is large enough to have been apparent in the earlier smaller trials focusing on glycaemic control (69-71). Case reports of necrotizing fasciitis of the perineum (Fournier's gangrene) attribute such devastating polymicrobial infections to SGLT-2 inhibitor use (72), but the rarity of the condition means there is insufficient randomized data to confirm or refute this hazard - a causal association remains unproven (28, 32, 35, 73). Large amounts of urinary glucose meant an increased incidence of urinary tract infection were expected and are listed

in the labels for all SGLT-2 inhibitors. However, this is yet to be borne out in the large randomized trials which have not confirmed any such risk (26-36).

The CANVAS program, which tested canagliflozin in individuals with type 2 DM at high risk of cardiovascular disease, raised two new safety considerations: an excess of bone fractures and separately, an increased risk of lower limb amputation were identified. *Post hoc* biological rationales have been proposed for these effects of canagliflozin (74), but a chance finding is a plausible alternative explanation**.**

Section 5 of this guideline document will provide a more detailed appraisal of the trials assessing the effects of SGLT-2 inhibition on metabolic and safety outcomes, with section 6 providing supporting information for patients with CKD being offered SGLT-2 inhibition.

1.4 LISTING OF KEY LARGE-SCALE PLACEBO-CONTROLLED CLINICAL OUTCOME TRIALS

Table 1.1: Large placebo-controlled SGLT-2 inhibitor clinical outcome trials, by population

Population **Trial (reference) (drug & daily dose)**	**Size**	**Median follow-up, years**	**Proportion with type 2 DM**	**Average (SD) eGFR, mL/min/1.73m²**	**Key eligibility criteria**	**Primary outcome(s)**	**Selected secondary outcomes**	**Completion status**
Ia. Heart failure (reduced ejection fraction) population								
DAPA-HF (30) (dapagliflozin 10mg)	4744	1.5	42%	Mean: 66 (19)	• Symptomatic chronic HF (class II-IV) with LVEF ≤40% • NT-proBNP ≥600 pg/mL • eGFR ≥30 • Appropriate doses of medical therapy and use of medical devices	• CV death or worsening HF (hospitalisation or an urgent visit for intravenous therapy)	• CV death or hospitalisation for HF • Total number of hospitalisation for HF • Sustained ≥50% decline in eGFR, sustained eGFR <15, ESKD, or renal death • Death from any cause	Reported
EMPEROR-REDUCED (33) (empagliflozin 10mg)	3730	1.3	50%	Mean: 62 (22)	• Class II-IV chronic HF with LVEF ≤40% • NT-proBNP above a certain threshold (stratified by LVEF) • Appropriate doses of medical therapy and use of medical devices	• CV death or hospitalisation for worsening HF	• Total number of hospitalisation for HF • Rate of eGFR decline • Death from any cause	Reported
Ib. Heart failure (preserved or mixed ejection fraction) population								
SOLOIST-WHF (34) (sotagliflozin 200-400mg)	1222	0.8	100%	Median: 50	• Type 2 DM • Hospitalised for heart failure requiring intravenous therapy • eGFR ≥30 • No recent coronary event	• CV death or total number of worsening HF events (hospitalisation or an urgent visit)	• Total number of worsening HF events (hospitalisation or an urgent visit) • Change in eGFR • Death from any cause	Reported
DELIVER (75) (dapagliflozin 10mg)	About 6100	Ongoing	People with & without DM eligible	Unknown	• Symptomatic chronic HF (class II-IV) with LVEF >40% & structural heart disease • Elevated NT-proBNP • eGFR ≥25	• CV death or worsening HF (hospitalisation or an urgent visit)	• Total number of worsening HF events (hospitalisation or an urgent visit) • Death from any cause • eGFR slope	Expected in 2021
EMPEROR-PRESERVED (76) (empagliflozin 10mg)	5988	Ongoing	People with & without DM eligible	Unknown	• Symptomatic chronic HF (class II-IV) with LVEF >40% & structural heart disease • NT-proBNP >300 pg/mL (or >900 if in AF) • eGFR ≥20	• CV death or hospitalisation for HF	• ESKD • All-cause hospitalisation • Death from any cause	Reported awaited
II. High cardiovascular risk + type 2 DM population								

EMPA-REG OUTCOME (26) (empagliflozin 10mg or 25mg)	7020	3.1	100%	Mean: 74 (21)	• Type 2 DM • History of coronary, cerebral or peripheral vascular disease • eGFR ≥30	• CV death, non-fatal myocardial infarction or non-fatal stroke	• Hospitalisation for HF • Incident or worsening nephropathy: macroalbuminuria, a doubling of the serum creatinine (accompanied by an eGFR of ≤45), ESKD or renal death	Reported
CANVAS Program (27) (canagliflozin 100-300mg)	10142	2.4	100%	Mean: 76 (20)	• Type 2 DM • History of coronary, cerebral or peripheral vascular disease OR age >50y with at least 2 CV risk factors • eGFR ≥30	• CV death, non-fatal myocardial infarction or non-fatal stroke	• CV death or hospitalisation for HF • 30% increase in albuminuria with change in category • Death from any cause	Reported
DECLARE-TIMI 58 (28) (dapagliflozin 10mg)	17160	4.2	100%	Mean: 85 (16)	• Type 2 DM • Age 40y + history of coronary, cerebral or peripheral vascular disease OR age ≥55y in men/≥60y in women with at least 1 CV risk factors • Creatinine clearance ≥60 mL/min	Co-primaries • CV death, myocardial infarction or ischaemic stroke • CV death or hospitalisation for worsening HF	• Sustained ≥40% decline in eGFR (to <60), ESKD, or death from kidney or CV causes • Death from any cause	Reported
VERTIS CV (32) (ertugliflozin 5 or 15 mg)	8246	3.0	100%	Mean: 76 (21)	• Type 2 DM • History of coronary, cerebral or peripheral vascular disease • eGFR ≥30	• CV death, non-fatal myocardial infarction or non-fatal stroke	• Hospitalisation for HF • Doubling of the serum creatinine, ESKD, or renal death	Reported
III. Chronic kidney disease population								
CREDENCE (29) (canagliflozin 100mg)	4401	2.6	100%	Mean: 56 (18)	• Type 2 DM • eGFR 30-90 • uACR 300-5000 mg/g • Stable maximally tolerated RAS blockade	• Sustained doubling of creatinine, sustained eGFR <15, ESKD, or death from renal or CV causes	• Hospitalisation for HF • CV death, non-fatal myocardial infarction or non-fatal stroke • Death from any cause	Reported
DAPA-CKD (35) (dapagliflozin 10mg)	4304	2.4	68%	Mean: 43 (12)	• eGFR 25-75 • uACR 200-5000 mg/g • Stable maximally tolerated RAS blockade, unless documented intolerance	• Sustained ≥50% decline in eGFR, sustained eGFR <15, ESKD, or death from renal or CV causes	• Hospitalisation for HF • Death from any cause	Reported

SCORED (36) (sotagliflozin 200-400mg)	10584	1.3	100%	Median: 45	• Type 2 DM • eGFR 25-60 • At least 1 CV risk factor	• CV death or total number of worsening HF events (hospitalisation or an urgent visit)	• CV death, non-fatal myocardial infarction or non-fatal stroke • Sustained ≥50% decline in eGFR, sustained eGFR <15, or ESKD • Death from any cause	Reported
EMPA-KIDNEY (51) (empagliflozin 10mg)	About 6600	Ongoing	About 45%	Mean: About 37	• eGFR 20-45, or eGFR 45-90 with uACR ≥200 mg/g • Clinically appropriate doses of RAS blockade, unless not tolerated	• Sustained ≥40% decline in eGFR, sustained eGFR <10, ESKD, or death from renal or CV causes	• CV death or hospitalisation for HF • All-cause hospitalisation • Death from any cause	Expected mid-2022

Footnote: AF=atrial fibrillation; CKD=chronic kidney disease; CV=cardiovascular; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate (mL/min/1.73m^2); ESKD=end-stage kidney disease (i.e. maintenance dialysis or receipt of kidney transplant); HF=heart failure; LVEF=left ventricular ejection fraction; RAS=renin angiotensin system; uACR=urinary albumin:creatinine ratio

(Table reproduced from an update from the European Society of Cardiology ad-hoc task force on sodium-glucose co-transporter-2 inhibitors (58))

1.5 GUIDELINE AIMS & DEVELOPMENT

1.5.1 Aims & recommendation types

Our overriding objective is to provide practical and pragmatic clinical practice guidelines to facilitate rapid and safe use of SGLT-2 inhibitors in the context of CKD in adults. In assessing the evidence base, we have deliberately focused on the relevant large-scale randomized evidence and have respected the relevant regulatory approvals for individual SGLT-2 inhibitors. More specifically, we aimed to:

(i) Provide guidance on use of SGLT-2 inhibitors in people with CKD, focusing on the potential to modify risk of kidney disease progression; and
(ii) Support safe implementation of SGLT-2 inhibitors into clinical practice in people with CKD.

In order to support both use and implementation, we therefore provide four types of Recommendation.

Recommendations for:
(i) Use (who should be offered SGLT-2 inhibition)
(ii) Implementation (how should SGLT-2 inhibition be used)
(iii) Research (what are areas of ongoing clinical uncertainty)
(iv) Audit (can you demonstrate effective implementation)

1.5.2 Evidence grading

In general, we followed the principles set out in the UK Kidney Association's "Clinical Practice Guideline Development Manual" and grade "Recommendations for Use" and "Recommendations for Implementation" according to its two-tier grading system (see Table 1.2). We use the term "recommend" within the guideline text where Recommendations are based on Grade 1 evidence, and prefer the term "suggest" for those based on Grade 2 evidence. Recommendations for Implementation could be considered a Practice Point but we avoid using this term for clarity. Our Recommendations for Research are not graded, and we offer Audit Measures for Recommendations with Grade 1 levels of evidence.

Table 1.2: UK-Kidney Association's grading system for Recommendations' strength and evidence quality

Level of evidence	Evidence quality
• Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients (i.e. recommendations) • Grade 2 recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain (i.e. suggestions)	• Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials, or overwhelming evidence of some other sort • Grade B evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength • Grade C evidence means low-quality evidence from observational studies, or from controlled trials with several very serious limitations • Grade D evidence is based only on case studies or expert opinion

1.5.3 Guideline structure

We recognize that the use of SGLT-2 inhibition is subject to a significant amount of ongoing research and there is likely to be further evidence that may influence the recommendations made within these guidelines. At the time of writing further large placebo-controlled trials of SGLT-2 inhibition in CKD and heart failure populations without DM are ongoing. Results from these trials may necessitate important updates to the present recommendations. This document is therefore structured into individual sections to facilitate efficient revisions as the evidence-base expands.

Recommendations for Use are provided, separately, for individuals with type 2 DM (section 2) and people without DM (section 3). Section 4 summarizes the current licensing of SGLT-2 inhibitors to support selection of SGLT-2 inhibitors in people with CKD. Section 5 focuses on the information on safety of SGLT-2 inhibitors, including considerations for older or multi-comorbid individuals. This section provides a series of Recommendations for Implementation. Section 6 provides patients' perspectives and template "Patient Information Leaflets". Lastly, section 7 provides consideration for populations of specific interest in which trial evidence is more limited currently. These populations include: (i) type 1 DM, (ii) kidney transplant recipients, and (iii) heart failure with preserved ejection fraction (HFpEF).

1.5.4 Evidence synthesis by systematic literature review

The generation of Recommendations was supported by a systematic literature search of relevant SGLT-2 inhibitor randomized controlled trials (see Methodological appendix for full details of the search strategy and results). In brief, a search of MEDLINE and Embase bibliographic databases via OVID from inception to 16th February 2021 was performed. Eligible trials were randomized parallel-group SGLT-2 inhibitor trials irrespective of size or duration. Trials which were placebo-controlled or offered comparisons with non-SGLT-2 inhibitor treatments (e.g. a sulfonylurea) were included, but trials randomizing participants to two different SGLT-2 inhibitors without a control group were excluded. The following other types of trials were also excluded: non-English language reports, purely pharmacokinetic/pharmacodynamics studies (e.g. in healthy volunteers or in phase 1), and duplicates.

Trials were subcategorized into large trials (i.e. those with >1000 participants randomized and with >500 participants in each arm), and into groups of specific interest relevant to specific guideline sections (i.e. type 1 DM, kidney transplant recipients, and HFpEF). Large trials were subject to a trial quality assessment using the Cochrane Risk of Bias 2 (ROB2) tool, with main and relevant subsidiary publications reviewed. Separate searches of pooled analyses from trials, meta-analyses and registries of ongoing trials were also performed, and relevant guidelines from UK stakeholders and elsewhere (e.g. KDIGO) reviewed along with regulatory licences for SGLT-2 inhibitors. Note that the 2021 Association of British Clinical Diabetologists - Renal Association (ABCD-RA) Clinical Practice Guidelines for the Management of Hyperglycaemia in Adults with Diabetic Kidney Disease is particularly relevant to this guideline, and we cross-reference relevant sections. However, our guidance was developed independently, and are consequently not identical.

From these published literature and search results, subgroups of the Guideline Working Groups developed summaries of the evidence and proposed evidence-based recommendations to a joint consensus meeting of all members. All members therefore had the opportunity to review all the proposed guidelines before publication.

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Section 2: SGLT-2 inhibition and renal protection in people with CKD in the context of type 2 diabetes mellitus

2.1 BACKGROUND

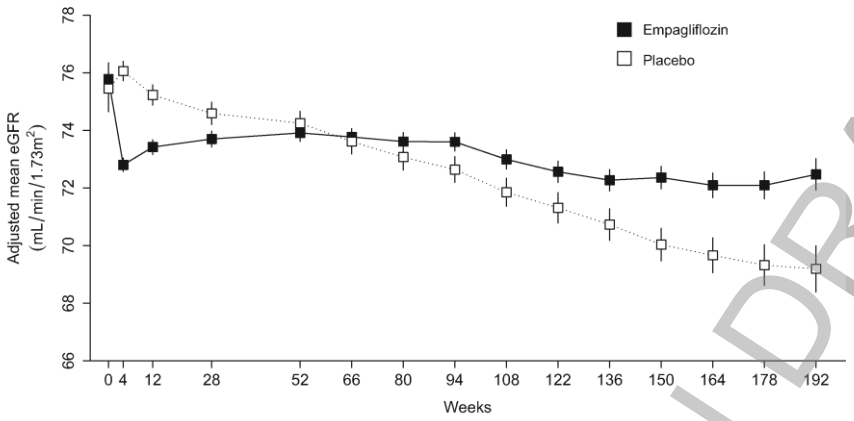
2.1.1 Summary of trial evidence on kidney disease progression

Our 'Recommendations for Use' of SGLT-2 inhibition in chronic kidney disease (CKD) in people with diabetes mellitus (DM) are, wherever possible, evidence-based. They were developed after review of the relevant published randomized trials. Particular emphasis was placed on trial analyses using categorical kidney disease progression outcomes as opposed to analyses using estimated glomerular filtration rate (eGFR) slopes. This is because some of these categorical outcomes have been shown to be valid surrogates for progression to end-stage kidney disease (ESKD) (1, 2) and were the more commonly pre-specified primary or secondary assessments in the SGLT-2 inhibitor trials (see section 1, Table 1.1 for a summary of large SGLT-2 inhibitor trial designs).

ESKD, the key goal of interventions targeting CKD progression, has been variably defined in SGLT-2 inhibitor trials (4-6). ESKD includes starting maintenance dialysis or receipt of a kidney transplant, and is often combined with renal death and a sustained reduction in eGFR below a certain threshold (e.g. <15 or <10 mL/min/1.73m^2). As progression to ESKD often takes longer than a trial's planned follow-up, eGFR-based surrogates of CKD progression have been combined into composite categorical outcomes with ESKD. The following proportional declines in eGFR from the randomization value have been validated for use in CKD progression trials: 40% or 50% declines in eGFR, or a doubling of creatinine (i.e. a 57% decline in eGFR) (2, 3). Such eGFR-based outcomes often require the decline in eGFR to be sustained on a repeat eGFR measurement, aiming to differentiate transient fluctuations in creatinine from true CKD progression. The majority of SGLT-2 inhibitors trials recruiting people with confirmed CKD have combined such kidney disease progression outcomes with cardiovascular death generating a cardiorenal primary composite outcome (see Table 1.1) (4-6). Note that new international initiatives have generated a common nomenclature and set of definitions for kidney disease-based outcomes using the term Kidney Failure (3), but the designing of the SGLT-2 inhibitor trials predates such consensus.

The first clear demonstration of the potential for SGLT-2 inhibitors to modify risk of CKD progression was based on these categorical outcomes and emerged from a sub-analysis of the EMPA-REG OUTCOME trial in a type 2 DM population with prior cardiovascular disease. Initial analyses plotting mean eGFR against time showed a modest reversible reduction in eGFR on initiating SGLT-2 inhibition compared to placebo, followed by a substantial decrease in the subsequent rate of chronic eGFR decline over time (Figure 2.1). The retardation of eGFR decline brought about a 46% reduction in the risk of the categorical composite kidney disease progression outcome of ESKD, renal death and a doubling of serum creatinine (hazard ratio [HR]=0.54, 95% confidence interval [CI] 0.40-0.75) (7). Subsequent trials have confirmed these findings, with information on renoprotection now available from trials conducted in a range of different types of people with several different SGLT-2 inhibitors. These results are summarized below.

Figure 2.1: Effect of allocation to empagliflozin 10 or 25mg versus placebo on CKD-EPI eGFR by time in EMPA-REG OUTCOME (reproduced from (6))



Number of patients analysed

Empagliflozin	4644	4533	4451	4318	4225	4018	4131	3710	3103	2654	2387	2087	1623	1037
Placebo	2323	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448

Pre−specified mixed model repeated measures analysis in patients treated with at least one dose of study drug who had a baseline and post−baseline measurement.

Kidney disease progression results from CREDENCE & DAPA-CKD

The key large trials designed to definitively test the effect of an SGLT-2 inhibitor versus placebo on CKD progression conducted in CKD populations are CREDENCE, DAPA-CKD and the ongoing EMPA-KIDNEY trial (4-6). Their key design features are summarized in Table 1.4 (in Section 1).

CREDENCE recruited people with type 2 DM with the following renal inclusion criteria: eGFR 30-90 mL/min/1.73m^2 plus a urinary albumin:creatinine ratio (uACR) of 300-5000 mg/g [UK units: 34-566 mg/mmol]. Participation required treatment with an angiotensin-converting–enzyme inhibitor (ACEi) or angiotensin-II receptor blocker (ARB) for ≥4 weeks at either the maximum labelled dose or a dose not associated with unacceptable side effects. Combined use of ACEi with ARB, or with a direct renin inhibitor, or with a mineralocorticoid-receptor antagonist (MRA) was excluded, as were people with a suspected non-diabetic cause of kidney disease.

DAPA-CKD recruited people with and without type 2 DM. Renal inclusion criteria were an eGFR 25-75 mL/min/1.73m^2 plus a uACR 200-5000 mg/g [23-566 mg/mmol] in patients who had received a stable dose of an ACEi or ARB for ≥4 weeks. Key exclusion criteria were polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, and immunotherapy for primary or secondary kidney disease within 6 months before enrolment (8).

At the time of writing, the EMPA-KIDNEY trial has completed recruitment and participants are in follow-up. People with CKD with and without DM are eligible, including people without albuminuria. Renal inclusion criteria are an eGFR 20-45 mL/min/1.73m² or an eGFR ≥45 <90 mL/min/1.73m^2 plus uACR ≥200 mg/g (≥23 mg/mmol, or protein:creatinine ratio ≥300 mg/g [≥34 mg/mmol]). Those on intravenous immunosuppression therapy in last 3 months or anyone currently on >45 mg prednisolone daily (or equivalent) are excluded, as are people with polycystic kidney disease. Note that all these large CKD trials of SGLT-2 inhibitors have excluded people with a history of kidney transplantation (see section 7b for the guideline group's considerations for use in people with a functioning kidney transplant).

A summary of the key characteristics of the populations with type 2 DM from CREDENCE and DAPA-CKD are provided in Table 2.1.

Table 2.1: Renal characteristics of people with DM in CREDENCE (4) and DAPA-CKD (8)

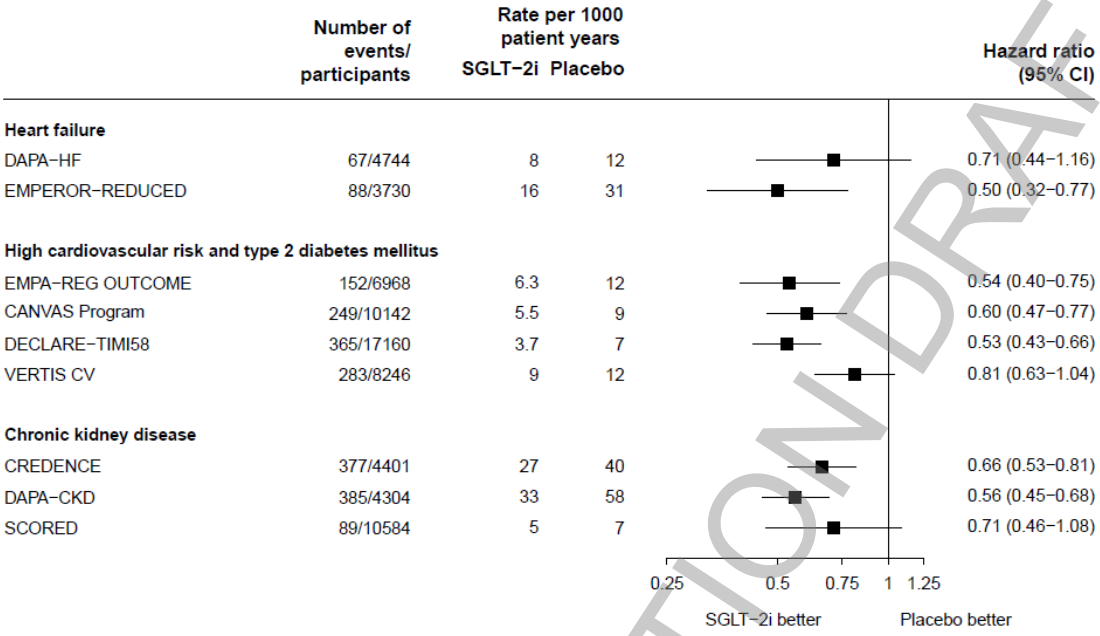
		CREDENCE	DAPA-CKD (DM only)
		n=4401	**n=2906**
eGFR, mL/min/1.73m^2	**Mean (SD)**	**56 (18)**	**44 (13)**
≥60		1809 (41%)	348 (12%)
45-59		1279 (29%)	918 (32%)
30-45		1313 (30%)	1239 (43%)
<30		-	401 (14%)
Albuminuria (uACR cut-off)	**Median (Q1-Q3)**	**927 (463-1833)**	**1017 (~475-1900)**
Normoalbuminuria (<30mg/g)		31 (1%)	1 (0%)
Microalbuminuria (30-300 mg/g)		496 (11%)	307 (11%)
Macroalbuminuria (>300 mg/g)		3874 (88%)	2597 (89%)

Data are n (%), or mean (standard deviation) or median (Q1-Q3) where stated. DM=diabetes mellitus; uACR=urinary albumin:creatinine ratio.

CREDENCE was stopped early for efficacy by the independent data monitoring committee. Canagliflozin reduced the risk of the primary cardiorenal composite outcome (a sustained doubling of creatinine, ESKD, or death from renal or cardiovascular causes) by 30% compared to placebo (245/2202 vs 340/2199: HR=0.70, 95%CI 0.59-0.82). Importantly, there were reductions in the risk of kidney disease progression, including ESKD (see Figure 2.2). Risk of receipt of maintenance dialysis, kidney transplantation or a renal death was significantly reduced by 28% (4). These benefits were unmodified by baseline level of eGFR and glycosylated haemoglobin (HbA1c).

DAPA-CKD was also stopped early due to efficacy, with dapagliflozin reducing its primary cardiorenal composite outcome (a sustained 50% decline in eGFR, ESKD, or death from renal or cardiovascular causes) by 39% compared to placebo (197/2152 vs 312/2152: HR=0.61, 95%CI 0.51-0.72). Importantly, these relative risks were again apparent for the kidney disease progression component of the primary composite (see Figure 2.2), and ESKD. They were also similar when analyses were performed separately in people with and without type 2 DM, and in pre-specified subgroups defined by eGFR and uACR (5). There was also a clear reduction in risk of kidney disease progression, with fewer initiations of maintenance dialysis overall and among those with DM considered in isolation. DAPA-CKD therefore reinforced the findings on albuminuric diabetic kidney disease from CREDENCE (4).

Figure 2.2: Effects of SGLT-2 inhibitors on kidney disease progression by population and trial (4, 5, 9-16) (adapted from (17))



Kidney Disease Progression was generally defined as death from renal causes, commencement of renal replacement therapy, or a % decline in eGFR/doubling of creatinine from baseline. The following trials used a 40% decline in eGFR: EMPEROR−REDUCED, CANVAS Program, DECLARE−TIMI58. The following trials used a 50% decline in eGFR: DAPA−HF, DAPA−CKD, SCORED. The following trials used a doubling of creatinine: EMPA−REG OUTCOME, VERTIS CV, CREDENCE. Results for kidney disease progression unavailable for SOLOIST−WHF. EMPA−REG OUTCOME population restricted to those that received at least one dose of study treatment.

More complete details on the potential for SGLT-2 inhibitors to modify risk of kidney disease progression in people with albuminuric CKD without DM are provided in section 3. DAPA-CKD results among people without DM are relevant to section 2 of this guideline, however, as there were only 28 kidney disease progression outcomes in people with type 2 DM and a non-diabetic primary renal diagnosis in DAPA-CKD, this is too few to assess effects directly in this specific subgroup of interest (5, 18). We therefore need to consider the data in those without DM alongside the data in people with DM. The key observations were that the relative risk reductions on the DAPA-CKD primary outcome were similar in size in people with and without DM, despite the absence of ambient hyperglycaemia and reduced levels of glycosuria in people without DM (18). Subsequent analyses dividing all DAPA-CKD participants into those with diabetic nephropathy, ischaemic or hypertensive disease, glomerulonephritis, or other/unknown categories also found no evidence that relative risk reductions on the pre-specified primary cardiorenal outcome, or on the kidney disease progression component of this composite, differed by primary renal diagnosis (18).

Kidney disease progression results from the other trials including mainly people without albuminuria

Establishing if albuminuria is a pre-requisite for renal benefits of SGLT-2 inhibition is an important clinical question to address, as perhaps as many as three-quarters of those with advanced CKD do not have albuminuria. Furthermore, if mechanistic theories about SGLT-2 inhibitors targeting intraglomerular hypertension are correct, it might be hypothesized that renal benefits may be attenuated in the absence of albuminuria.

People without albuminuria were excluded from CREDENCE and DAPA-CKD (4, 5). The SCORED trial recruited people with type 2 DM and an eGFR between 25 and 60

mL/min/1.73m^2 irrespective of level of albuminuria. SCORED was stopped after a median of 16 months' follow-up due to withdrawn funding and concerns about potential effects of the COVID-19 pandemic. The point estimates of effect on kidney disease progression outcome from SCORED were consistent with the results from CREDENCE and DAPA-CKD, but there was an insufficient number of outcomes to provide conclusive evidence (Figure 2.2) (16). Hypothesis-generating analyses from meta-analysis of the completed SGLT-2 inhibitor trials in type 2 DM at high cardiovascular risk suggest renal benefits extend to people without albuminuria (19). eGFR slope-based analyses from EMPEROR-REDUCED and DAPA-HF suggest the renoprotection afforded by SGLT-2 inhibition may also extend to people with heart failure (10, 20, 21). However, there are insufficient data on ESKD in all these trials to assess effects in non-albuminuric CKD definitively. The ongoing EMPA-KIDNEY trial will provide important information in this subgroup (6).

Co-prescription with mineralocorticoid receptor antagonism

There is likely to be increasing use of MRA in CKD populations due to recent positive results from FIDELIO-DKD and guideline recommendations. FIDELIO-DKD demonstrated the efficacy of finerenone compared to placebo at reducing risk of kidney progression in people with albuminuric diabetic kidney disease and type 2 DM (22). A European Society of Cardiology position paper has recommended early use of SGLT-2 inhibition in patients with heart failure with reduced ejection fraction (HFrEF) in addition to class IA recommended medications (i.e. beta-blockers, ACEi/ARBs and MRAs) (23), and a draft KDIGO guideline highlights MRA's effectiveness in the management of refractory hypertension.

Information on MRA use in the SGLT-2 inhibitor trials is generally reliant on data from the trials conducted in non-CKD populations as CREDENCE excluded use of MRA (4) and only 229 (5.3%) of DAPA-CKD participants were co-prescribed an MRA (8). Univariable subgroup analyses by baseline MRA co-prescription from several of the non-CKD trials have found that MRA use did not modify the key findings from these trials (11, 15, 16, 24-26).

Hyperkalaemia may result from use of MRA, but combining SGLT-2 inhibition with Renin-Angiotensin-System (RAS) blockade does not have the same potential as dual RAS blockade to cause hyperkalaemia (4, 5, 27, 28). This also appears true in people co-prescribed MRA in the HFrEF trials of SGLT-2 inhibitors (25, 26). A hypothesis that SGLT-2 inhibitors may even reduce the risk of severe hyperkalaemia among MRA users has also been raised by DAPA-HF data (26), but this was not confirmed in EMPEROR-REDUCED data (although allocation to empagliflozin led to fewer discontinuations of MRA (25)).

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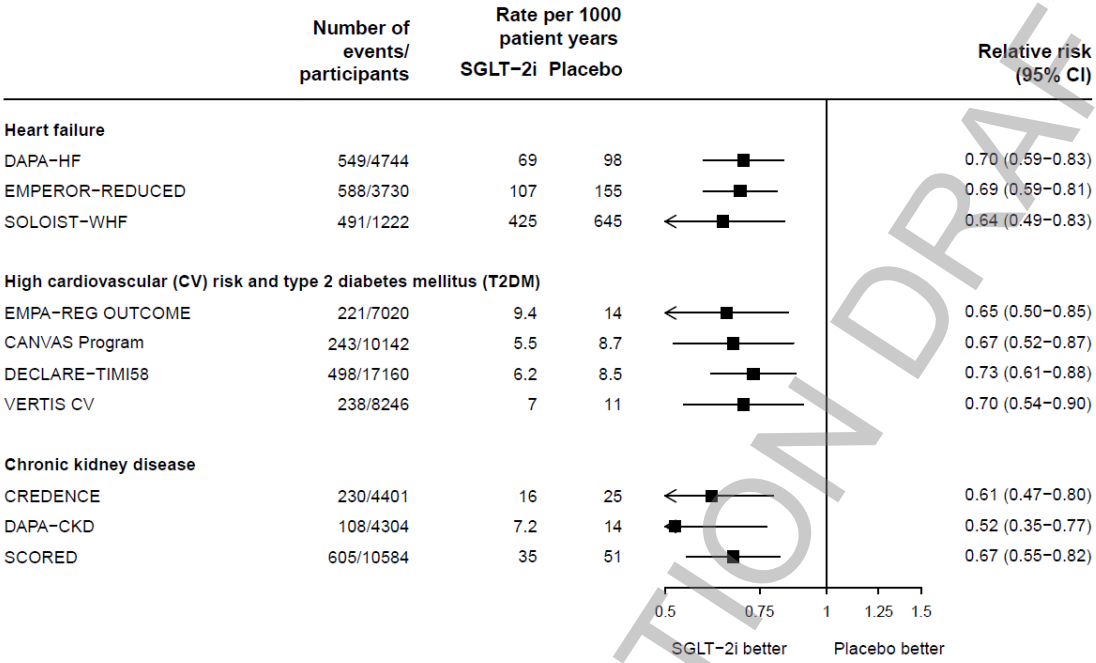
2.1.2 Summary of trial evidence on cardiovascular risk

Heart failure

The EMPA-REG OUTCOME trial provided the initial clinical evidence that SGLT-2 inhibition reduces hospitalisation due to heart failure. Compared to placebo, empagliflozin reduced the risk of heart failure hospitalisation by 35% (HR=0.65, 95%CI 0.50-0.85) (12). Subsequent trials in populations with type 2 DM which studied those at risk of atherosclerotic cardiovascular disease (DECLARE-TIMI 58 & the CANVAS Program) confirmed these findings (13, 14, 29). Among people with CKD, the relative benefits of SGLT-2 inhibitors on hospitalisation for heart failure in CREDENCE, DAPA-CKD, and SCORED were similar to aggregated results from the trials recruiting people at high cardiovascular risk with type 2 DM, despite substantial attenuation of glycosuria at lower levels of eGFR (4, 5, 16, 20, 21, 29-31) (Figure 2.3).

Figure 2.3: Effects of SGLT-2 inhibitors on hospitalisation for heart failure by population and trial (4, 5, 9-16)



Results are based on time to first event analyses and exclude urgent visits for heart failure, wherever possible. Event rates estimated from number of events and follow−up duration for SCORED.

DAPA-HF was the first of the large SGLT-2 inhibitor trials conducted in people with stable HFrEF to report. Compared to placebo, dapagliflozin reduced the risk of the primary composite outcome of cardiovascular death, heart failure hospitalisation or an urgent heart failure visit requiring intravenous therapy by 26% (HR=0.74, 95%CI 0.65-0.85) (9). There was direct evidence of benefit in people with and without type 2 DM, and among those with ischaemic and non-ischaemic heart failure aetiologies (9). The EMPEROR-REDUCED trial subsequently reinforced the findings of DAPA-HF with empagliflozin reducing risk of the primary composite outcome of cardiovascular death and heart failure hospitalisation by 25% (HR=0.75, 95%CI 0.65-0.86) (10). These trials recruited to eGFRs lower limits of 30 and 20 mL/min/1.73m^2, respectively, with sub-analyses suggesting cardiac benefits are unmodified at low eGFR (20, 21).

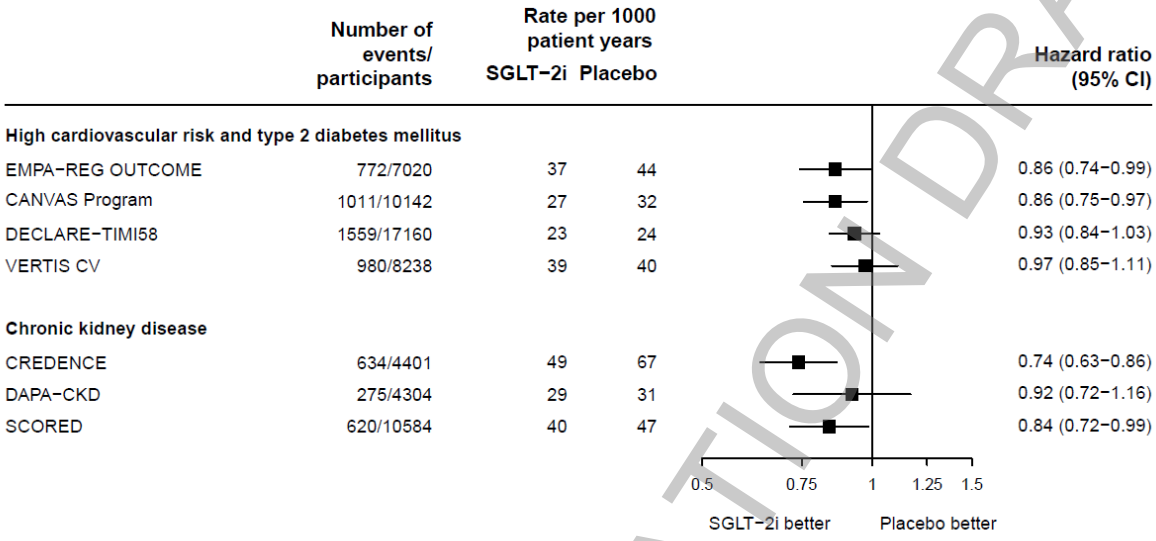
SOLOIST-WHF tested the dual SGLT-1/-2 inhibitor sotagliflozin in people with recent hospitalisation for worsening heart failure. Sotagliflozin reduced the risk of the trial's revised primary composite of cardiovascular death or total hospitalisations/urgent visits for heart failure by 33% (HR=0.67, 95%CI 0.52-0.85). Benefits were observed irrespective of ejection fraction at recruitment, including those with an ejection fraction ≥50% (11). This is an important result as heart failure in CKD is common and often structural heart disease with preserved ejection fraction (32). At the time of writing, trials assessing the effects of SGLT-2 inhibitors in people with heart failure with preserved ejection fraction (HFpEF) are ongoing: the details of the DELIVER and EMPEROR-PRESERVED trials are discussed in a dedicated Section 7c (33, 34).

Atherosclerotic cardiovascular disease

For major atherosclerotic/adverse cardiovascular events (MACE), meta-analysis of the key cardiovascular safety trials performed in people with type 2 DM show SGLT-2 inhibitors affords approximately a 10% relative risk reduction compared to placebo (29). Results for the MACE outcome from CREDENCE, DAPA-CKD and SCORED are also consistent with a similar sized

relative risk reduction (4, 5, 16), suggesting that the size of relative benefits on MACE are equivalent in people with CKD (Figure 2.4). Benefits on MACE result primarily from reduced risk of cardiovascular death and myocardial infarction with no clear effect on stroke (29).

Figure 2.4: Effects of SGLT-2 inhibitors on MACE by population and trial (4, 5, 7, 12-16) (adapted from (17))



Major atherosclerotic cardiovascular events (MACE) is a composite outcome including cardiovascular death, myocardial infarction or stroke. MACE results from heart failure population trials are unavailable. Rate of MACE was calculated from number of events and other information for SCORED. The following trials also included unstable angina in the composite: EMPA−REG OUTCOME & CREDENCE. VERTIS CV used a non−inferiority population.

Following the publication of DECLARE-TIMI 58 results (14), it was hypothesized that relative reductions in MACE risk might be larger among people with prior atherosclerotic cardiovascular disease than individuals without (35). However, with the availability of more data from subsequent trials, the evidence of any effect modification by pre-existing disease is less convincing (29). Nevertheless, given the larger relative risk reductions for heart failure than MACE, it is plausible that any cardiovascular deaths which include chronic heart failure in the train of morbid events leading to death may be more likely to be prevented by SGLT-2 inhibition than deaths which are purely atherothrombotic in origin.

2.1.3 Summary of trial evidence on glucose-lowering effects

Two pooled analyses have evaluated the effects of SGLT-2 inhibitors on HbA1c by baseline eGFR (30, 36). Both sets of analyses indicate that at lower eGFRs, the effect of SGLT-2 inhibition on HbA1c are diminished, with no good evidence for a clinically meaningful reduction in HbA1c at eGFRs <30 mL/min/1.73m^2. Despite this, there are still beneficial effects of SGLT-2 inhibition on blood pressure, weight and albuminuria at low eGFR. Table 2.2 also highlights several smaller randomized trials (37-41) which have reported similar findings with respect to HbA1c and eGFR, mirroring pharmacodynamics studies showing the linear reduction in measured urinary glucose excretion as eGFR falls (42). Analogous data exists from a trial in post-transplant DM, in which reductions in HbA1c were substantially attenuated, and arguably not clinically meaningful, in those with an eGFR <45 mL/min/1.73m^2 (43) (see Section 7b for more details). Section 5 of this guideline provides more detail on management of hypoglycaemic agents in people initiating SGLT-2 inhibition, and on the risks of hypoglycaemia.

Table 2.2: Randomized trial results assessing the effect of SGLT-2 inhibitors on %HbA1c reductions by level of kidney function (30, 36-41)

POOLED ANALYSES				
Author, year (no. of trials)	**SGLT-2 inhibitor**	**Duration**	**eGFR range, mL/min/1.73m^2**	**Change in %HbA1c compared to placebo (95% CI or SE)**
Cherney et al., 2017 n=2286, 11 trials	Empagliflozin	24 weeks	≥90 ≥60 to <90 ≥30 to <60 <30	-0.84% (-0.95, -0.72) -0.60% (-0.70, 0.51) -0.38% (-0.52, -0.24) -0.04% (-0.37, -0.29)
Petrikyv et al., 2017 n=4404, 11 trials	Dapagliflozin	24 weeks	≥90 ≥60 to <90 ≥45 to <60	-0.57% (-0.66, -0.47) -0.47% (-0.54, -0.40) -0.27% (-0.43, -0.11)
TRIALS				
Author, year (no. of participants)				
Allegretti et al., 2019 (n=312)	Bexagliflozin	24 weeks	45 to <60 30 to <45	-0.31% (-0.09, -0.53) -0.43% (-0.16, -0.69)
Barnett et al., 2014 n=290	Empagliflozin	24 weeks	≥60 to <90 ≥30 to <60 15 to <30	-0.68% (-0.88, -0.49) -0.42% (-0.56, -0.28) No reduction
Fioretto et al., 2014 n=321	Dapagliflozin	24 weeks	45 to <60	-0.34% (-0.53, -0.15)
Kohan et al., 2014 n=252	Empagliflozin	24 weeks	All: <60 ≥45 to <60 ≥30 to <45	-0.32% (SE 0.17) -0.33 (SE 0.24) 0.07 (SE 0.21)
Yale et al., 2014 n=269	Canagliflozin	52 weeks	≥30 to <50	-0.41% (-0.68, -0.142)

eGFR= estimated glomerular filtration rate; HbA1c= glycosylated haemoglobin; CI=confidence interval; SE=standard error

ABCD/RA Clinical Practice Guidelines for Management of Hyperglycaemia in Adults with Diabetic Kidney Disease: 2021 Update

This SGLT-2 inhibitor guideline does not consider glycaemic targets, as the cardiac and renal benefits of SGLT-2 inhibition appear, for the most part, to be preserved in those with CKD, at least to an eGFR >30 mL/min/1.73m^2 (4, 5). This is despite their attenuated effect on blood glucose lowering in CKD (30). Nevertheless, we recognize that the care of people with diabetic kidney disease is often shared between renal and DM clinical teams, as highlighted by the recently updated joint ABCD/RA guideline: Clinical Practice Guidelines for Management of Hyperglycaemia in Adults with Diabetic Kidney Disease (44). Instead, we provide a brief summary of the joint ABCD/RA's considerations and recommendations in the text and Table 2.3 below.

The ABCD-RA guideline group recognized that early intensive diabetic management leads to reduction in risk of subsequent diabetic kidney disease. A meta-analysis of randomized trials has demonstrated that more intensive glycaemic control reduces the risk of a composite renal outcome of ESKD, renal death, decline in eGFR to <30 ml/min/1.73m^2 or development of macroalbuminuria, by about 20% compared to more standard control (HR=0.80, 95%CI 0.72-0.88) (45). About two-thirds this result constituted the albuminuria-based component of the composite, with more limited information available for the eGFR and ESKD-based components. This contrasts the quality of information available in CREDENCE and DAPA-CKD which had larger numbers of eGFR-based and ESKD outcomes and larger relative risk reductions than the intensive glycaemic control trials (4, 5).

The ABCD-RA group highlighted that there are challenges with respect to increased risk of hypoglycaemia (both treatment and renal-related) and reliability of HbA1c monitoring required to achieve intensive glycaemic control in people with moderate-to-advanced CKD. They therefore provide glycaemic targets stratified by age, CKD stage and diabetic therapy to try and safely achieve tight glycaemic control targets in people with diabetic kidney disease.

Table 2.3: Summary of the glycaemic recommendations for patients with type 2 DM and CKD adapted from the ABCD-RA clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease: 2021 update (44)

Glycaemic target mmol/mol (%HbA1c)	CKD stage	Age & anti-diabetic regimen
Glycaemic targets should be individualised		
48-58 mmol/mol (6.5-7.5%) Aim <52 mmol/mol (6.9%)	1-2	- <40 years - Any age, if diet controlled*
52-58 mmol/mol (6.9-7.5%)	3-4	- Any age treated with a predominately oral hypoglycaemic regimen (i.e. non-insulin dominant)
58-68 mmol/mol (7.5-8.5%)	3-4	- Any age on an insulin-dominant regimen (aim 58 mmol/mol). - Age >75 years with stage 4 CKD on any regimen
58-68 mmol/mol (7.5-8.5%)	5, including dialysis	- Any age or any regimen

* Aim for HbA1c 58 mmol/mol if hypoglycaemia and/or anaemia occurs, and consider blood glucose or flash glucose monitoring. CKD= chronic kidney disease.

2.1.4 Quality of the evidence

For the large SGLT-2 inhibitor trials providing the majority of evidence underpinning our guidance, risk of bias is low, as assessed using the Cochrane Risk of Bias 2 (ROB2) tool. All trials employed strong randomization and blinding procedures, and compared efficacy to matching placebo. Intention-to-treat analyses were used (with modifications where appropriate for safety outcomes), and clearly-defined testing processes for secondary outcomes were used, minimising the risk of bias in all assessed domains.

Although risk of bias was low across assessed ROB2 domains for included trials, potential small sources of bias remain. Both CREDENCE and DAPA-CKD were terminated early, which may lead to over-estimation of the relative treatment effects. However, point estimates for the kidney disease progression outcomes from the other completed trials of SGLT-2 inhibitors are broadly consistent with those identified in DAPA-CKD and CREDENCE. The two sotagliflozin trials (SCORED and SOLOIST-WHF) underwent modification of their primary assessments prior to unblinding. Due to withdrawal of funding, both trials were also unable to complete endpoint adjudication, instead relying on investigator-reported events. In SOLOIST-WHF, 73% of events that were sent for adjudication matched the events reported by investigators (balanced between trial arms).

2.1.5 Summary of published cost-effectiveness analyses

We identified a single UK-specific cost-effectiveness analysis of SGLT-2 inhibition in CKD. The CREDEM-CKD group estimated UK-specific cost-effectiveness in diabetic kidney disease based on extrapolations from CREDENCE data (46). In their primary analysis, a gain of 0.28

quality-adjusted life years (QALYs) per individual treated with canagliflozin for 10 years was found. This benefit was determined primarily by longer survival in the canagliflozin arm and reduced progression through CKD stages. Cost-effectiveness was driven, in large part, by reduced need for dialysis. Canagliflozin was associated with overall cost savings of £4706 per individual over the course of 10 years compared to placebo. Savings on reductions in cardiovascular risk were largely offset by greater costs due to longer survival. At the time of writing, no equivalent peer-review published cost-effectiveness analyses from the DAPA-CKD or SCORED trials exists.

Economic assessments of the cost-effectiveness of dapagliflozin in people with type 2 DM at high atherosclerotic cardiovascular risk based on the DECLARE-TIMI 58 trial have been published. These analyses used extrapolative kidney disease progression models derived from eGFR slope data similar to the CREDEM-CKD approach. They found dapagliflozin to be dominant over standard of care and associated with an increase in QALYs for lower cost. As with CREDEM-DKD, both the increase in QALYs and the reduction in costs were primarily driven by renal benefits (47).

2.2 RECOMMENDATIONS FOR USE

1. In people <u>with</u> type 2 DM and an eGFR ≥25 mL/min/1.73m^2, we recommend initiating SGLT-2 inhibition* in those with:

(a) uACR of ≥25 mg/mmol attributed to diabetic nephropathy (Grade 1A)

(b) Established coronary disease, prior heart failure hospitalisation, or known symptomatic reduced ejection fraction heart failure[§] (Grade 1A)

Rationale: The CREDENCE and DAPA-CKD trials show that SGLT-2 inhibition can importantly reduce risk of progression of CKD in people with albuminuric diabetic nephropathy with relative risk reductions appearing similar across the range of eGFRs studied. CREDENCE's renal inclusion criteria were an eGFR 30-90 mL/min/1.73m^2 plus albuminuria of 34-566 mg/mmol. DAPA-CKD extended into slightly lower ranges of eGFR and albuminuria (inclusion criteria: eGFR 25-75 mL/min/1.73m^2 and uACR 23-566 mg/mmol), with 10% of participants having a uACR <34 mg/mmol at recruitment. We therefore provide a grade 1A recommendation for use of SGLT-2 inhibition among people with type 2 DM using lower cut-offs of ≥25 mL/min/1.73m^2 for eGFR and ≥25 mg/mmol for uACR.

SGLT-2 inhibition has been demonstrated to reduce risk of heart failure hospitalisation in people with stable established HFrEF in DAPA-HF and EMPEROR-REDUCED, and in people recently hospitalised for heart failure irrespective of ejection fraction in SOLOIST-WHF. These trials recruited participants with lower limits of GFR of between 20-30 mL/min/1.73m^2, with cardiac benefits appearing to be unmodified by low eGFR. Furthermore, secondary assessments in CREDENCE, DAPA-CKD and the SCORED trials report important reductions in risk of hospitalisation for heart failure in people with type 2 DM and CKD. We therefore provide a grade 1A recommendation for use of SGLT-2 inhibition in people with type 2 DM with certain types of heart failure using the same lower eGFR cut-off of 25 mL/min/1.73m^2. Those with prior coronary disease are at high risk of MACE and heart failure and are included in this recommendation based on the totality of the evidence (see Figure 2.4).

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2. In people <u>with</u> type 2 DM and an eGFR ≥25 mL/min/1.73m^2:

(a) We suggest initiating SGLT-2 inhibition* in those with a uACR of ≥25 mg/mmol attributable to a non-diabetic cause[†‡] (Grade 2B)

(b) We suggest initiating SGLT-2 inhibition* to modify cardiovascular risk in those with an eGFR 25-60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognizing effects on glycaemic control will be limited (Grade 2B)

Rationale: Analysis of DAPA-CKD by DM status suggests benefits on CKD progression are afforded to people with albuminuric CKD attributed to non-diabetic causes. It should be noted that the following types of non-diabetic kidney disease were excluded from DAPA-CKD: people with polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, and those receiving immunological therapy for renal disease in the last 6 months. This suggestion for use therefore does not extend to such people.

Although it remains uncertain whether albuminuria is a pre-requisite for important renal benefits of SGLT-2 inhibition, benefits on heart failure hospitalisation and MACE have been demonstrated in a range of populations at risk, including trials recruiting people with CKD without albuminuria. Therefore, although SGLT-2 inhibitors are not expected to provide important reductions in blood glucose in the presence of CKD and renal benefits are uncertain, we offer a grade 2B Suggestion for Use to modify risk of heart failure, myocardial infarction or

cardiovascular death in those with CKD without albuminuria. Note that the other Recommendations for Use above provide a grade 1A recommendation in people with type 2 DM irrespective of level of albuminuria for any of the following conditions: established coronary disease, prior heart failure hospitalisation, or known symptomatic HFrEF. Use in patients without such conditions should be based on sufficient cardiovascular risk (as per treating clinician's assessment).

Section 2: Recommendations for Use Footnote

All recommendations in sections 2 & 3 exclude people with type 1 DM (see section 7a) and exclude those with a kidney transplant (see section 7b).

**** See section 4 for summary of indications/licenced uses***
§ Left ventricular ejection fraction of ≤40%
† Randomization into a trial may also be appropriate to address clinical uncertainty (see Recommendations for Research)
‡ DAPA-CKD provides the key clinical evidence and excluded people with a kidney transplant, polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, and those receiving immunological therapy for renal disease in the last 6 months.

2.3 CLINICAL RESEARCH RECOMMENDATIONS

We recommend further research including, wherever possible, randomized trials to establish definitively:

1. Whether the cardiovascular and renal benefits of SGLT-2 inhibition extend to those who have an eGFR <25 mL/min/1.73m^2

2. Whether the renal benefits of SGLT-2 inhibition extend to people with lesser degrees of albuminuria (i.e. <25 mg/mmol)

3. The effects of SGLT-2 inhibition on cardiac and renal outcomes in people with less well-studied non-diabetic causes of kidney disease (i.e. those excluded or with low numbers of efficacy outcomes in trials)

4. Safety, cardiovascular and renal effects of SGLT-2 inhibition on kidney outcomes in people with a functioning kidney transplant (see Section 7b)

5. Pharmacokinetics, cardiovascular effects and residual renal function preservation effects of SGLT-2 inhibition in people on dialysis

6. Whether the cardiovascular benefits of SGLT-2 inhibition in people with CKD extend specifically to people with heart failure with preserved ejection fraction, and whether their use in acute decompensated heart failure is safe and beneficial

7. The safety and efficacy of adding MRA to SGLT-2 inhibition in people with CKD

8. The safety and efficacy of combining SGLT-2 inhibition with a glucagon-like peptide-1 (GLP-1) receptor agonists in people with CKD

2.4 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend using SGLT-2 inhibitors with demonstrated efficacy for their given indications* (Grade 1A)

Rationale: Government regulators review data from randomized trials and assess their reliability through regulatory inspections. Regulatory licences/indications therefore provide a key guide to which SGLT-2 inhibitors have generated definitive evidence of efficacy and safety for a given use. We therefore recommend selecting SGLT-2 inhibitors according to these licenced indications, wherever possible (summaries of which are provided in section 4).

2. We recommend using clinically appropriate single agent renin-angiotensin system (RAS) blockade in combination with SGLT-2 inhibition (Grade 1A), wherever RAS blockade is indicated and tolerated

Rationale: These clinical practice guidelines pertain to use of SGLT-2 inhibition in people with CKD. The standard of care in many forms of CKD is the use of RAS blockers (48, 49), with clear evidence of benefit in diabetic nephropathy (50-53). All CREDENCE participants were on stable maximally tolerated RAS blockade (4), as were 97% of DAPA-CKD participants (8). We therefore provide a grade 1A recommendation to prescribe RAS blockade and ensure clinically appropriate dosing alongside any SGLT-2 inhibitor use. Note that it has been suggested that, mechanistically, SGLT-2 inhibition may have the potential to activate RAS (54). However the large trials in people with type 2 DM at high atherosclerotic cardiovascular risk have been combined in meta-analysis and have raised a hypothesis that the benefits of SGLT-2 inhibitors on kidney disease progression could extend to in people with type 2 DM not on RAS blockade (19) (but were unable to provide definitive confirmation).

Note that we recommend single agent RAS blockade, as combination therapy (i.e. dual blockade with ACEi plus ARB) has been found to increase the risk of serious hyperkalaemia or acute kidney injury, and has not been shown to importantly slow CKD progression (27).

3. We suggest following NICE guidelines on screening for albuminuria (NICE CG182): a single uACR of ≥70 mg/mmol or a confirmed measurement between 25-69 mg/mmol fulfil recommendations for use of SGLT-2 inhibition based on albuminuria (Grade 2C)

Rationale: Many factors can cause transient increases in albuminuria (including urinary tract infection, exercise, and menstruation) and as such, NICE (55) and other international guideline groups (56) recommend that repeat testing should take place within 3 months if a single uACR result is between 25-69 mg/mmol. An early morning sample offers some advantages due to reduced impact of hydration status and exercise (57), but if unavailable, random sampling may still offer a reliable indication of total daily albuminuria (58). A uACR value ≥70 mg/mmol generally does not require further confirmation, as this is consistent with clinically significant proteinuria (59).

4. We suggest using uACR to assess for sufficient proteinuria to guide SGLT-2 inhibitor use: reagent strips and protein:creatinine ratio should not be used (Grade 2C, NICE CG182)

Rationale: We agree with the statement within the NICE CKD guidelines that reagent strips and PCR measurements should not be used to quantify albuminuria (55). Large-scale meta-analysis and other observational data have shown that dipstick values using reagent strips are neither sensitive, nor specific enough to predict uACR accurately (60).

5. We suggest that when used to slow kidney disease progression or heart failure risk, SGLT-2 inhibition can be continued until the need for dialysis or kidney transplantation arises (Grade 2B)

Rationale: CREDENCE and DAPA-CKD show SGLT-2 inhibition is safe in their recruited populations and SGLT-2 inhibitors were shown to prevent the need for dialysis or kidney transplantation. The cardiorenal benefits identified in their primary outcomes are not modified by baseline eGFR at recruitment, and so it would be reasonable to expect some ongoing benefit in CKD stage 5 not requiring renal replacement therapy.

6. We suggest that co-prescription of SGLT-2 inhibition with MRA can be considered, where each are individually indicated (Grade 2B)

Rationale: Subgroup analyses from the SGLT-2 inhibitor trials in non-CKD populations suggest cardiac and renal benefits are likely to be maintained in people co-prescribed an MRA with an SGLT-2 inhibitor, with no increased risk of hyperkalaemia caused by SGLT-2 inhibitor use. CREDENCE and DAPA-CKD provide reassuring evidence that SGLT-2 inhibition does not usually cause hyperkalaemia in CKD populations. We therefore provide a grade 2B suggestion that MRA can be used with SGLT-2 inhibitors. Note that guidance on how to monitor for changes in eGFR and potassium in those on MRA are outside of the scope of this guideline.

7. We suggest the beneficial effects of SGLT-2 inhibition on renal outcomes in people with type 2 DM are likely to be a class effect, but there is insufficient data in people without DM to be conclusive (Grade 2B)

8. We suggest the beneficial effects of SGLT-2 inhibition on heart failure hospitalisation in people with reduced ejection fraction heart failure[§] are likely to be a class effect, irrespective of the presence or absence of DM (Grade 2B)

Rationale for 7 & 8: We have recommended using SGLT-2 inhibitors with demonstrated efficacy for their given indications, but as more large trials report results testing the available SGLT-2 inhibitors in overlapping populations, it is increasingly apparent that any differences between the individual molecules do not appear to create large differences in clinical efficacy. For example, CREDENCE (canagliflozin) and DAPA-CKD (dapagliflozin) reported relative risk reductions on their respective kidney disease progression outcomes and on hospitalisation for heart failure which were comparable in their respective (sub)populations with type 2 DM (4, 5, 18). Likewise, DAPA-HF (dapagliflozin) and EMPEROR-REDUCED (empagliflozin) share a similar design and results of primary and secondary assessments overall and across subgroups are remarkably consistent (61). Relative risk reductions on MACE across key cardiovascular safety trials (29) and trials in dedicated CKD populations are also not statistically different from each other (5, 16) (see Figures 2.2 to 2.4). We therefore suggest there is increasing evidence that the cardiac and renal benefits of SGLT-2 inhibition represent a class effect.

It should be noted that SGLT-2 inhibitors differ in their respective receptor selectivity and there may be an increased propensity to cause diarrhoea and volume depletion when using SGLT-2 inhibitors that also meaningfully inhibit gut SGLT-1 (e.g. sotagloflozin (11)). Selectivity for SGLT-2 over SGLT-1 ranges from: ~20:1 for the dual SGLT-1/2 inhibitor sotagliflozin (62), and from ~250:1 for canagliflozin to ~2500:1 for empagliflozin (63) for the selective SGLT-2 inhibitors.

2.5 AUDIT MEASURES

We propose the following audit measures focusing on those guidelines supported by robust randomized evidence:

1. The proportion of people with each grade 1 recommendation for use prescribed an SGLT-2 inhibitor (with exploration of reasons for non-use to direct quality improvement projects)

2. The proportion of people prescribed an SGLT-2 inhibitor not on concomitant RAS blockade

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Section 3: SGLT-2 inhibition and renal protection in people with CKD without diabetes mellitus

3.1 BACKGROUND

3.1.1 Summary of trial evidence on kidney disease progression

The large-scale placebo-controlled trials of SGLT-2 inhibitors have not been powered to assess effects on kidney disease progression in people without diabetes mellitus (DM) considered in isolation (see Table 1.1 in Section 1a). Information on the efficacy and safety of SGLT-2 inhibitors in people without DM is currently reliant on subgroup analyses, with the main source of data in people with chronic kidney disease (CKD) provided by DAPA-CKD (1). Consequently, the evidence to support our "Recommendations for Use" in people with CKD without DM is more limited compared to that used to justify our guidance in those with DM (see Section 2).

Interpretation of subgroup analyses mandates additional considerations due to their more limited power compared to any primary assessment, the potential for multiplicity of testing to increase the likelihood of chance findings, and where relevant, their post-hoc nature. One advised approach to address some of these issues is statistical tests for effect modification. These assess whether or not the overall trial result for a given outcome is significantly different in a subgroup, and are often referred to as heterogeneity or interaction tests. In the absence of statistical evidence for heterogeneity, the most reliable quantitative estimate of the relative effect of the test intervention is the overall relative risk, with little weight given to relative risks calculated directly from a subgroup of participants considered in isolation. Despite such approaches, cautious interpretation is still required in underpowered situations. Further examples of considerations on subgroup analyses are provided in this introductory review (2).

In Section 2, our evidence-based 'Recommendations for Use' emphasize, wherever possible, analyses utilising categorical kidney disease progression outcomes. In Section 3, we also include review of analyses using estimated glomerular filtration rate (eGFR) slope methods. In trial populations in which the rate of eGFR decline is slow and follow-up only accrues small numbers of categorical kidney disease progression and end-stage kidney disease (ESKD) outcomes, such approaches may offer a practical surrogate for risk of kidney disease progression (3).

At the time of writing, several large SGLT-2 inhibitor trials which have recruited subgroups without DM are in their follow-up phase, with results expected in 2021/2022 (see Table 1.4 in Section 1) (4-6). The EMPA-KIDNEY trial is of most relevance to CKD, having completed recruitment of 6609 people with CKD with and without DM, including people without albuminuria (6). The reported randomized evidence from people without DM are summarized below and will be updated as more data become available.

Kidney disease progression results from DAPA-CKD

DAPA-CKD recruited people with albuminuric CKD with and without type 2 DM. Renal inclusion criteria were an eGFR 25-75 mL/min/1.73m^2 plus a urinary albumin:creatinine ratio (uACR) of 200-5000 mg/g (23-566 mg/mmol) on a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II receptor blockade (ARB) for ≥4 weeks. Key exclusion criteria were polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody

(ANCA) associated vasculitis, and immunotherapy for primary or secondary renal disease within 6 months before enrolment (7). DAPA-CKD randomized 4304 people to dapagliflozin 10mg versus matching placebo, including 1398 (32%) without DM. Overall, mean eGFR was 43 mL/min/1.73m^2 with ~1 gram per day of albuminuria (median uACR=949 mg/g [197 mg/mmol]) and 97% prescribed an ACEi or ARB. Those without DM had similar levels of eGFR and albuminuria to those with DM, but represented a much wider range of primary renal diagnoses (Table 3.1) (1, 7).

Table 3.1: Renal characteristics of DAPA-CKD participants overall and by DM status (1, 7)

		DM		No DM		All	
Number (%) of participants		2906	(68%)	1398	(32%)	4304	(100%)
eGFR, mL/min/1.73m^2	**Mean (SD)**	**43.8**	**(12.6)**	**41.7**	**(11.7)**	**43.1**	**(12.4)**
≥60		348	(12%)	106	(7.6%)	454	(11%)
45-59		918	(32%)	410	(29%)	1328	(12%)
30-45		1239	(43%)	659	(47%)	1898	(44%)
<30		401	(14%)	223	(16%)	624	(14%)
uACR, mg/g	**Median**	**1017**		**861**		**949**	
Normoalbuminuria (<30)		1	(0%)	0	(0%)	1	(0%)
Microalbuminuria (30-300)		307	(11%)	136	(9.7%)	444	(10%)
Macroalbuminuria (>300)		2597	(89%)	1262	(90%)	3859	(90%)
Primary renal diagnosis							
Diabetic nephropathy		2510	86%	0	0.0%	2510	58.3%
Ischaemic/hypertensive nephropathy/renovascular disease		203	7.0%	494	35%	697	16%
Any chronic glomerulonephritis		97	3.3%	598	43%	695	16%
- IgA nephropathy		38	1.3%	232	16.6%	270	6.3%
- Focal segmental glomerulosclerosis		22	0.8%	93	6.7%	115	2.7%
- Membranous nephropathy		10	0.3%	33	2.4%	43	1.0%
- Minimal change disease		2	0.1%	9	0.6%	11	0.3%
- Other glomerulonephritis		25	0.9%	231	16.5%	256	5.9%
Other		49	1.7%	139	9.9%	188	4.4%
- Chronic pyelonephritis		12	0.4%	57	4.1%	69	1.6%
- Chronic interstitial nephritis		13	0.4%	40	2.9%	53	1.2%
- Obstructive nephropathy		5	0.2%	20	1.4%	25	0.6%
- Other known		19	0.7%	22	1.6%	41	1.0%
Unknown		47	1.6%	167	11.9%	214	5.0%

Data are n (%), or mean (SD), or median. DM=diabetes mellitusHazard ; uACR=urinary albumin:creatinine ratio (uACR can be converted to mg/mmol by dividing mg/g by 8.84).

DAPA-CKD was stopped early due to efficacy, with allocation to dapagliflozin reducing its primary cardiorenal composite outcome (a sustained 50% decline in eGFR, ESKD, or death from renal or cardiovascular causes) by 39% compared to placebo (197/2152 vs 312/2152: hazard ratio [HR]=0.61, 95% confidence interval [CI 0.51-0.72). This included a 44% reduction in the risk of the kidney disease progression component of this composite (142 vs 243: HR=0.56, 95%CI 0.45-0.68) and a 34% reduction in the risk of initiation of maintenance dialysis, receipt of a kidney transplant or a renal death (71 vs 103: HR=0.66, 95% CI 0.49-0.90). Importantly, the relative risk reductions for the primary outcome were similar when analyses were performed separately in people with and without DM, and between eGFR and uACR subgroupings, with nominally significant relative risk reductions in each of these subgroups (see Table 3.2 for results – all heterogeneity test p>0.05) (1).

Table 3.2: Effects of dapagliflozin versus placebo on the DAPA-CKD primary outcome*, overall and by key subgroups (1)

	Dapagliflozin	Placebo	Hazard ratio (95%CI)	Het. test
All	**197/2152**	**312/2152**	**0.61 (0.51-0.72)**	
DM status				
Type 2 DM	152/1455	229/1451	0.64 (0.52-0.79)	0.24
No DM	45/697	83/701	0.50 (0.35-0.72)	
Urinary albumin:creatinine ratio				
≤1000 mg/g (≤113 mg/mmol)	44/1104	84/1121	0.54 (0.37-0.77)	0.52
>1000 mg/g (>113 mg/mmol)	153/1048	228/1031	0.62 (0.50-0.76)	
Estimated glomerular filtration rate (eGFR)				
<45 mL/min/1.73m^2	152/1272	217/1250	0.63 (0.51-0.78)	0.22
≥45 mL/min/1.73m^2	45/880	95/902	0.49 (0.34-0.69)	

* Primary outcome=a sustained 50% decline in estimated glomerular filtration rate, end-stage kidney disease, or death from renal or cardiovascular causes. DM=diabetes mellitus; Het. test=heterogeneity test; CI=confidence interval Urinary albumin:creatinine ratio can be converted to mg/mmol by dividing mg/g by 8.84.

The analyses in Table 3.2 in people without DM were based on 128 primary outcomes from the 1398 participants without DM at randomization, including 51 participants who started maintenance dialysis and 7 who received a kidney transplant (8). Subsequent subgroup analyses dividing all DAPA-CKD participants (i.e. combining those with and without DM) into those with diabetic nephropathy, ischaemic or hypertensive disease, glomerulonephritis, or other/unknown categories also found no evidence that the relative risk reductions for the primary outcome or its kidney disease progression component differed by primary renal diagnosis (8). There were too few renal outcomes in participants with specific causes of non-diabetic disease (e.g. the individual causes of glomerulonephritis listed in Table 3.1) to provide reliable information, but explorations of the 26 kidney disease progression outcomes in DAPA-CKD participants with IgA nephropathy generated the hypothesis that renal benefits may exist in people with albuminuric IgA nephropathy (9). Due to the limited power and the post-hoc nature of exploratory analyses, however, the most appropriate conclusion from all these results is that the overall DAPA-CKD result is the most reliable estimate of the relative effects of SGLT-2 inhibition on albuminuric CKD, irrespective of DM status or the studied primary renal diagnoses (1, 8).

eGFR-slope analyses from the heart failure trials recruiting people without DM

Two reported placebo-controlled trials in heart failure with reduced ejection fraction (HFrEF) called DAPA-HF and EMPEROR-REDUCED have provided information on renal outcomes in people without DM. The effects on categorical kidney disease progression outcomes are provided in Figure 2.2 in Section 2. Briefly, DAPA-HF recruited 4744 participants with HFrEF and a mean eGFR of 66 (SD 19) mL/min/1.73m^2, with 58% of participants free from DM at recruitment. Allocation to dapagliflozin versus placebo had no clear effect on a categorical kidney disease progression outcome, incorporating a 50% decline in eGFR (HR=0.71, 95%CI 0.44-1.16), but such analyses were based on only 67 outcomes and 1.5 years of median follow-up (10). EMPEROR-REDUCED recruited 3730 people with HFrEF with a mean eGFR of 62 (SD 22) mL/min/1.73m^2 and 50% were without DM at recruitment. Allocation to empagliflozin reduced risk of kidney disease progression (using a composite incorporating a 40% decline in eGFR) by 50% (HR=0.50, 95%CI 0.32-0.77; 88 events over 1.3 years median follow-up) (11). There were insufficient numbers of kidney progression outcomes in either trial to compare effects in people with or without DM (Figure 3.1) (10-12).

Nevertheless, eGFR slope-based analyses from EMPEROR-REDUCED and DAPA-HF raise the possibility that, despite acute dips in eGFR on initiation of SGLT-2 inhibition, longer term changes in eGFR over time were slowed. In EMPEROR-REDUCED, the difference in total

annual eGFR slope between those allocated empagliflozin 10mg versus placebo was 1.7 mL/min/1.73m^2 per year (95%CI 1.1-2.4), with almost double this difference once the acute change in eGFR had been taken into account (13). In DAPA-HF, eGFR-slope analyses separated the acute change in eGFR within the first 14 days from the chronic eGFR slope. A significant difference in chronic annual eGFR slope of about 1.7 mL/min/1.73m^2/year was identified, composed of a 1.4 mL/min/1.73m^2 difference in people without DM and 2.3 mL/min/1.73m^2/year difference in those with DM (14). Significant slowing of CKD progression was also identified, with differences in eGFR slope apparent in people with and without CKD. Section 3.1.2 summarizes the cardiac benefits of SGLT-2 inhibitors in HFrEF in people without DM.

Ongoing trials in people without DM

There are insufficient data on kidney disease progression and ESKD in people with non-albuminuric CKD to make definitive recommendations. The ongoing EMPA-KIDNEY trial has the widest eligibility criteria of the four SGLT-2 inhibitor trials recruited from CKD populations (Table 1.1, section 1). Renal inclusion criteria are an eGFR 20-45 mL/min/1.73m² or an eGFR ≥45 <90 mL/min/1.73m^2 plus uACR ≥200 mg/g [≥23 mg/mmol] or protein:creatinine ratio ≥300 mg/g [≥34 mg/mmol]. Those on intravenous immunosuppression therapy in last 3 months or anyone currently on >45 mg prednisolone daily (or equivalent) are excluded, as are people with polycystic kidney disease. EMPA-KIDNEY will help assess more precisely which individuals with non-diabetic causes of albuminuric CKD obtain renal benefits from SGLT-2 inhibition, and test whether the renal benefits consistently identified in trial populations studied to date extend to those without albuminuria or those not taking RAS inhibitors (6).

Note that all these large CKD trials of SGLT-2 inhibitors have excluded people with a history of kidney transplantation (see section 7b for the guideline group's considerations for use in people with a functioning kidney transplant).

Two other trials have recruited patients with heart failure with preserved ejection fraction (HFpEF) including people without DM. EMPEROR-PRESERVED has pre-specified eGFR slope analyses as a secondary outcome (5).

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3.1.2 Summary of trial evidence on cardiovascular risk

Among the 1398 DAPA-CKD participants without DM, 34 died from cardiovascular disease or were hospitalised for heart failure during follow-up. This is too few outcomes for reliable assessments of effect in people with CKD without DM (Figure 3.1) (8). The ongoing EMPA-KIDNEY trial includes cardiovascular death or hospitalisation for heart failure as a key secondary outcome. From the HFrEF trials, DAPA-HF included people with an eGFR down to 30 mL/min/1.73m^2, and 1926 (41%) of the trial population had an eGFR <60 mL/min/1.73m^2. EMPEROR-REDUCED included people with an eGFR down to 20 mL/min/1.73m^2, with 1799 (48%) with an eGFR <60 mL/min/1.73m^2 (12-14). Both trials reported that SGLT-2 inhibition versus placebo reduced the risk of their primary composite outcomes based on cardiovascular death or hospitalisation for heart failure by about a quarter, with these relative risk reductions appearing similar in size and nominally significant in people with and without DM (Figure 3.1) (12-14). Cardiovascular benefits were also unmodified among those with evidence of CKD (13, 14).

3.1.3 Quality of the evidence

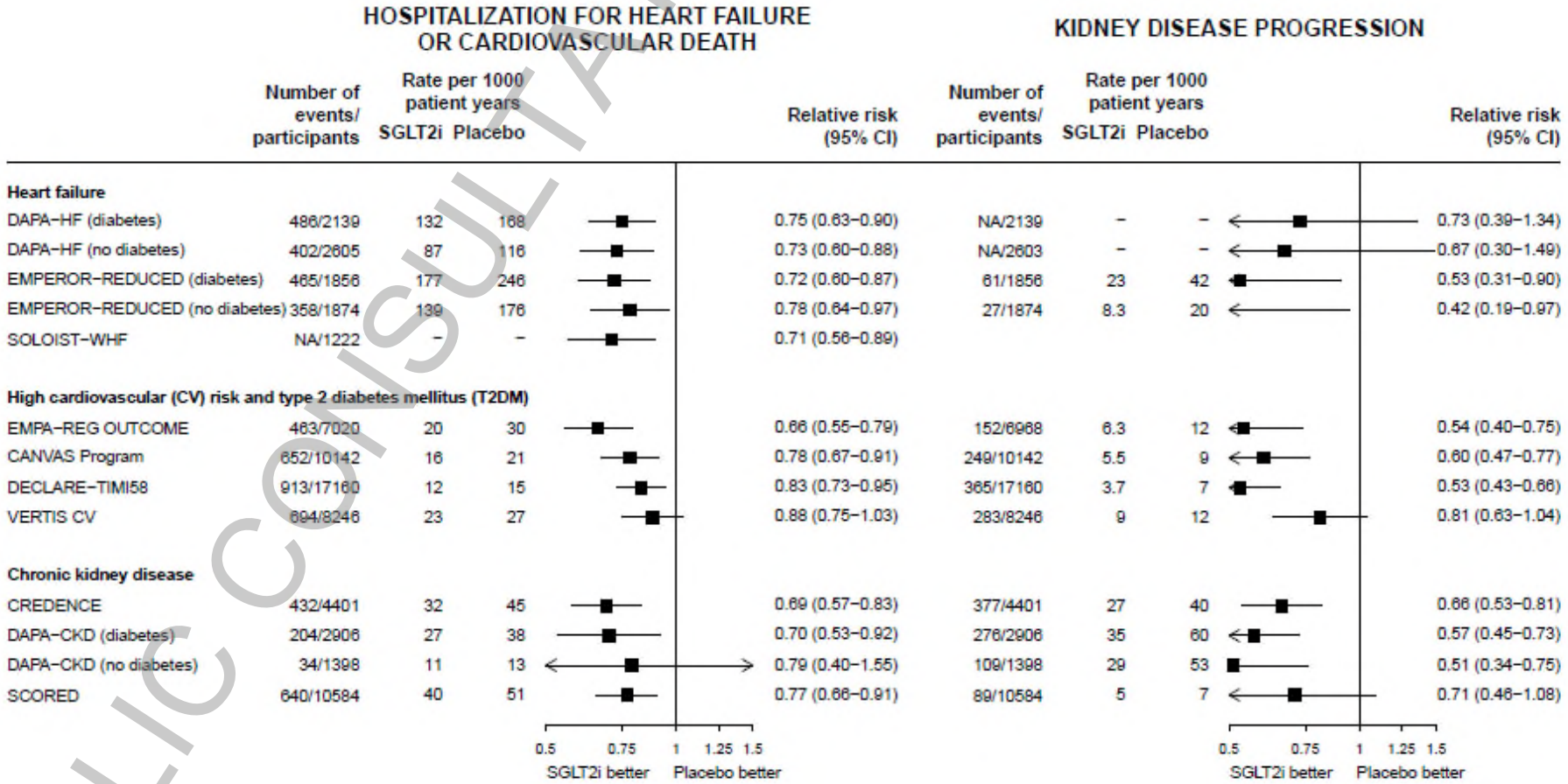
See section 2.1.4 for details of quality of evidence of the large placebo-controlled trials in SGLT-2 inhibitors. Briefly, DAPA-CKD was found to be low risk of bias as assessed using the

Cochrane Risk of Bias 2 tool, due to high quality of randomization, blinding, outcome assessment and reporting. It should be noted that DAPA-CKD was stopped early due to evidence of efficacy, which may lead to overestimation of the primary outcome overall, or in subgroups.

3.1.4 Summary of published cost-effective analyses

At the time of writing, we were unable to identify peer-review publications of cost-effectiveness of SGLT-2 inhibition in people with CKD without type 2 DM.

Figure 3.1: Effects of SGLT-2 inhibitors on the outcomes of (a) cardiovascular death or hospitalisation for heart failure; and (b) kidney disease progression, by population, trial, and by diabetes status (1, 8, 10, 11, 13, 15-26)



NA=number of events unavailable. See footnote to Figure 2.2 for details of the definitions of kidney disease progression used in each trial.

3.2 RECOMMENDATIONS FOR USE

1. We recommend initiating SGLT-2 inhibition* in those with symptomatic reduced ejection fraction heart failure [§] (Grade 1A)

Rationale: SGLT-2 inhibition has been demonstrated to reduce the risk of heart failure hospitalisation in people with stable established symptomatic HFrEF by the DAPA-HF and EMPEROR-REDUCED trials, with relative effects similar in people with and without DM. These trials recruited a substantial proportion of people with CKD, with cardiac benefits appearing to be unmodified by moderately reduced levels of eGFR. We therefore provide a grade 1A recommendation for use of SGLT-2 inhibition in people without DM with HFrEF using the same lower eGFR cut-off of 25 mL/min/1.73m^2 as recommended for people with DM (see Section 2.2). This recommendation will be reviewed when information on HFpEF are available from the ongoing trials (see Section 7c).

2. We recommend initiating SGLT-2 inhibition* in those with a uACR of ≥25 mg/mmol, excluding people with polycystic kidney disease or on immunological therapy for renal disease[†‡] (Grade 1B)

Rationale: DAPA-CKD demonstrated the renal benefits of SGLT-2 inhibition with dapagliflozin 10mg in people with albuminuric CKD, with average levels of albuminuria in the recruited population of about 1 gram a day. Its renal inclusion criteria had an eGFR lower limit of 25 mL/min/1.73m^2 and uACR lower limit of 200 mg/g (~23 mg/mmol), with 10% of participants with microalbuminuria. Benefits on kidney disease progression were similar in people with and without DM, and were also unmodified by baseline eGFR or uACR.

DAPA-CKD excluded certain primary renal diagnoses leaving residual uncertainty in these types of participant who may be less likely to benefit from dapagliflozin's renal modes of action, and perhaps at higher risk of infective side effects. Nevertheless, DAPA-CKD recruited a wide range of non-diabetic causes of albuminuric CKD and exploratory analyses suggest the relative renal benefits of dapagliflozin were unmodified by primary renal diagnosis.

Information on renal benefits in albuminuric non-diabetic CKD is currently limited to this subgroup of a single trial that was stopped early with 128 primary outcomes. Although stopping a trial early may result in overestimates of treatment effects, necessitating caution when interpreting subgroups, we are of the opinion that renal benefits are likely to exist for a range of non-diabetic causes of CKD in people with albuminuria. SGLT-2 inhibition appears to be safe in people without DM, with no reports of ketoacidosis or severe hypoglycaemia in people without DM in DAPA-HF, EMPEROR-REDUCED or DAPA-CKD (see Section 5). We therefore provide a grade 1B recommendation for use of SGLT-2 inhibition in the types of patient with albuminuric CKD recruited into DAPA-CKD. The grading and content of this recommendation will be reviewed when results of EMPA-KIDNEY are available.

Section 3: Recommendations for Use Footnote

All recommendations in sections 2 & 3 exclude people with type 1 DM (see section 7a) and exclude those with a kidney transplant (see section 7b).

**** See section 4 for summary of indications/licenced uses***
[§] Left ventricular ejection fraction of ≤40%
[†] Randomization into a trial may also be appropriate to address clinical uncertainty (see Recommendations for Research)

‡ ***DAPA-CKD provides the key clinical evidence and excluded people with a kidney transplant, polycystic kidney disease, lupus nephritis, ANCA vasculitis, and those receiving immunological therapy for renal disease in the last 6 months.***

3.3 CLINICAL RESEARCH RECOMMENDATIONS

See Section 2.3 which includes Recommendations for Research irrespective of DM status

3.4 RECOMMENDATIONS FOR IMPLEMENTATION

See Section 2.4 which includes Recommendations for Implementation irrespective of DM status

3.5 AUDIT MEASURES

See Section 2.5 which provides audit measures irrespective of DM status.

3.6 REFERENCES

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Section 4: Selection of SGLT-2 inhibitors

(a summary of current UK licences)

4.1 BACKGROUND

There are currently four sodium-glucose co-transporter-2 (SGLT-2) inhibitors that have a licence for use within the UK: canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.

Licences for medications in the UK are issued by the Medicines and Healthcare products Regulatory Agency (MHRA). A product licence will set out the criteria for which a medication has been approved for use and is granted based on review of clinical trial efficacy and safety data. The pharmaceutical company responsible for the manufacture of the medication will produce a document called the Summary of Product Characteristics (SmPC) outlining the properties, conditions for use and licensing information of the product.

The term 'off-label' describes the use of a medication outside of the criteria defined within the licence. The term 'unlicensed' refers to the use of a medication that has not had a licence granted for use by the MHRA in the UK.

SGLT-2 inhibitors are prescription-only medicines (POM). The UK licences for the SGLT-2 inhibitors were primarily focussed on glycaemic effectiveness, however they are regularly being updated in response to any new data published on the individual medications. For example, the empagliflozin (Jardiance) licence was updated in 2017 after the cardiovascular benefit data from the EMPA-REG OUTCOME trial were published (1). These data resulted in a subsequent amendment to the wording of the therapeutic indication, whereby the limitation of treatment goals to 'glycaemic control' only was removed. In June 2020, canagliflozin also underwent a licence update expanding its indications based on trial data from CREDENCE (2).

In late 2020, dapagliflozin had a new therapeutic indication added to the licence as a consequence of the DAPA-HF trial to include the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF), closely followed by empagliflozin in July 2021 also adding HFrEF as a licensed indication after review of the EMPORER-REDUCED data (3, 4).

Most recently, in August 2021, an additional update to the dapagliflozin licence based on review of the results from the DAPA-CKD study gave dapagliflozin an indication to be used for the treatment of chronic kidney disease (CKD) (5).

An additional medication to consider is sotagliflozin; a combination SGLT-1/SGLT-2 inhibitor. Sotagliflozin, although not yet licensed or currently available in the UK, has been approved for use in the EU by the European Medicines Agency, where it is limited to use in people with type 1 diabetes mellitus (DM) who have a BMI of ≥27 kg/m^2, where optimal insulin therapy has failed to adequately maintain glycaemic control. The National Institute for Health and Care Excellence (NICE) have pre-emptively published a technology appraisal (NICE TA622) recommending the use of sotagliflozin, but also only for use in people with type 1 DM, who have a BMI of ≥27 kg/m^2, where optimal insulin therapy has failed to adequately maintain glycaemic control (6).

A summary for the use of the different SGLT-2 inhibitors in relation to CKD stage can be found in Table 4.1 below:

Table 4.1 Dosing of SGLT-2 Inhibitors based on current UK regulatory licences (all doses are once daily)

	eGFR, mL/min/1.73m^2					
SGLT-2 inhibitor	**>90**	**60-90**	**45-60**	**30-45**	**15-30**	**<15**
Canagliflozin	✓ 100 mg – 300 mg	✓ 100 mg – 300 mg	✓ 100 mg	✓ 100 mg *Initiate if for treatment of DKD and uACR >30mg/mmol*	– 100 mg *Continue if initiated for albuminuria*	– 100 mg *Continue if initiated for albuminuria*
Dapagliflozin (type 2 DM)*	✓ 10 mg	✓ 10 mg	– 10 mg	×	×	×
Dapagliflozin (CKD)	✓ 10 mg	✓ 10mg	✓ 10 mg	✓ 10 mg	✓ 10 mg Limited experience at eGFR <25	– 10 mg Limited experience at eGFR <25
Dapagliflozin (HFrEF)	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg Limited experience at eGFR <30	✓ 10 mg Limited experience at eGFR <30
Empagliflozin (type 2 DM)	✓ 10-25 mg	✓ 10-25 mg	– 10 mg	×	×	×
Empagliflozin (HFrEF)	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg Limited experience at eGFR <20	×
Ertugliflozin	✓ 5-15 mg	✓ 5-15 mg	– 5-15 mg	×	×	×

Footnote: * Dapagliflozin is also indicated for the treatment of type 1 DM as an adjunct to insulin with a BMI ≥27 kg/m^2 under the direction of a specialist. CKD=chronic kidney disease; DKD=diabetic kidney disease; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate (mL/min/1.73m^2); HFrEF=heart failure reduced ejection fraction; uACR=urinary albumin:creatinine ratio.

✓ Initiate

– Continuation, not for Initiation

× Discontinue

4.2 CURRENT LICENSED INDICATIONS FOR SGLT-2 INHIBITOR USE

Based on major clinical trial evidence of SGLT-2 inhibitors for cardiorenal protection, the smallest labelled dose of SGLT-2 inhibitors would be sufficient to achieve this target.

The current indications of the UK licensed SGLT-2 inhibitors are stated below:

Canagliflozin (Invokana) (7)

1. Canagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 DM as an adjunct to diet and exercise:
   - As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
   - In addition to other medicinal products for the treatment of diabetes

   For this indication, initiation can be at either the 100 mg or 300 mg dose at an estimated glomerular filtration rate (eGFR) of above 60 mL/min/1.73m^2 but once the eGFR has moved below 60 mL/min/1.73m^2 the dose should be reduced to the 100 mg dose and the treatment stopped if the eGFR drops below 45 mL/min/1.73m^2.
2. For treatment of diabetic kidney disease as add on to standard of care (e.g. angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-II receptor blockers (ARBs)).

   Initiation can occur down to an eGFR 30 mL/min/1.73m^2 if urinary albumin:creatinine ratio (uACR) is >30 mg/mmol, and can be continued if started for this indication down to the need to commence dialysis or renal transplantation.

Dapagliflozin (Forxiga) (8)

1. Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 2 DM as an adjunct to diet and exercise:
   - As monotherapy when metformin is considered inappropriate due to intolerance
   - In addition to other medicinal products for the treatment of type 2 DM

   For this indication, dapagliflozin can be initiated at a dose of 10 mg if the eGFR is >60 mL/min/1.73m^2 but the treatment should be stopped if the eGFR drops <45 mL/min/1.73m^2.
2. Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 1 DM as an adjunct to insulin in patients with BMI ≥27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

   For this indication, dapagliflozin can be initiated at a dose of 5 mg if the eGFR is >60 mL/min/1.73m^2 but the treatment should be stopped if the eGFR drops <45 mL/min/1.73m^2.
3. Dapagliflozin is indicated in adults for the treatment of symptomatic chronic HFrEF.

   There is no lower limit of eGFR stipulated but there has been little reported experience in people with eGFR less than 30 mL/min/1.73m^2
4. Dapagliflozin is indicated in adults for the treatment of CKD.

Empagliflozin (Jardiance) (9)

1. Empagliflozin is indicated in adults for the treatment of insufficiently controlled type 2 DM as an adjunct to diet and exercise:

   - As monotherapy when metformin is considered inappropriate due to intolerance
   - In addition to other medicinal products for the treatment of diabetes

   When used for treatment of insufficiently controlled type 2 DM, empagliflozin can be initiated at a dose of either 10 or 25 mg a day above an eGFR of 60 mL/min/1.73m^2. If the eGFR drops between 45 and 60 mL/min/1.73m^2 then the dose needs to be reduced to 10 mg a day, and the treatment stopped when the eGFR drops below 45 mL/min/1.73m^2.

2. Empagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

   For treatment of heart failure in patients with or without type 2 DM, empagliflozin 10 mg may be initiated or continued down to an eGFR of 20 mL/min/1.73 m^2

Ertugliflozin (Steglatro) (10)

1. Ertugliflozin is indicated in adults aged 18 years and older with type 2 DM as an adjunct to diet and exercise to improve glycaemic control:

   - As monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications
   - In addition to other medicinal products for the treatment of diabetes

   Currently ertugliflozin can be initiated at a dose of either 5 or 15 mg a day above an eGFR of 60 mL/min/1.73m^2. Ertugliflozin should not be initiated at an eGFR of <60 mL/min/1.73m^2, but if already established on treatment, it may be continued down to an eGFR of 45 mL/min/1.73m^2. Treatment should be stopped when the eGFR drops below 45 mL/min/1.73m^2.

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Section 5: Prescribing SGLT-2 inhibitors safely

All medications have both beneficial and adverse effects. This section is designed to highlight the key adverse effects identified to result from use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors and guide how these medicines can be initiated and continued safely, minimising the risk of harm.

5a. DIABETIC KETOACIDOSIS

5a.1 Background and evidence review

Pathophysiology

SGLT-2 inhibition induces glycosuria, which causes widespread changes in metabolism, including an increase in lipid mobilisation, free fatty acid oxidisation and increased plasma ketone levels, in particular β-hydroxybutyrate and acetoacetate (1, 2). States of relative insulin deficiency or reduced carbohydrate intake augment hepatic ketogenesis. Therefore factors such as infection, fasting or reduction in insulin levels can precipitate diabetic ketoacidosis (DKA) in people treated with SGLT-2 inhibitors. Risk is highest in those who require prescription of insulin, and incredibly low among people without diabetes mellitus (DM).

Relative insulin deficiency and reduced carbohydrate intake, with concomitant carbohydrate deficit related to glycosuria contributes to normal or near normal glycaemia (3), making it possible for ketoacidosis to be present with normal or low capillary blood glucose levels (sometimes referred to as “euglycaemic” ketoacidosis) (2).

Large trial evidence

The evidence of DKA risk for people with type 1 DM is discussed in Section 7a, as the large randomized placebo-controlled trials have largely excluded people with type 1 DM. In the large trials that included people with type 2 DM, ketoacidosis risk was found to be significantly increased in four trials: DECLARE-TIMI 58 (relative risk [RR]=2.18, 95%CI 1.10-4.30) (4), VERTIS CV (RR=4.75, 1.11-20.37) (5), CREDENCE (RR=10.8, 1.39-83.7) (6), and SCORED (RR=2.14, 1.14-4.03) (7).

People with chronic kidney disease

The CREDENCE trial included participants with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) of 30-90 mL/min/1.73m^2 and reported a statistically significant increased risk of DKA. Although the relative risk for DKA was 10.8 (1.39-83.7), DKA was rare (canagliflozin 11/2200 vs placebo 1/2197), and the absolute excess risk in the canagliflozin group was ~2.0 per 1000 patient years (6), meaning the absolute benefits clearly exceeded the DKA risk.

The DAPA-CKD trial included participants with eGFR between 25-75 mL/min/1.73m^2, 68% of whom had type 2 DM (8). There was no increased risk of DKA in the SGLT-2 inhibitor arm of this trial (dapagliflozin 0/2152 vs placebo 2/2152).

Physiologically, as eGFR reduces, the amount of glucose filtered by the glomeruli also reduces (9). The glucose-lowering action of SGLT-2 inhibition is therefore limited by eGFR and one can argue that this could protect people from the glycosuria-induced metabolic changes that increase the risk of DKA. However, it is also established that as eGFR reduces, insulin and sulphonylurea (SU) clearance is reduced and the risk of hypoglycaemia from these medications increases (10, 11). Reactive reductions in insulin doses in order to reduce the risk of hypoglycaemia could conceivably have contributed to the risk of DKA seen in CREDENCE and other trials.

People without diabetes melliltus

People without DM accounted for 58% of total participants recruited to DAPA-HF (12), 50% of those recruited to EMPEROR-REDUCED (13), and 32% of those recruited to DAPA-CKD (8). DKA as a consequence of SGLT-2 inhibitor use was not seen in any of the 5877 people without DM included in these trials.

Factors increasing risk of DKA

The Association of British Clinical Diabetologists have identified characteristics of people with type 2 DM that may place them at greater risk of developing DKA when using SGLT-2 inhibitors (14). These characteristics are highlighted in Table 5a.1. People with these characteristics may benefit from ketone monitoring, therefore, we suggest discussing with the diabetes team prior to initiating SGLT-2 inhibitors in such people (See Recommendation 5a.2.2).

Table 5a.1. People with type 2/3 DM at higher risk of DKA

People with HbA1c >86 mmol/mol (10%)	People with past history of DKA
BMI ≤27 kg/m^2 (adjusted for ethnicity)	The possibility of Latent Autoimmune Diabetes in Adults (known as LADA)*
Excess alcohol consumption/ dependence	Known pancreatic exocrine/endocrine dysfunction – particularly if DM is a result of pancreatic disease (Type 3 DM)
People who have rapidly progressed to requiring Insulin (within 1 year of diagnosis)	

Footnote: * Latent Autoimmune Diabetes in Adults – suspect if type of DM unclear, type 2 DM and responding poorly to oral hypoglycaemic drug therapy or low BMI. These people may benefit from specialist input and glutamic acid decarboxylase antibody testing (15). BMI=Body Mass Index; DKA=Diabetic ketoacidosis; DM=Diabetes mellitus; HbA1c=Glycosylated haemoglobin.

5a.1.2 Sick day guidance

Medicines and Healthcare products Regulatory Agency (MHRA) reports of DKA suggest that concomitant illnesses such as vomiting, dehydration, reduced food intake, infection or a surgical procedure preceded some DKA events (16). Similar to the MHRA reports, the U.S Food and Drug Administration (FDA) statement in 2015 stated that 50% of the cases presenting with DKA were associated with precipitating events (17). Following appropriate sick day guidance may significantly reduce the risk of developing DKA on SGLT-2 inhibitors.

It is therefore important that individuals initiated on SGLT-2 inhibitors are given sick day guidance on what to do in these situations.

Sick day guidance is highlighted below:

- Hold SGLT-2 inhibitor if unwell, restricted food intake, or dehydration
- Individuals on insulin treatment should always be advised never to stop or significantly reduce their insulin as part of the sick day response
- SGLT-2 inhibitor treatment should be interrupted in people who are hospitalised for surgical procedures or serious medical illnesses
- Treatment should be restarted when the person's condition has recovered

During periods of planned restricted food intake (for example, fasting for Ramadan), we suggest following the guidance by the ADA/EASD 2020 consensus update on the management of DM during Ramadan. If unwell during fasting, ketone testing may be

considered, and for the elderly, those with CKD or those on diuretics, consider stopping or reducing dose of SGLT-2 inhibitor during the period of fasting (18).

5a.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend that people with type 1 DM should only have SGLT-2 inhibitors initiated under the strict direction of the diabetes team (see Section 7a) (Grade 1C).

2. We recommend that people with type 2 DM at greater risk of DKA (defined in Table 5a.1) should have SGLT-2 inhibitors initiated with caution after discussion with the diabetes team (Grade 1C).

3. We recommend SGLT-2 inhibitors are discontinued when a patient develops DKA (Grade 1A).

4. We suggest that after an episode of DKA and where a clear contributing factor has been identified, there should be discussion with the person and clinical team to establish whether the benefits of re-introducing an SGLT-2 inhibitor outweigh the risks (Grade 2D).

5. When initiating SGLT-2 inhibitors, we suggest that individuals should be advised on the signs and symptoms of DKA and be instructed to temporarily withhold SGLT-2 inhibitors and to seek immediate medical advice if symptoms develop (Grade 1C).

6. We recommend always offering advice on sick day guidance when initiating SGLT-2 inhibitors and reminding them of this at every medication review (Grade 1C).

7. We suggest that individuals taking SGLT-2 inhibitors should be advised against following a ketogenic diet (Grade 2C).

8. We suggest that for people who choose to intermittently fast (e.g. for Ramadan), ketone testing should be undertaken if unwell (Grade 2D).

Rationale: The evidence from the studies reviewed indicates that DKA is a recognised complication in people treated with SGLT-2 inhibitors and that it is more commonly found in conjunction with dehydration or infection. DKA is also likely to occur more frequently in people who are insulin deficient which would include people with type 1 DM, people with type 2 DM with a relative insulin deficient phenotype, and situations where people on insulin have their insulin dose reduced substantially. These recommendations will allow clinicians to use SGLT-2 inhibitors in those who are likely to benefit from this treatment and yet also minimise the risk of the complication of DKA.

5a.3 AUDIT MEASURES

1. The proportion of people with CKD on SGLT-2 inhibitors with evidence of provision of sick day guidance.

2. The proportion of people with CKD in whom SGLT-2 inhibitors were withheld during acute illness, and the proportion appropriately re-initiated on recovery.

5b. HYPOGLYCAEMIA

5b.1 Background and evidence review

Pathophysiology and trial data

SGLT-2 inhibition does not increase the risk of hypoglycaemia when used in isolation or when combined with metformin, pioglitazone, dipeptidyl peptidase-4 inhibitors (DPP-4i) or glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy (19). Results from the large placebo-controlled trials suggest they may even help reduce risk of hypoglycaemia. DECLARE-TIMI 58 and DAPA-CKD found that severe hypoglycaemia (plasma glucose <70 mg/dL or <3.9 mmol/L or hypoglycaemia requiring assistance) was more frequent in placebo than in the SGLT-2 inhibitor groups (4, 8), whilst results from EMPA-REG OUTCOME (20), VERTIS CV (5) and the other trials conducted in CKD populations (CREDENCE and SCORED) found no significant excess of hypoglycaemia (6, 7).

The CREDENCE trial reported all hypoglycaemia (severe or not) and found no excess in its population of patients with type 2 DM and albuminuric diabetic nephropathy (hazard ratio (HR)=0.92, 95%CI 0.77-1.11; absolute difference -4.6 per 1000 patient years) (6). DAPA-CKD reported about a reduction in the risk of severe hypoglycaemia (14/2149 vs 28/2149: an absolute excess among those allocated placebo of about 2.7 per 1000 patient years) (8). Despite the additional effect of sotagliflozin inhibiting SGLT-1, there was no suggestion of increased risk of severe hypoglycaemia in SCORED (53/5291 vs 55/5286) (7).

It is possible that reductions in doses of other hypoglycaemia-inducing therapies (i.e. insulin/SU) to mitigate against perceived risk of hypoglycaemia associated with an additional glycaemia-lowering agent may explain these modest benefits on severe hypoglycaemia observed in the placebo-controlled large SGLT-2 inhibitor trials.

No incidence of severe hypoglycaemia was reported by the 5877 people without DM included in EMPEROR-REDUCED, DAPA-HF or DAPA-CKD (DAPA-CKD included 1398 people with CKD without DM) (13, 12, 8).

Insulin in combination with SGLT-2 inhibition

Insulin therapy is associated with an increased risk of hypoglycaemia in people with DM. Meta-analyses and observational data suggest that, when added to insulin therapy, SGLT-2 inhibition does not increase this risk of hypoglycaemia following a 10-20% reduction in total daily insulin dose (21, 22). Insulin doses were also reduced by up to 20% to prevent hypoglycaemia in people with type 1 DM in the SGLT-2 inhibitor arm of the DEPICT trials (23, 24). Any further insulin dose reduction (beyond 20%) should be cautious and targeted at avoiding hypoglycaemia (25), as excessive insulin dose reduction may increase risk of DKA. Those with more labile blood glucose control may benefit from discussion with the diabetes team for consideration of ketone monitoring (see Section 5a).

Sulphonylurea and meglitinide in combination with SGLT-2 inhibition

Insulin secretagogues, whether used as monotherapy or in combination with other glucose lowering drugs, are associated with an increased risk of hypoglycaemia. Meta-analyses of relatively short-term phase 3 placebo-controlled studies found an excess risk of hypoglycaemia when SGLT-2 inhibitors are added to metformin and sulphonylureas (SU) (Odds Ratio=1.75, 95%CI 1.43-2.15) (26), but did not consider the impact of CKD. Conversely, the large clinical outcome trials found no excess risk of severe hypoglycaemia with SGLT-2 inhibition (with several reporting reductions in risk). This has generated some clinical uncertainty leading to variation in clinical practice, with some clinicians recommending SU doses are reduced when starting SGLT-2 inhibitors, and others proposing SUs should be

stopped altogether (25). It should be remembered that in people with an eGFR <45 mL/min/1.73m^2, SGLT-2 inhibition has only modest effects on glucose lowering (27).

There is very little evidence for the use of SGLT-2 inhibitors in combination with meglitinides. However, as the risk of hypoglycaemia with meglitinide use is increased in people with advanced CKD (28), we do recommend consideration of meglitinide dose reductions when initiating SGLT-2 inhibitors.

5b.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend considering reducing the dose of insulin/SUs/meglitinides when initiating SGLT-2 inhibitors to reduce the risk of hypoglycaemia (Grade 1C).

2. We recommend that when initiating SGLT-2 inhibitors in people taking SUs (e.g. gliclazide) or meglitinides (e.g. repaglinide) when the HbA1c <58 mmol/mol AND eGFR >45 mL/min/1.73m^2, consider reducing dose of SU or meglitinide by 50% to reduce risk of hypoglycaemia (Grade 1C).

3. We recommend that when starting SGLT-2 inhibitors in people taking insulin when the HbA1c <58 mmol/mol AND eGFR >45 mL/min/1.73m^2, consider reducing the insulin dose by 20% to avoid hypoglycaemia (Grade 1C).

4. We recommend that when starting SGLT-2 inhibitors in people taking only metformin ± pioglitazone ± DPP-4i/gliptins or GLP-1RA therapy, no dosage adjustment is necessary (Grade 1C).

Rationale: SGLT-2 inhibitors are effective drugs at reducing hyperglycaemia when they are used in people with preserved kidney function (e.g. eGFR >60 mL/min/1.73m^2), however, their glycaemic effectiveness reduces as the eGFR declines. Where a treatment for DM carries a risk of hypoglycaemia (such as SUs and insulin use), the addition of an SGLT-2 inhibitor may potentiate that risk, particularly if baseline glycaemic control is reasonable at the time of initiation of treatment. There is no evidence that SGLT-2 inhibitors cause significant hypoglycaemia on their own or in addition with DM medicines that are not associated with hypoglycaemia.

5b.3 AUDIT MEASURES

1. The proportion of people on Insulin/SUs with HbA1c <58 mmol/mol and eGFR >45 mL/min/1.73m^2, whose therapy was appropriately reduced when initiating SGLT-2 inhibitors.

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5c. ACUTE KIDNEY INJURY, HYPOVOLAEMIA AND POTASSIUM

5c.1 Background and evidence review

Acute kidney injury

The introduction of SGLT-2 inhibitors was accompanied by early concerns that their use may be linked to an increased risk of acute kidney injury (AKI) and volume depletion. This was largely driven by specific features of their mechanism of action, including an initial reduction in eGFR (which is, thereafter, followed by stabilisation of eGFR slope and improved renal outcomes compared to placebo), induction of osmotic diuresis and natriuresis, alongside post-marketing reports of AKI events following their initiation. Of note, more than half of these reported AKI events occurred within the first 4 weeks of initiation. The US Food and Drug Administration (FDA) dictated caution to health care professionals with regards to their use, especially in the context of other factors that may predispose to AKI such as CKD, heart failure and certain pharmacological agents such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin-II receptor blockers (ARBs) and diuretics (1). Since then, several randomized placebo-controlled trials, which have included traditionally considered "high AKI risk" populations, have suggested that serious AKI risk is reduced by SGLT-2 inhibition.

More specifically, CREDENCE (2) and DAPA-CKD (3), the two large trials exploring renal outcomes in CKD populations treated with SGLT-2 inhibitors, demonstrated comparable AKI event rates between canagliflozin or dapagliflozin, respectively, and placebo. The heart failure trials have yielded consistent results. In DAPA-HF (4) and EMPEROR-REDUCED (5), the AKI rate was similar between the treatment and placebo groups in trial populations which represented a wide range of people with reduced ejection fraction heart failure and CKD (eGFR <60 mL/min/1.73m^2 evident in ~40%).

In the EMPA-REG OUTCOME trial (6), there were fewer AKI events with empagliflozin compared to placebo with similar findings in subgroup analyses by baseline eGFR category (eGFR <60 vs eGFR ≥60 mL/min/1.73m^2) in its population of people with type 2 DM and established prior cardiovascular disease (7). There was no difference in AKI cases for ertugliflozin versus placebo in VERTIS CV (8), and between canagliflozin versus placebo in the CANVAS Program of trials (9), whilst allocation to dapagliflozin in DECLARE-TIMI 58 found a lower AKI risk compared to placebo (HR=0.69, 95%CI 0.55–0.87) (10).

A meta-analysis of four major cardiovascular outcome trials (CANVAS, CREDENCE, EMPA-REG OUTCOME and DECLARE-TIMI 58) (11), suggested a protective effect with a 25% lower AKI risk with SGLT-2 inhibitor use compared to placebo in populations with conditions traditionally considered high risk for AKI (CKD and/or high cardiovascular risk), a finding which is consistent with those of an earlier meta-analysis (12). The mechanisms by which SGLT-2 inhibitors reduce risk of AKI are introduced in Section 1. With regards to sotagliflozin, there was no increased AKI event rate in either SCORED (13) or SOLOIST-WHF (14) trials.

Initiation of SGLT-2 inhibitors is followed by a reduction in eGFR which is inherent to their mechanism of action (2, 3, 6, 15-17), accompanied by stabilisation of the eGFR slope within weeks (2, 6, 16, 17), and appears to be largely reversible upon discontinuation (7). In CREDENCE, the reported average eGFR decrease at 3 weeks was 3.72 ±0.25 mL/min/1.73m^2 versus 0.55 ±0.25 mL/min/1.73m^2 in the canagliflozin and placebo group, respectively, while in DAPA-CKD the eGFR decline at 2 weeks was 3.97 ±0.15 mL/min/1.73m^2 in the dapagliflozin versus 0.82 ±0.15 mL/min/1.73m^2 in the placebo group (3). This initial eGFR decline, also referred to as 'eGFR dip', does not appear to have any clinical impact on AKI risk and does not appear to modify benefits or risks of treatment. In a post-hoc analysis of EMPA-REG OUTCOME, factors like diuretic use and worsening KDIGO CKD stage appear to predispose to a larger (>10%) eGFR dip 4 weeks after initiation of empagliflozin (18). Regardless, eGFR stabilised after 4 weeks and in the study the eGFR dip resolved upon

discontinuation of study treatment. The treatment-mediated cardiovascular and renal benefits were not modified by the presence of a more pronounced eGFR dip, and eGFR remained stable from week 12 onward in all 'eGFR dipping' categories. In CREDENCE (25), the extent of eGFR drop did not affect the long-term change in eGFR slope, or the safety and tolerability of treatment (19).

Hypovolaemia

CANVAS reported an increased rate of volume depletion events with canagliflozin compared to placebo (26.0 vs 18.5/1000 patient years, p=0.009) (20), while CREDENCE found no significant excess in people with albuminuric diabetic kidney disease (28.4 vs 23.5/1000 patient years) (2). More frequent episodes of volume depletion were reported with the use of dapagliflozin compared to placebo in DAPA-CKD (5.9 vs 4.2%, p=0.001) (3), but no significant excess was apparent in DECLARE-TIMI 58 (2.5 vs 2.4%) (10). Rates of adverse events consistent with hypovolaemia did not differ between the empagliflozin and placebo arms in EMPA-REG OUTCOME overall (6) or by eGFR categories (eGFR <60 vs ≥60 mL/min/1.73m^2) (7), with similar findings for ertugliflozin in VERTIS CV (8).

In the large heart failure trials (4, 5, 14, 21), hypovolaemia-related adverse event rates were similar between the treatment and placebo arms, with the vast majority of participants concurrently prescribed other diuretics. Of note, in a subgroup analysis of data from DAPA-HF by diuretic dosage, volume depletion events were more common with dapagliflozin than with placebo in participants on the higher dose diuretics (22), however, there was no increase in renal adverse events.

Sotagliflozin, which also inhibits gut SGLT-1 and can cause diarrhoea, resulted in significantly more frequent volume related adverse events than placebo in the SCORED trial in CKD and type 2 DM (13) (5.3 vs 4.0%, p=0.003), but with no significant excess reported in those with recent hospitalisation for worsening heart failure in SOLOIST-WHF (14) (9.4% vs 8.8%).

In a meta-analysis of the data from some of these large trials combined with a series of smaller trials, there was an increased risk of hypovolaemia-related trial adverse event reports with use of SGLT-2 inhibitors (OR=1.20, 95%CI 1.10-1.31) (23).

Potassium

Combining an SGLT-2 inhibitor with an ACEi or ARB does not have the same potential as dual renin-angiotensin system (RAS) blockade to cause hyperkalaemia (4, 5, 24). There were no meaningful differences in potassium between treatment groups on serial measurements in the CANVAS trial (24). There were also no reported significant differences in adverse events for hyperkalaemia between treatment groups in the large placebo-controlled CKD trials of SGLT-2 inhibitors (in which nearly all participants were treated with single RAS blockade). CREDENCE reported hyperkalaemia event rates of 29.7/1000 patient-years among people allocated canagliflozin vs 36.9 events/1000 patient-years for those allocated placebo. In DAPA-CKD, there were 6 (0.3%) events of serious hyperkalaemia among those allocated dapagliflozin versus 12 (0.6%) among those allocated placebo. Data from HFrEF populations are similarly reassuring, with no effect of SGLT-2 inhibitors on laboratory measurements of potassium or clinical events of hyperkalaemia overall, or among those co-prescribed mineralocorticoid receptor antagonists (MRA) (25, 26). These subanalyses from DAPA-HF and EMPEROR-REDUCED have generated hypotheses that SGLT-2 inhibition may even reduce the risk of severe hyperkalaemia among MRA users or lead to fewer discontinuations of MRA (see Section 2 for details of data on hyperkalaemia with SGLT-2 inhibition among those with heart failure/MRA users).

5c.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend that individuals initiated on an SGLT-2 inhibitor do not routinely require an early assessment of renal function or potassium following initiation of treatment (Grade 1C).

2. We suggest that if an individual has a renal function assessment within the first few weeks post initiation of an SGLT-2 inhibitor, a decline in eGFR needs to be interpreted with caution and in the context of an expected drug effect to avoid unwarranted discontinuation of treatment (Grade 2B).

3. We suggest that individuals on diuretics are counselled on the symptoms of hypovolaemia and advised to seek medical attention if they develop any such symptoms (Grade 2B).

4. We suggest that clinicians consider an early clinical review and if appropriate a diuretic or antihypertensive dose reduction in individuals they consider at high risk of hypovolaemia (Grade 2C).

5. We recommend that SGLT-2 inhibitors are temporarily withheld during acute illness (Grade 1C)

6. We suggest that for people who choose to fast, and particularly for those who are elderly, on diuretics or have CKD, consider withholding SGLT-2 inhibitors for the duration of the fasting period (Grade 2D).

Rationale: SGLT-2 inhibitors have proven benefit in relation to reducing the rate of long-term decline in kidney function in certain groups of people with CKD. The means by which they provide this benefit may involve changes to intraglomerular pressure and reduction in hyperfiltration at an individual glomerulus level. This can result in a reduction in eGFR over the initial few weeks following initiation of SGLT-2 inhibitors, which is relatively small, largely reversible and should not usually be seen as an adverse effect of the drug. None of the major studies have demonstrated an increased risk of AKI in people treated with SGLT-2 inhibitors, and it seems likely they have renal tubular protective effects that reduce risk of AKI. It is therefore important that early changes in eGFR that occur following initiation of SGLT-2 inhibitors do not routinely result in withdrawal of SGLT-2 inhibition when people are likely to gain significant benefit from them.

In addition, SGLT-2 inhibitors have a combined osmotic diuretic and natriuretic effect, so clinicians and the people treated with SGLT-2 inhibitors need to be aware of this effect in order to ensure that any risk of hypovolaemia is minimised.

5c.3 CLINICAL RESEARCH RECOMMENDATIONS

1. Research should be conducted to confirm or refute the apparent renoprotection of SGLT-2 inhibitors against AKI.

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5d. PERIPHERAL VASCULAR DISEASE AND AMPUTATION RISK

5d.1 Background and evidence review

An interim safety analysis of the CANVAS trial (1) raised concern over an increased amputation signal with canagliflozin which led to protocol amendments to the contemporaneously recruiting CREDENCE trial (2) to exclude those with recent amputation history and to interrupt therapy in the event of foot disease onset. However, whilst the CANVAS trial reported an almost two-fold increased risk of amputation with canagliflozin (HR=1.97, 95%CI 1.41-2.75), no significantly increased amputation risk was detected in CREDENCE (HR=1.11, 95%CI 0.79-1.56). Amputation events in the CANVAS trial were significantly increased for both major (ankle and above) and minor amputation, but the majority (71%) were minor (predominantly toe amputations). Relative risks of amputation in CANVAS were also similar across a range of subgroups, including history of peripheral vascular disease (PVD), prior amputation, and eGFR <60 vs ≥60 mL/min.1.73m^2. Secondary analyses of CANVAS and CREDENCE have failed to identify any participant or trial factors to explain the difference in reported amputation risk, with the aforementioned late protocol amendment (implemented about three quarters of the way through recruitment) not thought to have contributed to the absence of amputation signal in CREDENCE (3, 4).

In the large placebo controlled trials of dapagliflozin (DAPA-HF (5), DAPA-CKD (6), DECLARE-TIMI 58 (7)), no increased amputation risk was seen across all subcategorised PVD adverse events. Similarly, no increased amputation risk has been reported in large placebo controlled trials of empagliflozin (8, 9), sotagliflozin (10, 11) or ertugliflozin (12).

A network analysis of large placebo controlled trials up to September 2020 has reported no increased risk compared to placebo, but a slight and statistically significant increased risk compared to other hypoglycaemic agents (HR=1.38, 95%CI 1.02-1.91). Notably, this result was driven by the increased risk seen with canagliflozin in the CANVAS trial (13).

Whilst the results of non-canagliflozin trials have been reassuring regarding amputation risk, the results from CANVAS, and the subsequent MHRA drug safety notice of 2016, mandate ongoing caution with the use of canagliflozin in those at high risk of amputation. Of note, large canagliflozin placebo controlled trials to date have been exclusively in people with DM, and there was no increased amputation risk among people without DM in the SGLT-2 inhibitor trials testing empagliflozin and dapagliflozin in heart failure or CKD populations (5, 6, 8). Furthermore, meta-analysis of 3 trials found a baseline eGFR <60 mL/min/1.73m^2 did not modify the relative risk for amputation compared to those with an eGFR ≥60 mL/min/1.73m^2 (14).

Our recommendation is to avoid initiation of SGLT-2 inhibitors in individuals with active foot disease and withhold SGLT-2 inhibitors should this complication arise. We also stress the importance of shared decision making in initiating SGLT-2 inhibitors, and reinstating use following resolution of foot complications, recognising that individuals at high risk of amputation may also stand to gain significant cardiorenal benefit from these agents. As an example, the number needed to treat (NNT) to prevent the composite primary outcome of renal/cardiovascular death, end-stage kidney disease (ESKD) or doubling of creatinine in CREDENCE was ~22 over 2.6 years, and number needed to harm (NNH) from amputation events in CANVAS was ~277 over 3 years (15). Given the absence of amputation signal seen in CREDENCE, there is insufficient evidence to disadvantage one of the SGLT-2 inhibitors over the other for individuals at high risk of amputation events. However, attention to routine preventative foot care should be advised for all people with DM initiated on SGLT-2 inhibitors.

5d.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We suggest avoiding initiation of SGLT-2 inhibitors in the presence of active foot disease (infection, ulceration and ischaemia) and withholding treatment in those who develop foot complications whilst taking an SGLT-2 inhibitor (Grade 2B).

2. We suggest a shared decision-making approach, with appropriate counselling on risks and benefits of treatment and the importance of routine preventative foot care measures for:

- **Individuals at high risk of amputation (previous amputations, existing PVD, peripheral neuropathy)**
- **Re-initiation of SGLT-2 inhibitors after treatment and full resolution of a foot complication that occurred whist taking SGLT-2 inhibitors (Grade 2B).**

Rationale: A significant finding from a single large trial using the SGLT-2 inhibitor canagliflozin alerted clinicians to the possibility that SGLT-2 inhibitors could increase the risk of lower limb amputations. This finding has not been confirmed in other large trials and furthermore it is important to appreciate that people with PVD are a group of individuals who have more to gain from the initiation of SGLT-2 inhibitors in relation to protection against risk of cardiovascular death, myocardial infarction, heart failure complications and progression of CKD. It is therefore important not to exclude these individuals from the potential benefits of SGLT-2 inhibitors, but to ensure that these medicines are used appropriately and safely in people at risk, or with evidence of PVD.

5d.3 CLINICAL RESEARCH RECOMMENDATIONS

1. Research to investigate amputation risk in people with non-diabetic CKD when initiated on SGLT-2 inhibitors.

5e. FRACTURE RISK

5e.1 Background and evidence review

A safety notice for fracture risk with SGLT-2 inhibitors was published following increased incidence of upper and lower limb fracture in the CANVAS trial of canagliflozin (HR=1.26, 95%CI 1.04-1.52). The excess fracture risk was detected in only one of the two large subcohorts that comprise the CANVAS Program of trials (i.e. it was not apparent in CANVAS-R), for reasons that could not be explained by baseline participant demographic or protocol heterogeneity, and could conceivably represent a finding which resulted from the play of chance (1). A fracture risk with canagliflozin was not identified in the CREDENCE trial of canagliflozin, nor has it been identified in large large placebo controlled trials of other SGLT-2 inhibitors (including those inclusive of participants with low eGFR) (5-12). Outside of trial populations, a recent systematic review of 37 large population based studies found no association between SGLT-2 inhibitor prescription and fractures (16). A hypothesised link to hypovolaemia-related falls has not been substantiated, although the incidence of non-serious falls is often not recorded in large outcome trials (17).

Data from preclinical and phase 1 studies have reported short-term alterations in mineral biochemistry, including increases in phosphate, FGF-23 and parathyroid hormone (PTH) levels with SGLT-2 inhibitor use (18, 19), which were replicated in a cohort of 31 participants with type 2 DM and albuminuria treated with dapagliflozin (20). A trial of canagliflozin versus placebo in older individuals with type 2 DM demonstrated significantly reduced bone mineral density at the hip, but at no other site, with canagliflozin treatment over 104 weeks (21).

Whilst experimental data indicate that SGLT-2 inhibitors may modify bone mineral metabolism, precise mechanisms have not been elucidated. Based on current evidence, it is likely that either these bone metabolism changes do not translate into increased fracture risk, or that any small increased fracture risk with canagliflozin is outweighed by the cardiorenal benefits in populations at risk of heart failure or progressive CKD. Our recommendation therefore highlights the importance of routine CKD-mineral bone disease (MBD) monitoring and management in these individuals. More research is required into the mechanisms of SGLT-2 inhibitor-induced bone biochemical alterations, potential interactions with other drugs that modify osteoporosis risk (e.g. thiazolidinediones) and the clinical significance of this in a CKD +/- type 2 DM population already at risk of bone disease.

5e.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. In people with CKD treated with SGLT-2 inhibitors, we suggest monitoring of bone parameters including calcium, phosphate and PTH should be performed as appropriate for CKD stage (NICE CG182) (Grade 2D).

Rationale: Whilst there has been report of an increased risk of fractures in one trial where participants were treated with canagliflozin, this has not been confirmed in any other study and may represent the play of chance. People with CKD are at increased risk of bone disease and their clinician should be monitoring them to ensure that interventions are utilised to maintain good bone health irrespective of the prescription of SGLT-2 inhibitors. NICE CG182 CKD guidance available at www.nice.org.uk/guidance/cg182.

5e.3 CLINICAL RESEARCH RECOMMENDATIONS

1. Establishing any long-term impact of SGLT-2 inhibition on the development and progression of CKD-MBD

2. Establishing if SGLT-2 inhibition modifies osteoporosis risk posed by thiazolidinediones.

5f. MULTIMORBIDITY AND FRAILTY

5f.1 Background and evidence review

Multimorbidity and frailty are interrelated but distinct conditions that are important to consider when individualising treatment decisions for SGLT-2 inhibitor prescription. Multimorbidity, (defined as the presence of two or more long term health conditions) is common in the UK. In a cross-sectional study of 1.75 million people registered with a general practitioner in Scotland, 40% of people had single health conditions and 23% were multimorbid (22). In UK Biobank, which recruited half a million people between the ages of 40 and 69 years living in the UK, 19% of people were multimorbid (23).

The exclusion criteria of trials often result in underrepresentation of people with certain types of comorbidity from large placebo controlled trials. This is arguably the case for many of the SGLT-2 inhibitor trials. The CANVAS, CREDENCE, EMPA-REG OUTCOME, DAPA-CKD, DAPA-HF, DECLARE-TIMI 58 and VERTIS CV trials all excluded participation where there was evidence of certain conditions (e.g. liver disease, cancer, and haematologic conditions). Such approaches may be justified by the need to ensure participants will survive long enough to be at risk of the studied outcomes. For example, progression of CKD can take years, and so exclusion of people with active cancer is necessary to ensure the trial can address its primary question. However, these exclusion criteria pose a challenge when aiming to generalise the evidence from large placebo controlled trials to people with these conditions/multimorbidity.

Of note, individual trials had additional exclusions which also limit generalisability. For example, people with prior or current immunosuppressive therapy, or people affected by endocrine diseases other than DM, and potentially at risk of certain safety outcomes (e.g. at risk of DKA or amputation) were excluded from many of the SGLT-2 inhibitor trials.

People with multimorbidity and frailty may suffer from a particularly high burden of treatment. They are at high risk for adverse drug reactions and, in the case of multimorbid people, may be considered for treatment with multiple different drugs for their different health conditions. Conversely, they may also be at high absolute risk of a trial's key efficacy outcomes and therefore particularly benefit from the effects of SGLT-2 inhibition on risk of cardiovascular death, heart failure complications, acute kidney injury and the reduced risk of hospitalisation observed in some of the SGLT-2 inhibitor trials.

Our recommendations for this group are in line with the UK guidelines for multimorbidity and frailty (Multimorbidity: clinical assessment and management, NICE Guideline NG56, Published September 2016) which places emphasis on individual preference, awareness of the potential burden of polypharmacy and consideration of life expectancy in balancing risks and benefits of SGLT-2 inhibitor treatment.

5f.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We suggest an approach to care that takes account of frailty and multimorbidity where these apply. This can include:

- **Establishing the person's goals, values and priorities**
- **Consideration of the balance of disease and treatment burden (for example, prognostic benefits in people with limited life expectancy or frailty)**
- **Agreeing an individualised management plan (Grade 2D).**

Rationale: When making decisions on which individuals would benefit from SGLT-2 inhibition one has to consider the participants included in the relevant trials that provided the evidence for their use. These trials generally excluded people with greater degrees of frailty and certain comorbidities. Therefore, caution must be exercised when extending evidence of safety (and perhaps also benefit) of SGLT-2 inhibitors to such individuals, although one needs to also consider at the same time that many of these individuals, and particularly those with heart failure, are likely to achieve significant benefit from the use of SGLT-2 inhibitors.

5f.3 CLINICAL RESEARCH RECOMMENDATIONS

1. Future trials of SGLT-2 inhibitor use in people with CKD that seek to extend inclusivity to those of advanced age and multimorbid status.

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5g. MYCOTIC GENITAL INFECTIONS AND FOURNIER'S GANGRENE

5g.1 Background and evidence review: Mycotic genital Infections

SGLT-2 inhibitors reduce blood glucose in individuals with DM by causing urinary excretion of glucose (1). The presence of an increased concentration of glucose in the urine results in a 2.5-6 fold increase in the risk of mycotic genital infections in those on an SGLT-2 inhibitor compared to control (2, 3, 4). In women, this presents as candida vulvovaginitis and in men as balanitis.

The large placebo controlled trials reported an increased incidence of mycotic genital infections in the SGLT-2 inhibitor treatment arms compared to placebo (Table 5g.1)

Table 5g.1 Mycotic genital infections in SGLT-2 inhibitor trials

Trial	SGLT-2 inhibitor (per 1000 patient years)	Placebo (per 1000 patient years)	p value
EMPEROR-REDUCED (n = 3726)	12.5	4.8	-
SOLOIST-WHF (n = 1216)	11.0	2.2	-
EMPA-REG OUTCOME (n = 7020)	Male 13.1 Female 39.6	Male 4.8 Female 8.4	Male <0.001 Female <0.001
CANVAS Program (n = 10142)	68.8	17.5	<0.001
DECLARE-TIMI 58 (n = 17143)	76	9.0	<0.001
VERTIS CV (n = 8238)	Male 7.0-9.7 Female 30.7-33.6	Male 3.4 Female 6.3	Male <0.001 Female <0.001
CREDENCE (n = 4397)	Male 5.8 Female 14	Male 0.8 Female 5.2	-
DAPA-CKD (n = 4298)	-	-	-
SCORED (n = 10577)	17.7	6.4	<0.001

People with type 2 DM are at an increased risk of recurrent mycotic genital infections compared with the general population. Given this increased incidence, propensity to mycotic genital infection is an important consideration prior to initiation of SGLT-2 inhibitors. Factors which may predispose an individual to mycotic genital infection include female sex, pregnancy, hormonal contraception, recent antibiotic use, and immunosuppression. People with DM not achieving their HbA1c target may be immunosuppressed as hyperglycaemia has effects on the immune system resulting in an increased susceptibility to infection (5). When these risks factors are considered together in multivariate models, female gender, higher BMI and previous genital infections are independently associated with a greater risk of mycotic genital infections, whilst a high HbA1c is not consistently associated with greater risk (6, 7). Development of mycotic genital infections is a common reason to stop SGLT-2 inhibitors, particularly if they occurred early after treatment initiation (8). Counselling on the risks and prevention of mycotic genital infections may help improve adherence.

Prevention

Prevention comes mainly in the form of managing risk factors. Personal hygiene education has been shown to reduce incidence of genital infection in a small study of 250 people where 5% of participants who were advised on personal hygiene developed a genital infection compared to 41% of those in the control group. Personal hygiene strategies include rinsing after voiding (but not douching), loose fitting absorbent underwear and cleaning under foreskin (9).

Treatment

Despite good preventative measures, some individuals may still develop mycotic genital infections. Prescribing guidance suggests discontinuation of the SGLT-2 inhibitors is not necessary (10). People can self-manage with over the counter treatments or be prescribed appropriate antifungal therapy such as topical creams or a single dose of an oral antifungal (9). For those with recurrent infections, prophylactic or maintenance therapy is suggested (9).

5g.1.2 Background and evidence review: Fournier's Gangrene

Fournier's gangrene is an acute polymicrobial infection of the scrotum, penis or perineum with necrosis. It presents with scrotal or perineal pain and redness and has a rapid progression to gangrene (with pain being a key feature). Treatment is surgical debridement and broad-spectrum intravenous antibiotics. It is rare, with an overall incidence of about 1.6 per 100,000/year (11). The large placebo-controlled trials of SGLT-2 inhibitors have reported only a few cases of Fournier's gangrene, with no suggestion of an increased incidence in the SGLT-2 inhibitor treatment arms compared to placebo.

The MHRA advised of a risk of developing Fournier's gangrene whilst treated with SGLT-2 inhibitors in February 2019, following an EU review and an FDA safety announcement. Six yellow card reports were received corresponding to 548,565 patient years of treatment. Warnings have been added to product information and letters were sent to health professionals. These warnings advise that people should be informed of the signs and symptoms and when to seek help. In particular, they should be advised to be alert for symptoms of severe pain, tenderness, erythema, or swelling in the genital or perineal area accompanied by fever or malaise. In addition, people on SGLT-2 inhibitors should be advised to stop their treatment on suspicion of Fournier's gangrene and treatment started urgently.

5g.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend that all people are counselled on the risks of mycotic genital infections prior to initiation of SGLT-2 inhibitors (Grade 1D).

2. We recommend that all people are counselled on self-care to maintain good genital hygiene (Grade 1C).

3. We recommend that all people are counselled on the symptoms of mycotic genital infections and how to seek help including self-management (Grade 1D).

4. We suggest that for those individuals with a history of recurrent mycotic genital infections on SGLT-2 inhibition, consideration is given to offering prophylactic anti-fungal treatment, which should be reviewed after 6 months of therapy or earlier if clinically indicated (Grade 2D).

5. We suggest that SGLT-2 inhibitor therapy can be continued during the treatment of mycotic genital infections (Grade 2D).

6. We highlight the specific MHRA warning and suggest that all people are counselled on the symptoms of Fournier's gangrene and advised to stop SGLT-2 inhibitors and to seek urgent help if they develop such symptoms (Grade 2D).

7. We highlight the specific MHRA warning and suggest that SGLT-2 inhibitors are discontinued if Fournier's gangrene is diagnosed or suspected (Grade 2D).

Rationale: Mycotic genital infections are recognised to occur more frequently in people treated with SGLT-2 inhibitors (on average risk is about 3-4 fold higher) and particularly in those individuals with DM. These infections are usually mild and easily treated. Good clinical care should include ensuring that individuals prescribed SGLT-2 inhibitors are aware of this

complication, how to reduce the risk of it occurring and appropriate actions should they develop symptoms consistent with mycotic genital infections. In contrast to mycotic genital infections, Fournier's gangrene is a rare condition that results from bacterial infection and it requires prompt and intensive medical and surgical management. This disorder is identified in people with DM and whilst the evidence to suggest that it may be increased in people treated with SGLT-2 inhibitors is limited to post-marketing surveillance, all people starting SGLT-2 inhibitors should be advised on the symptoms of Fournier's gangrene and what to do if they develop such symptoms.

5h. URINARY TRACT INFECTIONS

5h.1 Background and evidence review

DM is a known risk factor for urinary tract infections (UTIs), and this may be attributable to glycosuria enhancing bacterial growth in the urinary tract or to bladder dysfunction impairing complete bladder emptying (12, 13). The mechanism of action of SGLT-2 inhibitors suggests a theoretical increased risk of UTIs through the enhancement of glycosuria. In 2015, the FDA reported 19 cases of urosepsis and pyelonephritis in individuals on SGLT-2 inhibitor therapy between March 2013 and October 2014, and subsequently issued a warning surrounding the risk of UTIs with SGLT-2 inhibitor use (14).

Except for VERTIS CV, this finding is not reflected in the randomized data from the large placebo controlled trials (15-22). It is notable that VERTIS CV did report a statistically significant increase in any UTIs in the ertugliflozin arm (absolute increase in risk with ertugliflozin 5mg vs placebo +2.1% over 3.5 years, 95%CI 0.4-3.7%; 15mg vs placebo, +1.8%, 95%CI 0.2-3.5%), but found no difference in the subset of these infections which were serious (<10% of UTIs were serious).

The lack of serious UTI risk with SGLT-2 inhibition might be explained by the hypothesis that any effects of glycosuria on potentiating bacterial growth are countered by those of diuresis and polyuria that prevent bacterial ascension of the urinary tract (23). Alternatively, glycosuria per se is actually not a common precipitant for UTIs.

In CKD, there is reassuring data. In CREDENCE, the event rate for UTI per 1000 patient years was 48.3 in the canagliflozin-treated group versus 45.1 in the placebo arm (HR=1.08, 95%CI 0.90–1.29), and in SCORED, the event rate for UTI per 1000 patient years was 86 in the sotagliflozin-treated group versus 83 in those allocated placebo (HR=1.04, 95%CI 0.94-1.16) (21, 22).

Despite the identified absence of a clear causal link between SGLT-2 inhibitors and UTIs, sick-day rules still apply and SGLT-2 inhibitors should be withheld during episodes of urosepsis and pyelonephritis in order to reduce the risk of ketoacidosis.

5h.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend temporary discontinuation of SGLT-2 inhibitors when treating pyelonephritis or urosepsis (see sick-day guidance 5a.1.2) (Grade 1C).

Rationale: Whilst there were concerns that the use of SGLT-2 inhibitors might cause an increased risk of UTIs, randomized data from the major trials have not confirmed any significant increase. However, these drugs are being prescribed in people who have a high risk of UTIs and effective prompt management of these infections should be undertaken.

5i. CHILDREN, PREGNANCY AND BREAST FEEDING

5i.1 Background and evidence review

Children

There are no data available for the use of SGLT-2 inhibitors in children under 18 years of age, and therefore risks of use posed to this population are unknown.

Pregnancy

There are no human data for the use of SGLT-2 inhibitors during pregnancy. Standard practice has been to switch SGLT-2 inhibitors to insulin in the preconception period and for the duration of pregnancy, hence the lack of safety and efficacy data in this group (24).

In animal studies, at higher than recommended human doses, there have been class-wide toxicity effects highlighting potential links to ossification delays, renal maturation and tubular dilatations (10, 25-27). UK manufacturers are consistent in their advice that, due to a lack of human safety data, SGLT-2 inhibitors should not be used during pregnancy.

Breastfeeding

There are no human data for the use of SGLT-2 inhibitors whilst breastfeeding. Given the highly significant protein binding of SGLT-2 inhibitors, excretion into breast milk is unlikely to be in clinically important quantities (28, 29). Nevertheless, based on data from juvenile toxicity studies in rats whereby renal pelvic and tubular dilatations were observed through exposure via breastmilk, the manufacturers of all UK licensed SGLT-2 inhibitors are consistent in their advice that extent of excretion in human milk is unknown and therefore a risk to breastfeeding infants/newborns cannot be excluded (10, 25-27).

5i.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We suggest SGLT-2 inhibitors are not used in children under 18 years of age (Grade 2D).

2. We suggest that all women of child-bearing potential are counselled, prior to conception, on the risks of SGLT-2 inhibitors during pregnancy (Grade 2D).

3. We suggest SGLT-2 inhibitor therapy is discontinued upon planning, suspicion or confirmation of pregnancy (Grade 2D).

4. We suggest SGLT-2 inhibitors are not used in women who are breastfeeding (Grade 2D).

Rationale: There is no evidence at present to support the safe use of SGLT-2 inhibitors in children under the age of 18 and there is theoretical evidence to advise against using these drugs in people either planning pregnancy, who become pregnant or who are breastfeeding. Clinical trials in the paediatric setting are suggested.

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Section 6: Lay summaries and patient information leaflets

This section is designed for patients and carers and for healthcare workers who wish to obtain a lay summary of this guideline. The section contains a one-page executive lay summary followed by a full lay guideline summary. The section also contains examples of patient information leaflets that can be used when initiating sodium-glucose co-transporter -2 (SGLT-2) inhibitors for people with diabetes and also for those without diabetes. It is anticipated that by providing a clear description of the contents of this guideline there will be greater understanding of the benefits and the risks of using SGLT-2 inhibitors for people with chronic kidney disease (CKD).

6.1 LAY EXECUTIVE SUMMARY

CKD is a significant medical problem affecting anything between 6 to 11% of the UK adult population. It is a disorder in which the kidneys are damaged causing a reduction in their ability to clean the blood. If the CKD is progressive (which means it slowly deteriorates over time) the person suffering this disorder is at risk of kidney failure and the need to start a treatment to replace their kidney function in the form of either dialysis or kidney transplant. Importantly, as well as the issue of suffering kidney failure, people with CKD have a much higher chance of suffering cardiovascular diseases in the form of heart attacks, heart failure, strokes and damage to the blood supply to the legs and feet.

The treatment of CKD has been centred around control of blood pressure, the reduction in other cardiovascular risk factors (for example, stopping smoking and managing cholesterol) and the use of a group of medications known as angiotensin-converting enzyme inhibitors (or ACE inhibitors - the names of which usually end with "-pril") or angiotensin-II receptor blockers (ARBs - the names of which usually end with "-sartan"). However, even with the use of these interventions, people with CKD still suffer considerable harm related to their underlying kidney disorder.

The SGLT-2 inhibitors is the name given to a group of medications that were initially developed to treat people with diabetes by providing them with better control of their blood glucose (sugar) and can be recognized by the drug name ending in "-gliflozin". As part of the developmental program for this group of medications, each of the individual SGLT-2 inhibitors underwent a large study to ensure that, not only are they effective in helping people with diabetes reduce blood glucose, but that they also did not cause any increased risk of cardiovascular disease. The findings from these large studies, which have been undertaken and reported over the last six years, has had a significant impact on the care of people with heart disease and CKD. This is because all of these medications have been shown to have unexpected beneficial effects in relation to reducing the rate of progression of CKD and reducing the risk of heart failure complications. In relation to CKD, this benefit was seen even though the study participants were already being treated with current best practice and even in this circumstance the SGLT-2 inhibitor provided very significant additional benefit.

As a result of these studies and the further specific studies directly examining the effects of SGLT-2 inhibitors in people with kidney disease and heart failure, it is recognized that these medications need to be offered to people who are likely to experience benefit from taking this medication. It is the purpose of this guideline to review the evidence related to the benefits and the potential adverse risks of SGLT-2 inhibitors, in order to provide clear recommendations as to which people with CKD are most likely to benefit from this medication, and in order to encourage the healthcare system to ensure that those individuals receive this beneficial treatment as speedily as possible.

All medical interventions can have side effects and for SGLT-2 inhibitors, we are clear as to the nature of the side effects and their frequency. These medications have a low risk of side effects but it is also possible to reduce that risk further by making careful choices about which individuals receive the medications and, most importantly, informing people prescribed SGLT-2 inhibitors of the side effects themselves and how to take specific actions to reduce the risk of coming to any harm by taking these medications. It is to be remembered that people with CKD should only be offered an SGLT-2 inhibitor if the benefits significantly outweigh the risks. Therefore, this guideline also provides information around the side effects of SGLT-2 inhibitors and how those side-effect risks can be reduced.

6.2 FULL SUMMARY OF GUIDELINE

6.2.1 Introduction

Between 6 to 11% of the adult population of the United Kingdom is thought to have CKD. These individuals are not just at risk of progressive decline of kidney function resulting in them suffering symptoms related to poor kidney function and requiring them to be considered for end-stage kidney disease treatment (dialysis or transplant) but they also have a greatly increased risk of cardiovascular disease (heart attacks, heart failure, strokes and narrowing of the arteries to the legs termed peripheral vascular disease). This represents a significant burden for both the health economy of the United Kingdom and, more importantly, for the individuals themselves.

Treatment for CKD aims to halt or slow down progression of declining kidney function and reduce cardiovascular risk. These treatments have up until now been centred on a group of medications known as the inhibitors of the renin angiotensin system, which is a system that has a controlling influence on blood pressure and fluid status. In addition, control of blood pressure, blood glucose and blood lipids (or fats) remain key to reducing progression of CKD and the poor cardiovascular outcome. However, these treatments are only partially effective and there has been a pressing need to identify new treatments to help the large number of people with CKD avoid the requirement for dialysis or transplant, or from suffering cardiovascular harm.

SGLT-2 inhibitors are medications that were initially developed as a treatment for diabetes because they effectively reduce blood glucose (sugar). New research has found that these medications provide significant benefit to people with CKD both in terms of reducing decline in kidney function and reducing the poor cardiovascular outcomes people with CKD suffer.

The purpose of this guideline document is to produce practical advice for clinicians caring for people with kidney disease in relation to when and how to use SGLT-2 inhibitors.

It is the purpose of this section to provide lay individuals a greater understanding of the nature of SGLT-2 inhibitors, the benefits they offer, in which individuals they are most likely to be effective and to obtain a greater appreciation of the risks of these medications and how these risks can be reduced.

6.2.2 SGLT-2 inhibitors: what are they?

The kidneys function to clean the blood and control the concentration of many constituents of the blood. They do this by “filtering” the blood through individual filtering units (called glomeruli, of which there are approximately 1 million within each kidney in healthy adults) and thereafter the filtered fluid or “filtrate” passes into small pipes or “tubules” within the kidneys where its

content is adjusted. The filtrate eventually becomes the urine, which is passed from the kidneys to the bladder and removed when we pass urine.

Glucose is freely filtered from the blood but normally all of this filtered glucose is returned back into the blood within the early part of the tubule of the kidneys called the proximal tubule. This return is undertaken by co-transporter proteins called SGLT-2 which sit in the wall of the proximal tubule. Every person has a maximal amount of glucose that their kidney can reabsorb and in individuals who have high amounts of filtered glucose (typically in people with diabetes) the SGLT-2 co-transporters become flooded and residual glucose is lost in the urine (and in fact it is the resulting sweet urine which gives diabetes mellitus its name).

SGLT-2 inhibitors are medicines that block the activity of the SGLT-2 co-transporter and by blocking this protein's actions, SGLT-2 inhibitors cause a loss of glucose into the urine and is the reason these medicines have been developed as a treatment to help reduce blood glucose in people with diabetes.

In addition to SGLT-2 co-transporters there are, within the body, a group of related proteins called SGLT-1 co-transporters. These proteins are found more predominantly in the gut where they are involved in the uptake of glucose from the food into the bloodstream. They are also found, albeit to a much lesser extent, in the kidney tubules where they make only a very minor contribution to total glucose reuptake in the kidneys.

6.2.3 Benefits of SGLT-2 inhibitors

All new medications being introduced to treat diabetes are required to demonstrate that not only do they improve blood glucose control but they do not have an adverse effect on cardiovascular outcomes in people with diabetes. This is because there has been an example of a previous medication which provided significant benefit in relation to reducing blood glucose but at the same time was associated with an increased risk of heart attacks. Therefore, all new medications being introduced to treat diabetes are required to undergo what are termed cardiovascular outcome trials.

All the major SGLT-2 inhibitor medications have now reported on their cardiovascular outcomes and the findings from these studies has provided significant information in relation to additional benefits that these medications provide.

It was already known that these medications have benefits over and above their glucose reducing effect, which included a reduction in weight of around 2 to 4 kg and a small reduction in blood pressure. These additional effects were believed to result from the loss of salt in the urine (called the diuretic effect) and the loss of calories in the form of glucose within the urine. In addition to these effects, the cardiovascular outcome studies identified significant benefits in relation to reducing cardiovascular harm, most particularly in relation to reducing admission to hospital with heart failure and in reducing the progression of CKD.

6.2.4 How this guideline was developed

This guideline has been developed by a writing group containing a broad range of healthcare clinicians with experience in kidney disease, diabetes and primary care who have worked together to review the evidence for the use of SGLT-2 inhibitors in people with kidney disease. In addition writing group has also included people with kidney disease to provide the patients' perspective. As a group, they have followed good practice in relation to reviewing the evidence and using that evidence to provide recommendations for the use of SGLT-2 inhibitors in people with CKD.

In generating the recommendations, the guideline writing committee gave the greatest priority to the results of trials that were most effective at discriminating both beneficial and adverse effects of SGLT-2 inhibitors. These were trials comparing people who were allocated to take SGLT-2 inhibitors at random (like a toss of a coin) to those who were allocated to take a dummy pill (known as the placebo group) and containing large (greater than 1000) numbers of participants.

From this evidence base, the guideline writing committee have developed summaries of evidence and proposed draft recommendations which were discussed at a consensus meeting of all members before final recommendations were made.

When making recommendations, the evidence that supported each recommendation was graded according to the UK Kidney Association's recommended grading system, which defines the level of evidence and the quality of evidence for each recommendation. Broadly, a grade 1 recommendation is a strong recommendation while a grade 2 recommendation is a weaker one. In addition, there is a letter designating the quality of the evidence that supports that recommendation.

Where the evidence to support a recommendation is strong (grade 1) we use the term "recommend" and where it is weaker (grade 2) we use the term "suggest".

We have also subdivided our recommendations into the following categories:

a) recommendations for use which defines who should be offered SGLT-2 inhibitors
b) recommendations for implementation which defines how SGLT-2 inhibitors should be used
c) recommendations for clinical research which defines where there is ongoing clinical uncertainty
d) recommendations for audit which defines how to demonstrate effective implementation of grade 1 recommendations

6.2.5 Benefits of SGLT-2 inhibitors: cardiovascular benefits

The cardiovascular outcome trials identified the fact that SGLT-2 inhibitors had a small effect on reducing the incidence of heart attack which varied between the individual SGLT-2 inhibitors. However, all the trials demonstrated a significant reduction in heart failure hospitalizations that pointed to a significant benefit in people with heart failure, and most particularly those where the heart failure is due to a reduction in the pumping power of the heart, termed "heart failure with reduced ejection fraction" or "HFrEF". This benefit has now been confirmed in studies that have specifically looked at the use of SGLT-2 inhibitors in people with heart failure including people with and without diabetes.

6.2.6 Benefits of SGLT-2 inhibitors: kidney protection

An unexpected and consistent finding from the cardiovascular outcome trials was that individuals treated with SGLT-2 inhibitors as opposed to placebo or dummy medications had improved kidney outcome in terms of a reduction in decline of kidney function, the need to commence treatment for end-stage kidney failure and death due to kidney causes.

These findings have been tested in further studies called CREDENCE and DAPA-CKD which have specifically looked at kidney outcomes in people with evidence of protein in the urine (protein in the urine signifies underlying kidney disease and is a key predictor for future loss of kidney function). In both of these trials, the reduction in risk of adverse kidney events compared to placebo was equivalent to that seen in the cardiovascular outcome trials, confirming benefits of SGLT-2 inhibitors in people with CKD.

6.2.7 Separation of glucose from cardiac and kidney benefit

The benefits of SGLT-2 inhibitors in relation to the improvement in blood glucose control is known to be related to the glomerular filtration rate (GFR). This is a measure of global kidney filtering function and is the measure that progressively reduces as kidney function declines in CKD. A normal GFR should be approximately 90 mL/min/1.73m^2, but there is a progressive normal decline with ageing. However, excessive decline down to single figures (i.e. less than 10 mL/min/1.73m^2) is usually an indicator of the need to commence end-stage kidney failure treatment.

As the GFR declines so also does the ability of SGLT-2 inhibitors to improve glucose control in diabetes, such that by the time the GFR has reduced to 45 mL/min/1.73m^2, the glucose reducing effect of SGLT-2 inhibitors virtually disappears in people with diabetes treated with these agents. It is for this reason that these medications have not been recommended for use as a treatment for diabetes in people whose kidney function is already deranged because they have CKD.

In both the kidney specific outcome studies and studies looking at SGLT-2 inhibitors in people with heart failure, the benefits in relation to the cardiac and kidney outcomes did not appear to diminish as the kidney function declined, down to at least a GFR of about 25-30 mL/min/1.73m^2.

This separation of the glucose and cardiac and kidney protective effect was exemplified further by the fact that, in the DAPA-CKD study and the heart failure specific studies, SGLT-2 inhibitors were beneficial even in people without diabetes.

6.2.8 Identifying individuals where there is benefit in prescribing SGLT-2 inhibitors

SGLT-2 inhibitors can only be recommended as a treatment if there is sufficient evidence to support that use and this is usually obtained from randomized controlled trials where participants in the trials are split randomly into those given the treatment and those given a dummy treatment. There are now a significant number of trials with SGLT-2 inhibitors that were designed first of all to assess the cardiovascular safety of these medications (cardiovascular outcome trials) as well as trials looking at these medications in people with heart failure and in people with kidney disease.

As these results have emerged, the licences (which determines how the treatment can be prescribed in the UK) for a number of SGLT-2 inhibitors have been broadened to allow the use of that specific SGLT-2 inhibitor for the purpose not just of glucose control, but also as protection against cardiovascular or kidney disease.

In assessing the evidence for benefit, one also needs to be clear about the outcomes that are being measured. For kidney disease there are many different potential outcomes that have been used in previous studies, however, not all of these clearly define outcomes that truly benefit people with CKD. Therefore, determination of benefit of SGLT-2 inhibitors for the purpose of generating recommendations in this guideline is based on real evidence for the reduction in progression of kidney disease which has been measured by the need to commence any form of kidney replacement therapy, death caused by kidney disease and significant reduction in decline in kidney function.

In the major cardiovascular outcome trials of all four of the SGLT-2 inhibitors, kidney effects were monitored and in all of these studies there was a decline in progression of kidney disease, need to commence kidney replacement therapy or death due to kidney disease. However, these effects were not the primary purpose of the studies and therefore there is a risk that the findings could have been identified by chance. Therefore, further studies have

been undertaken that have looked primarily at the effect of SGLT-2 inhibitors in people with kidney disease. These studies include:

1) CREDENCE which tested the SGLT-2 inhibitor canagliflozin in people with type 2 diabetes and evidence of diabetic kidney disease in the form of some reduction in GFR and the presence of protein in the urine
2) DAPA-CKD which tested the SGLT-2 inhibitor dapagliflozin in people with evidence of kidney disease in the form of a reduction in GFR and presence of protein in the urine but, importantly, not just in people with diabetes as a cause for their kidney disease.

Further studies looking at the effect of specific SGLT-2 inhibitors are currently underway and in particular this includes the EMPA-KIDNEY study which will extend the findings of CREDENCE and DAPA-CKD by including people both with and without diabetes, down to a lower level of GFR and people with CKD with much lower, or indeed absent, levels of protein in the urine.

CREDENCE and DAPA-CKD have confirmed the safety findings from the cardiovascular outcome trials and demonstrated significant kidney benefits of SGLT-2 inhibitors in people with CKD. These benefits included clear reduction in progression of diabetic kidney disease by approximately 30 to 50%. Overall, they also reduced occurrences of heart attacks and deteriorations of heart failure in people with CKD. The evidence is strongest for people with diabetes and protein in the urine but DAPA-CKD provided evidence that this benefit also extends to people with CKD without a diagnosis of diabetes, but with some degree of protein in the urine.

Because of these findings **this guideline recommends the initiation of SGLT-2 inhibitors in people with kidney disease caused both by type 2 diabetes and other causes down to an eGFR of 25 mL/min/1.73m^2, if the level of protein in the urine exceeds a urine albumin to creatinine ratio (this is the common way to represent the degree of protein in the urine) of 25 mg/mmol.** The guideline highlights that the evidence for this is strongest in people with type 2 diabetes. In addition, **the guideline recommends initiation of SGLT-2 inhibitors in people with CKD and a history of heart failure** (although only if they have a particular type of heart failure associated with reduction in the heart's pumping ability termed heart failure with reduced ejection fraction).

Once initiated, **this guideline recommends that the SGLT-2 inhibitor can be continued until the individual reaches end-stage kidney disease**.

Practically, the SGLT-2 inhibitor that would be utilised would be dependent on the current licence for that individual SGLT-2 inhibitor and whether primary care (general practitioners) are able to prescribe that specific medicine.

6.2.9 Groups where there is uncertainty

As described, it is only possible to recommend SGLT-2 inhibitor treatment for cardiac and kidney benefit in people who were represented in the studies of these medications, and in whom there is clear evidence of benefit.

There are a number of groups of people in whom it is not yet possible to be specific about the cardiac and kidney benefits of SGLT-2 inhibitors.

Currently, this includes people who have CKD caused by the genetically inherited condition called adult polycystic kidney disease and also in people who have specific inflammatory diseases that require the use of powerful medicines to suppress the immune system.

Type 1 Diabetes Mellitus

There are two main types of diabetes which include type 1 diabetes (which occurs more usually at a younger age and in which there is loss of the ability to produce insulin) and the much more common type 2 diabetes. Type 2 diabetes usually occurs in the older age group and is related to the ability of insulin to be effective, with the most common reason for this being association with obesity.

Whilst there have been some studies of SGLT-2 inhibitors in type 1 diabetes, these have not been sufficient to make a clear recommendation on the use of SGLT-2 inhibitors in people with type 1 diabetes. There may be benefits in people with type 1 diabetes, but there is a risk of a condition called diabetic ketoacidosis which is particularly high in people with type 1 diabetes. This means any potential benefits of SGLT-2 inhibitors may be finely balanced with potential risk of harm (more details below).

Heart failure with preserved ejection fraction

Heart failure has many different causes but broadly is divided into two main groups: those in which there is a reduction in the pumping ability of the heart, which is termed heart failure with reduced ejection fraction, and those where that pumping ability appears preserved but there are other factors that result in the failure of the heart to effectively pump blood around the circulation. This second group is termed heart failure with preserved ejection fraction.

SGLT-2 inhibitors have been demonstrated to provide significant benefit in people with heart failure and reduced ejection fraction, which is why they are recommended for use in those individuals both with CKD and with normal kidney function. In regard to those individuals with heart failure preserved ejection fraction, studies are likely to report in 2021/2022 and this guideline will be updated following the publication of this evidence.

People with functioning kidney transplants

Whilst it would be appealing to assume that the benefits that SGLT-2 inhibitors provide in relation to reduction in progression of CKD and protection against cardiovascular disease is present in all people with abnormal kidney function, kidney transplant recipients were not included in any of the trials. There is currently insufficient evidence at this time to recommend that people with a kidney transplant should be included in those initiated on SGLT-2 inhibitors. Whilst there are ongoing studies in this area, SGLT-2 inhibitors should only be offered to people with a kidney transplant after careful consideration and discussion between the kidney transplant team and the diabetes teams and with clear discussion undertaken with the individual with the kidney transplant.

6.2.10 Side effects of SGLT-2 inhibitors and how to avoid them

Every medication has potential to result in adverse events and it is important that these are appropriately understood in order for people to be advised appropriately about the risks of the medication and how it is possible for them to take steps to reduce any harm that could occur from taking a medication.

All people who are being prescribed new medications need information given to them that allows them to make an informed choice as to whether they wish to commence the treatment. This information needs to include a balance between both the risks of the medication and the potential benefit to them as an individual. Furthermore, the information needs to include advice on actions that would reduce the chance of harm coming to them by taking a particular medication.

SGLT-2 inhibitors have been found to have a number of adverse effects that people need to be informed about prior to initiation of this therapy. It is important to also appreciate that the likelihood of suffering an adverse effect may depend on the individual as well as the medication, and this would include factors such as whether they have diabetes, their age and their frailty.

6.2.11 Diabetes specific: diabetic ketoacidosis

SGLT-2 inhibition has an effect on the breakdown of carbohydrates and fats, which results in an excess of a group of substances known as ketones. These molecules are not dangerous of themselves, however, if the level of these ketones increases this can result in a dangerous situation in which the blood becomes very acidic which is termed ketoacidosis.

Ketoacidosis is a dangerous complication, seen most particularly in people with type 1 diabetes, but can occur in people with type 2 diabetes and there is evidence that SGLT-2 inhibitors increase the risk of this happening. Diabetic ketoacidosis usually occurs in conjunction with high levels of glucose, however, when it occurs in a person taking an SGLT-2 inhibitor, the excess glucose can be lost in the urine and this dangerous complication can occur in conjunction with normal levels of glucose which has the potential to confuse both the person with diabetes and the healthcare worker assessing the person.

The risk of diabetic ketoacidosis increases in the presence of infection or if the individual becomes dehydrated because of diarrhoea, vomiting or fasting. It also occurs in situations where there is not enough insulin, such as in people with type 2 diabetes who have low levels of their own insulin production and in situations when people who are treated with insulin have their insulin reduced, or even stopped.

A further factor that can be associated with an increased risk of diabetic ketoacidosis in people prescribed SGLT-2 inhibitors is the use of specific diets which are termed “very low carbohydrate” or ”ketogenic” diets and which increase the blood levels of ketones (such as the Atkins diet).

Because of their greater risk of suffering diabetic ketoacidosis, **people with type 1 diabetes should only be commenced on SGLT-2 inhibitors under strict direction of the diabetes team**, and may be offered lower doses.

It is also recognized that there are a group of people with type 2 diabetes who are at greater risk of diabetic ketoacidosis because they have lower levels of insulin. One can identify this group of individuals by features associated with low insulin levels, of which the most important are the rapid requirement for insulin treatment following diagnosis (within one year) and the presence of type 2 diabetes and low body weight. **It is recommended that for these people with type 2 diabetes who are at greater risk of diabetic ketoacidosis, SGLT-2 inhibitors should only be initiated after discussion with the diabetes team**.

If an individual prescribed SGLT-2 inhibitors develops diabetic ketoacidosis, it is recommended that the SGLT-2 inhibitor should be stopped and that individual should be reviewed by a member of their clinical team to determine whether treatment could be re-initiated in the future. That decision will be dependent on the analysis of the reasons why the diabetic ketoacidosis occurred, and whether with changes to treatment, or better advice on management, the risk of future diabetic ketoacidosis can be significantly reduced. That decision should be discussed between the clinical team and that individual themselves.

Because of the risk of diabetic ketoacidosis, **people started on SGLT-2 inhibitors need to be told about diabetic ketoacidosis and in particular the signs and symptoms of this**

disorder and the importance of seeking immediate medical advice if those symptoms develop.

Perhaps one of the most effective ways of preventing the occurrence of diabetic ketoacidosis is to use what are termed "sick day guidance". This is where a medication, which ordinarily has a significant benefit to the individual, can cause an adverse effect if it is continued when they become unwell with features of a fever or inability to maintain their fluid status (such as vomiting or diarrhoea). In this instance, it is important to miss out the specific medication (such as the SGLT-2 inhibitors) if they become unwell or if they are hospitalized. The medication should be resumed once the illness has passed or the person has been discharged from hospital. If a person stops their SGLT-2 inhibitor because of ill health and there is no improvement beyond a period of 48 hours they should seek medical attention. **It is for this reason that all people prescribed SGLT-2 inhibitors should be taught about sick day guidance to be used if they become unwell and that this advice is reiterated at every medication review.**

Because of the relationship of diabetic ketoacidosis to specific diets and to situations where the individual is taking a reduced fluid intake such as when fasting, **the individual should be advised not to follow these particular diets when on an SGLT-2 inhibitor and be given specific advice if they do choose to fast. This might include missing out the SGLT-2 inhibitors on fast days or testing for the presence of ketones if they become unwell**.

6.2.12 Diabetes specific: Low blood glucose or hypoglycaemia

SGLT-2 inhibitors have beneficial effects in improving blood glucose control, which is dependent on good kidney function. Hypoglycaemia is a situation where the person's blood glucose drops to a low level causing harm that varies from mild symptoms to profoundly significant symptoms including coma. Furthermore, severe hypoglycaemia can be associated with long-term damage affecting both the cardiovascular system and the brain. People who have suffered episodes of hypoglycaemia may have limitations on their ability to drive or to undertake certain occupational activities. Therefore, hypoglycaemia is a complication of diabetes that needs to be avoided and certainly minimised.

Whilst SGLT-2 inhibitors on their own do not produce hypoglycaemia, this can occur if they are used with a diabetes agent that has such a risk, such as insulin or the group of diabetes medications that work by directly stimulating insulin release (these are termed insulin secretagogues and include gliclazide, glimeprimide, glipizide, repaglinide etc.).

In people treated for their diabetes with insulin or insulin secretagogues, consideration needs to be given as to whether to reduce the current diabetes treatment when commencing an SGLT-2 inhibitor. The decision on whether to make this change should be discussed by the clinician prescribing the SGLT-2 inhibitor and the individual who is receiving it. This decision should be based on a number of factors and should include an assessment of the underlying blood glucose control of that individual. For example, someone who has poor blood glucose control as assessed by their HbA1c (this is the blood test that is used to assess average blood glucose control over the preceding 8 to 12 weeks), may benefit from the addition of the SGLT-2 inhibitor without the need for any reduction in their insulin or insulin secretagogues dose. Conversely, an individual with better controlled HbA1c may need a reduction in the SGLT-2 inhibitor, insulin or insulin secretagogue dose. Also, as has been described, if the kidney function of that individual is poor (GFR <45 mL/min/1.73m^2), then the blood glucose reducing effect of the SGLT-2 inhibitor will be significantly reduced and there may therefore be no reason to make that reduction in insulin or insulin secretagogue.

It is therefore recommended that **where the person being prescribed the SGLT-2 inhibitor has diabetes and is on insulin or an insulin secretagogue, the dose of these**

medications should be reviewed together with their prescribing clinician. If they are on a sulphonylurea and their HbA1c is <58 mmol/mol and their eGFR >45 mL/min/1.73m^2, the insulin secretagogue dose should be reduced by approximately 50% and the insulin by approximately 20% in order to avoid the risk of hypoglycaemia.

Where the person with type 2 diabetes is being prescribed an SGLT-2 inhibitor and they are not on an insulin secretagogue or insulin then there is no need to adjust any other diabetes medications.

There is no evidence to suggest that there is a risk of low blood glucose in people prescribed SGLT-2 inhibitors who do not have type 2 diabetes.

6.2.13 Acute kidney injury

Because of their mechanism of action, there can be an initial small, reversible reduction in kidney function over the first few weeks after commencing an SGLT-2 inhibitor. This results from changes to the blood flow in the kidneys with a small reduction in the blood flow going through the filtering units (glomeruli). This effect is believed to be protective rather than an indicator of harm. In all the major cardiovascular outcome trials, there was an initial small fall in GFR (of the order of 2 to 5% but with wide variation within the individual studies) and thereafter stabilisation of the GFR in participants given an SGLT-2 inhibitor. In the placebo group, there was a slow progressive decline in GFR such that the kidney function of the placebo-treated participants was significantly lower than the SGLT-2 inhibitor treated participants at the end of the study.

Further reassurance of the lack of harm and indeed possible beneficial effect of SGLT-2 inhibitors in relation to acute kidney injury is the fact that in all the major cardiovascular outcome trials, kidney studies and heart failure studies, the incidence of acute kidney injury (this is where there is a significant drop in kidney function which is usually reversible) was always greater in the placebo-treated groups compared to the SGLT-2 inhibitor-treated groups. It may even be that SGLT-2 inhibitors protect against acute kidney injury.

It is important that this effect is properly understood so that people who are prescribed SGLT-2 inhibitors and who may gain significant benefit from these medications do not have them stopped because of changes in GFR if measured in the period following prescription of these agents.

It is therefore recommended that when a person is commenced on an SGLT-2 inhibitor, there is no need to check the kidney function in the early period following initiation of treatment, but this should be undertaken at the next usual review appointment for that individual. Furthermore, it is also recommended that if kidney function is assessed for another reason within the first few weeks following initiation of an SGLT-2 inhibitor, the result needs to be interpreted carefully and unwarranted discontinuation of treatment should not occur.

6.2.14 Dehydration issues

SGLT-2 inhibitors do cause an increase in urine output (diuretic effect), both because of the fact they result in loss of sodium (salt) in the urine but also because the extra glucose in the urine pulls in water to the urine. As a result, people started on these agents can experience an increased frequency of passing urine which is most prominent in the first few weeks after commencing the medication.

For the vast majority of people this is nothing more than a minor issue which reduces over time but there are occasional individuals who are at risk of dehydration when starting an SGLT-

2 inhibitor. It is difficult to be certain how often this occurs because in all the trials that have been undertaken with SGLT-2 inhibitors there is variation in how this side effect is reported. In studies where there has been an increased frequency of dehydration issues reported, the increase has been small, affecting an extra 1-2 people out of 100. It is, however, most probable that it is only really relevant to individuals who are already taking "water-tablets" (diuretics) and particularly if they are taking these at high doses.

It is therefore recommended that if a person who is prescribed an SGLT-2 inhibitor is already on either diuretic or blood pressure medication, the prescriber should consider whether an early review to assess for dehydration or low blood pressure is undertaken and if either of these are identified, a reduction in the dose of either of these additional diuretic or blood pressure medications is required. Furthermore, if a person being commenced on an SGLT-2 inhibitor is already on a diuretic, they should be counselled on symptoms of dehydration or low blood pressure so they can seek medical attention if they develop such symptoms.

In addition it is important again to remind people being treated with SGLT-2 inhibitors to use good sick day guidance and omit SGLT-2 inhibitors if they are unwell.

6.2.15 Peripheral vascular disease

People with CKD, and especially those with diabetes, are at an increased risk of suffering disorders of their cardiovascular system which includes disorders that affect the blood supply to their legs, termed “peripheral vascular disease”.

In all the cardiovascular outcome trials for SGLT-2 inhibitors, issues relating to peripheral vascular disease were monitored and recorded. In one of the larger trials in people with type 2 diabetes (called CANVAS), the medication canagliflozin significantly increased the number of amputations undertaken in the group allocated to an SGLT-2 inhibitor compared to those allocated to placebo. This increased incidence of amputation (mainly of toes) was not identified in any of the other cardiovascular outcome trials which included large numbers of participants who were broadly similar to those recruited to CANVAS. Furthermore, in a study that looked at people with kidney disease and diabetes known as CREDENCE, and which also used canagliflozin, there was no increased risk of amputation despite the fact that this group of participants were at high risk of vascular disease.

Because of these findings a warning has been placed by the regulators in relation to using canagliflozin in people at high risk of amputation.

It is important to understand that any increased risk of amputation, if it exists, is significantly less than the benefits canagliflozin treatment would have in those individuals. **It is for this reason that we recommend that when a person has evidence of active foot disease caused by problems with the blood supply, no SGLT-2 inhibitor should be started and if they have already been commenced on one of these agents then this should be withheld.** However, because of the benefits that are likely to occur in these individuals it is also a recommendation **that once the active foot disease has been effectively treated, discussion should occur with the individual in relation to the risks and benefits so that a decision can be made whether the resumption of an SGLT-2 inhibitor is in the person’s interests and in accordance with their wishes.** Similarly, a discussion of this nature should be held prior to commencing an SGLT-2 inhibitor in a person with high risk of vascular disease.

We define active peripheral vascular disease as the presence of foot ulcers, what is termed intermittent claudication (which is when there is pain over the back of the calves associated with walking) or where there is other evidence of reduced blood supply to the legs and feet.

In order to reduce the chance of any harm occurring to a person prescribed SGLT-2 inhibitors, we recommend **that all such individuals (and most particularly individuals with diabetes) should be given advice on good foot care and the importance of seeking early attention should any problems develop**.

6.2.16 Bone Health

Within the CANVAS trial there was a small increase in fractures in the group allocated to canagliflozin. However, this has not been identified in any other cardiovascular outcome trial using an SGLT-2 inhibitor, nor in other studies using canagliflozin, such as CREDENCE. Therefore it is uncertain as to whether this is a real effect or just a result of the play of chance in that trial. People with CKD are at a greater risk of suffering from bone disorders and good practice already recommends that all these individuals should have measurements of good bone health monitored on a regular basis. **It is our recommendation that any person with kidney disease who is commenced on an SGLT-2 inhibitor should receive the good care in relation to their bone health as recommended by national guidelines**.

6.2.17 Fungal genital infections (i.e. thrush)

Because the use of SGLT-2 inhibitors results in an increase in sugar in the urine, this can provide an environment in which certain fungal infections thrive and therefore an increase in these infections locally. These infections are termed genital infections and are typified by thrush, which is not an uncommon infection, particularly in women and particularly in people with diabetes.

All SGLT-2 inhibitors increase the risk of thrush. This is not a dangerous complication, but can cause irritation and needs to be managed appropriately. Symptoms involve irritation or itchiness and redness or inflammation in the genital area (vulva-vagina for women and tip of the penis in men (inflammation of which is known as balanitis)). It is most likely that the risk is greater if the person being treated has type 2 diabetes.

Before anyone starts an SGLT-2 inhibitor **they need to be counselled on the risk of fungal genital infections such as thrush and on simple measures that they can implement to maintain good genital hygiene and thereby reduce the risk of thrush. They also need to be counselled on the symptoms of genital infections and how to seek help which can often be attained simply by attending a local pharmacist** to obtain an antifungal cream. This advice is most particularly important for men as they may not have as much knowledge of thrush as women.

If genital infections such as thrush occur while a person is using an SGLT-2 inhibitor they should be treated, but they do not necessarily need to stop the SGLT-2 inhibitor. Usually once treated the genital infection does not recur but if the individual suffers recurrent infections their GP can give them treatment to prevent infections which is either a cream or a tablet they take intermittently.

6.2.18 Fournier's gangrene

Fournier's gangrene is a serious infection caused by bacteria infecting the skin in the genital area. It is exceedingly rare but theoretically it could be increased if the individual has an increased glucose concentration in the urine and it is recognized to occur, albeit very rarely, in people with diabetes. Occasional reports have been made of people suffering this complication while being treated with an SGLT-2 inhibitor and because of this the regulators have placed a warning of this complication for people using SGLT-2 inhibitors. It should be pointed out that no increased cases of Fournier's Gangrene were identified in any of the

cardiovascular outcome trials undertaken, which included large numbers of participants. However, even though we do not know whether SGLT-2 inhibitors truly increase the risk of this disorder, **we recommend that all people started on an SGLT-2 inhibitor are counselled on the symptoms of Fournier's Gangrene and advised to stop their SGLT-2 inhibitor and seek urgent medical attention if they develop such symptoms**. The main symptom to be aware of is severe pain on pressing the skin over the groin area.

6.2.19 Urinary infections

SGLT-2 inhibitors produce an increased amount of glucose in the urine and although there were initial reports that this could be associated with an increased risk of urine infections, there has been very little evidence from the studies of such an increase. The absence of increase may relate to the fact that bacteria do not thrive in environments with high glucose and also there is an increase in urine output which works to help "flush away" bacteria in the urinary tract. There is a need to be alert to this, but it is unlikely that a person with a normal bladder and bladder function will have an increased risk of urine infection when using SGLT-2 inhibitors.

6.2.20 Special populations: Children, pregnancy and breastfeeding

There is little experience in using SGLT-2 inhibitors in children and therefore it is not recommended that these medications are used in people under the age of 18.

There is some theoretical evidence that SGLT-2 inhibitors, at much higher doses and in animal models, can potentially result in malformations and therefore the use of these medications in pregnancy should be avoided. If a person who is being treated with SGLT-2 inhibitors wishes to consider pregnancy they should discuss this with their doctor and plan the pregnancy in advance with a plan to stop the SGLT-2 inhibitor prior to becoming pregnant, or if an unplanned pregnancy occurs.

Whilst there is no real evidence to suggest that SGLT-2 inhibitors is passed in the breastmilk in important quantities, it is not recommended that these agents should be used when breastfeeding.

6.3 EXAMPLE PATIENT INFORMATION SHEET FOR A PERSON BEING INITIATED ON AN SGLT-2 INHIBITOR WHO ALSO HAS DIABETES

Getting the most from your sodium glucose co-transporter-2 inhibitors (SGLT-2i) (for people with diabetes)

Information for patients, relatives and carers

Introduction

This leaflet has been designed to give you information about sodium glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) and answers some of the questions that you or those who care for you may have about these medicines. It is not meant to replace the discussion between you and your medical team but aims to help you understand more about what is discussed. If you have any questions about the information below, please contact the person who provided you with this leaflet.

What are SGLT-2 inhibitors and who benefits from using them?

You are being treated with one of the SGLT-2 inhibitor medicines, sometimes known as "gliflozins" or "flozins". These include, canagliflozin (*Invokana*), dapagliflozin (*Forxiga*), empagliflozin (*Jardiance*) and ertugliflozin (*Steglatro*).

These medicines lower blood glucose (sugar) by increasing the amount of glucose in the urine, which is why these medicines are used for people who have diabetes. They have added benefits that include protecting the kidneys and heart, slowing the decline in kidney function and reducing the risk of heart failure and heart attacks in individuals at most risk.

Are there any side effects?

Common:

- **Hypoglycaemia (low blood glucose)** – this usually only occurs if SGLT-2 inhibitors are used in combination with certain other diabetes medicines and your doctor may therefore need to reduce other diabetes medicines. However, never stop insulin altogether if you are already on this.

- **Dehydration** – Dehydration is when your body does not have as much water as it needs. These medicines increase the amount of urine that you pass so may cause dehydration. To prevent dehydration, drink fluids when you feel any dehydration symptoms and you should drink enough during the day so your urine is a pale clear colour (unless otherwise instructed by your doctor). It is also important to drink when there is a higher risk of dehydrating, for example, if you're vomiting, sweating or you have diarrhoea.

- **Fungal genital infections** – As these medicines increase the glucose in your urine, there is an increased risk of certain infections, such as thrush around the vagina and penis. However, this is easily treated (usually with a cream) and a pharmacist or your GP can

give you advice if irritation or itching occurs in these areas. Washing your genital area with warm water using non-perfumed soap and avoiding wearing tight underwear will reduce the risk of infection.

Uncommon:

- **An increase of acid in the blood**– SGLT-2 inhibitors may cause certain acids (ketones) to build up in the blood. This is called **diabetic ketoacidosis (DKA).** This is a rare event but can happen ***even when your blood glucose is normal.*** Symptoms include nausea and vomiting, abdominal pain, rapid breathing, and dehydration e.g. dizziness and thirst. Suffers' breath smells like pear-drops/nail varnish remover.

  The risk of DKA is increased if you do not eat for long periods, become dehydrated, reduce your insulin dose too quickly, drink excessive alcohol or are unwell. **Please seek medical advice before starting any new diet** particularly very low carbohydrate diets (also called ketogenic diets) as these can increase the ketones in the blood.

  DKA is a serious health condition. **If you believe you are developing symptoms of DKA then please seek urgent medical assessment** reporting your concern and the medication you are taking.

- **Foot disease leading to toe or other amputation** – if you have been told you have an "at risk foot" you should clarify with your doctor if you should start or remain on one of these medicines. If you have an active foot ulcer or problem with the blood supply in your leg you should stop these medicines.

Exceedingly rare:

- **"Fournier's gangrene" –** this is an exceedingly rare infection in the groin area requiring urgent medical attention. The main symptom to be aware of is severe pain on pressing the skin over the groin area. If this develops, stop your SGLT-2 inhibitor and seek clinical advice.

Should I stop taking these tablets if I become unwell?

It is best practice to use **good sick day guidance** with these medications. You should miss them out if unwell especially in the presence of vomiting, diarrhoea or fever. You should also miss out your SGLT-2 inhibitor if you are fasting (e.g. before an elective surgical operation). You can restart them when you are better, however if you remain unwell (e.g. for longer than 48 hours), we advise you seek medical advice from your GP/Pharmacist/NHS 111.

Sick day guidance for people with diabetes

If you are unwell (vomiting, diarrhoea, fever, sweats and shaking), you should **temporarily** miss out the medicines listed below. If you are unsure or have any questions please seek medical advice.

- **blood pressure pills** – e.g. ramipril, lisinopril, losartan or other medicines ending with -sartan or -pril
- **diuretics** - (water tablets) e.g. furosemide, bumetanide, spironolactone
- **diabetes pills** -e.g. metformin, and your SGLT-2 inhibitor/'gliflozin'. Do **not** stop taking your insulin

If you have diabetes, you must increase the number of times you check your blood glucose levels. If they run too high or low, please seek medical advice.

Restart your medicines as soon as you are well and eating normally. Please seek medical advice if you continue to feel unwell after 48 hours.

6.4 EXAMPLE PATIENT INFORMATION SHEET FOR A PATIENT BEING INITIATED ON AN SGLT-2 INHIBITOR WHO DOES NOT HAVE DIABETES

Getting the most from your sodium glucose co-transporter-2 inhibitors (SGLT-2i) (for people without diabetes)

Information for patients, relatives and carers

Introduction

This leaflet has been designed to give you information about sodium glucose co-transporter-2 inhibitors (SGLT- 2 inhibitors) and answers some of the questions that you or those who care for you may have about these medicines. It is not meant to replace the discussion between you and your medical team but aims to help you understand more about what is discussed. If you have any questions about the information below, please contact the person who provided you with this leaflet.

What are SGLT-2 Inhibitors and who benefits from using them?

You are being treated with one of the SGLT-2 inhibitors medicines, sometimes known as "gliflozins" or "flozins". These include, canagliflozin (*Invokana*), dapagliflozin (*Forxiga*), empagliflozin (*Jardiance*) and ertugliflozin (*Steglatro*).

These medicines were initially developed to treat people with diabetes as they lower blood glucose (sugar) by increasing the amount of glucose in the urine. They have been found to have additional benefits that include protecting the kidneys and heart, slowing the decline in kidney function and reducing the risk of heart failure and heart attacks in individuals at most risk.

Are there any side effects?

Common:

- **Dehydration** – Dehydration is when your body does not have as much water as it needs. These medicines increase the amount of urine that you pass so may cause dehydration. To prevent dehydration, drink fluids when you feel any dehydration symptoms and you should drink enough during the day so your urine is a pale clear colour (unless otherwise instructed by your doctor). It is also important to drink when there is a higher risk of dehydrating, for example, if you are vomiting, sweating or you have diarrhoea.

- **Fungal genital infections** – As these medicines increase the glucose in your urine, there is an increased risk of certain infections, such as thrush around the vagina and penis. However, this is easily treated (usually with a cream) and a pharmacist or your GP can give you advice if irritation or itching occurs in these areas. Washing your genital area with warm water using non-perfumed soap and avoiding wearing tight underwear will reduce the risk of infection.

Uncommon side effects that are expected to be extremely rare in people without diabetes

There are a series of side effects which may almost exclusively affect people with diabetes. These are uncommon or extremely rare, and are highly unlikely to affect people without diabetes:

- **An increase of acid in the blood** – SGLT-2 inhibitors may cause certain acids (ketones) to build up in the blood. This is called **ketoacidosis.** This is an event that occurs rarely in people without diabetes. The risk of ketoacidosis is increased if you do not eat for long periods, become dehydrated, drink excessive alcohol or are severely unwell. Please seek medical advice before starting any new diet particularly very low carbohydrate diets (also called ketogenic diets) as these can increase the ketones in the blood. Ketoacidosis presents with nausea and vomiting, abdominal pain, rapid breathing, and dehydration e.g. dizziness and thirst. Suffers' breath smells like pear-drops/nail varnish remover. Ketoacidosis requires urgent medical assessment.
- **Foot disease leading to toe or other amputation –** if you have been told you have an "at risk foot" because of poor blood supply you should clarify with your doctor if you should start or remain on one of these medicines. If you have an active foot ulcer or problem with the blood supply in your leg you should stop these medicines.
- **Hypoglycaemia (low blood glucose)** – this usually only occurs if SGLT-2 inhibitors are used in people with diabetes in combination with insulin.
- **"Fournier's gangrene" –** this is an exceedingly rare infection in the groin area requiring urgent medical attention. The main symptom to be aware of is severe pain on pressing the skin over the groin area. If this develops, stop your SGLT-2 inhibitor and seek clinical advice.

Should I stop taking these tablets if I become unwell?

It is best practice to use **good sick day guidance** with these medications. You should miss them out if unwell especially in the presence of vomiting, diarrhoea or fever. You should also miss out your SGLT-2 inhibitor if you are fasting (e.g. before an elective surgical operation). You can restart them when you are better, however if you remain unwell (e.g. longer than 48 hours), we advise you seek medical advice from your GP/Pharmacist/NHS 111.

Sick day guidance for people without diabetes

If you are unwell (vomiting, diarrhoea, fever, sweats and shaking), you should **temporarily** miss out the medicines listed below. If you are unsure or have any questions please seek medical advice.

- **blood pressure pills** – e.g. ramipril, lisinopril, losartan or other medicines ending with -sartan or -pril
- **diuretics** - (water tablets) e.g. furosemide, bumetanide, spironolactone
- **your SGLT-2 inhibitor/"gliflozin"** – i.e. canagliflozin, dapagliflozin, empagliflozin or ertugliflozin being used to treat your kidney disease

Restart your medicines as soon as you are well and eating normally.
Please seek medical advice if you continue to feel unwell after 48 hours.

Section 7: Use in special populations of specific interest

7a Type 1 diabetes mellitus (DM)

7a.1 BACKGROUND

7a.1.1 Summary of trial evidence

Dapagliflozin is currently the only sodium-glucose co-transporter-2 (SGLT-2) inhibitor licensed for use in people with type 1 diabetes mellitus (DM). Although the National Institute for Health & Care Excellence (NICE) have issued a Technology Appraisal on dapagliflozin and sotagliflozin in people with type 1 DM and BMI >27 kg/m^2, sotagliflozin is not yet available in the NHS. The Association of British Clinical Diabetologists (ABCD) & Diabetes UK have released some guidance on the use of SGLT-2 inhibitors in type 1 DM, which highlights the need for closer monitoring and education in this population, particularly in relation to ketone monitoring (1).

Glycaemic control

There are a number of randomized controlled trials (RCTs) evaluating the use of SGLT-2 inhibitors in people with insufficiently controlled type 1 DM. The DEPICT-1 and -2 trials demonstrated that the addition of dapagliflozin (at either 5 mg and 10 mg daily doses) to existing insulin-based regimens reduces glycosylated haemoglobin (HbA1c) and body weight compared to placebo without provoking additional hypoglycaemia (2,3). The EASE-1 trial examined the short-term (28 days) efficacy of adding empagliflozin to insulin and found that HbA1c was significantly reduced by between −3.8 to −5.4 mmol/mol (-0.35% to -0.49%, p<0.05) when compared with placebo (4). Similarly, a trial assessing canagliflozin in people with type 1 DM found that significantly more people achieved a reduction of >0.4% in HbA1c with 100 mg and 300 mg of canagliflozin versus placebo (36.9%, 41.4% vs 14.5%; p<0.001) (5). In summary, evidence from RCTs indicates that SGLT-2 inhibitors as an adjunct to insulin improves glycaemic control in people with insufficiently controlled type 1 DM.

Renal outcomes

There are no large clinical trials reporting renal outcomes of SGLT-2 inhibitors in people with type 1 DM. There are *ad hoc* analyses of larger trials that show benefit in reduction of urinary albumin:creatinine ratio (uACR). DEPICT-1 and -2 trials showed that after a year, the addition of dapagliflozin to insulin resulted in a dose-dependent reduction of uACR (≥3 mg/mmol) of −13.3% (95%confidence interval [CI]−37.2 to 19.8; for the 5mg dose) and −31.1% (95%CI −49.9% to −5.2%; for 10 mg dose), compared to placebo (2,3).

The Tandem-1 and -2 trials evaluated the effect of sotagliflozin versus placebo in people with type 1 DM. *Ad hoc* analysis of the Tandem-1 and -2 showed that in a subgroup of participants (n = 196) with mean elevated albuminuria (uACR ≥30 mg/g [3.4 mg/mmol]) at baseline, an initial dose-dependent reduction of mean albuminuria by −31.4% (SE 11.3: p=0.003) from baseline was observed for sotagliflozin 400 mg at week 24. This reduction was attenuated (and non-significantly different to placebo) at week 52 (−18.3% (SE 13.8): p=0.18) (6,7). Small trial size and short follow-up means there are no data available on regulator-accepted endpoints based on glomerular filtration rate (GFR) or need for renal replacement therapy (or cardiovascular outcomes) in type 1 DM, even from the 1402 participant in Tandem-3 trial (8).

Safety

In the DEPICT-1 Trial, insulin dose was reduced by an average (mean) of 14% in the first 2 weeks of starting dapagliflozin (2). In the DEPICT-2 trial, the reduction of insulin was between 10-11% (3). Both trials found no significant difference in the rates of hypoglycaemia between SGLT-2 inhibitors and placebo. During the first 7 days of the EASE-1 trial, insulin doses were kept as stable as possible, thereafter being adjusted according to glycaemic control. During these first 7 days, the rate of hypoglycaemia was higher in the 10 mg and 25 mg empagliflozin arm, than the 2.5 mg empagliflozin and placebo arm. After the first week however, when insulin doses were adjusted, there was no significant difference in hypoglycaemia rates (4). See Section 5b for more information on severe hypoglycaemia risk with SGLT-2 inhibition.

Whilst there were no diabetic ketoacidosis (DKA) events during the short EASE-1 trial (4), the DEPICT-1 and -2 trials demonstrated an increased risk of DKA in the SGLT-2 inhibitor group when compared to placebo (46.2 versus 12.7 events per 1000 patient years). In an 18 week trial, the DKA rates were increased in the canagliflozin 100 mg or 300 mg, at 4.3% and 6.0% in comparison to 0% in the placebo group (5). Differences in the adjudication definitions of DKA and recruited populations can influence the cross-trial comparability and generalisability of these DKA rates from trials. It is not necessarily the case that one SGLT-2 inhibitor carries greater susceptibility for DKA than another. See Section 5a for more details on DKA.

7a.1.2 Quality of the evidence

There are no data as yet, indicating whether SGLT-2 inhibitors provide renal benefits in relation to regulatory accepted renal endpoints based on GFR in people with type 1 DM. There are data that clearly demonstrate substantial excess absolute risk of DKA in people with type 1 DM. The lack of trial evidence on renal outcomes in people with type 1 DM precludes direct comparisons of the potential balance of the definite risks versus the potential benefits.

7a.2 RECOMMENDATIONS FOR IMPLEMENTATION

1. We recommend that SGLT-2 inhibitors be initiated in people with type 1 DM, only under the strict direction of the diabetes team (Grade 1C).

2. We suggest considering referring people with type 1 DM to the specialist Diabetes team, for consideration of an SGLT-2 inhibitor, if they have an eGFR ≥25 mL/min/1.73m^2 and an uACR ≥25 mg/mmol attributable to diabetic nephropathy despite being on maximum tolerated ACEi/ARB (Grade 2D).

3. We recommend all people with type 1 DM started on SGLT-2 inhibitors be provided with ketone monitoring, be advised on the signs and symptoms of DKA and to seek immediate medical advice if any of these symptoms develop or ketone levels are >0.6 mmol/L (Grade 1B).

Rationale: There is currently insufficient evidence to recommend the use of SGLT-2 inhibitors as an adjunct to existing therapies in the management of diabetic nephropathy in people with type 1 DM. Evidence of renal benefits in people with type 2 DM makes this plausible but such results cannot be readily extrapolated to people with type 1 DM. Clinicians may wish to discuss treatment options with their patients and other specialists in cases where proteinuria persists despite current standard treatment.

7a.3 CLINICAL RESEARCH RECOMMENDATIONS

1. To establish whether the cardiovascular and renal benefits of SGLT-2 inhibitors extend to those with type 1 DM

2. To establish the safety of SGLT-2 inhibitors in people with type 1 DM and chronic kidney disease

7a.4 REFERENCES

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Section 7: Use in special populations of specific interest

7b Kidney transplant recipients

7b.1 BACKGROUND

7b.1.1 Summary of trial evidence

Kidney transplantation offers advantages compared to other forms of renal replacement therapy for many subtypes of patient with end-stage kidney disease (ESKD), including people with diabetic nephropathy. These include potentially better quality of life and longer survival (1, 2). Currently, about 18% of incident UK kidney transplants are performed for diabetic nephropathy (3), and once transplanted new onset diabetes after transplantation (NODAT [also known as post-transplant DM) is common. NODAT is important to identify as it predicts future mortality and graft failure (4). Its incidence has fallen over the last two decades and varies by diagnostic criteria and immunosuppressive protocol, but can still be as high as 10-20% during the first year after transplantation (5).

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors may have the potential to prevent and treat NODAT. From their mechanism of action, they may also provide cardioprotective and renal benefits in people with a kidney transplant (see Section 1 for details of SGLT- inhibitors' mechanisms of action). However, kidney transplant recipients are also particularly susceptible to graft function loss with ascending urinary tract infections, and immunosuppression predisposes to genital mycotic infections. People on immunosuppression for renal disease and those with kidney transplants have been excluded from the reported large placebo-controlled clinical outcome SGLT-2 inhibitor trials, including those specifically recruiting people with chronic kidney disease (CKD) (see Table 1.1 in Section 1) (6, 7).

A series of small observational studies have reported experience of prescribing SGLT-2 inhibitors to kidney transplant recipients (8, 9), but our literature review identified a single randomized trial by Halden and colleagues (10). This single-centre 24-week placebo-controlled trial was conducted in a population of people with NODAT who were at least one year since transplantation with stable graft function. Below we provide a summary of this single trial and offer a summary statement.

Effects of SGLT-2 inhibition on hyperglycaemia, weight, blood pressure, kidney function, and adverse events in NODAT from Halden et al. (10).

Halden *et al.* analysed 44 participants with NODAT randomized 1:1 to empagliflzoin 10mg versus matching placebo. Mean baseline kidney function was just over 60 mL/min/1.73m^2 and median glycosylated haemoglobin (HbA1c) was ~6.9% (~52 mmol/mol). At 24 weeks, median change in HbA1c from baseline was -0.2% (-2.0 mmol/mol) among those allocated empagliflozin versus +0.1% (+1.0 mmol/mol) among those allocated placebo (difference in change between arms p=0.025: Table 7b.1). There were no significant differences in other glycaemic or insulin parameters, including fasting or 2-hour blood glucose, insulin or c-peptide concentrations (Table 7b.1) (10). The effect on HbA1c varied by baseline estimated glomerular filtration rate (eGFR), with the expected pattern of larger HbA1c reductions among those with an eGFR ≥60 mL/min/1.73m^2, and almost no difference in HbA1c among those with an eGFR of 40-50 mL/min/1.73m^2 (people with an eGFR <30 mL/min/1.73m^2 were excluded). This attenuated effect on HbA1c corresponded to a linear decrease in glucose excretion with lower eGFR.

Table 7b.1: Effects of empagliflozin 10mg versus placebo on glycaemia, weight, blood pressure and kidney function in kidney transplant recipient with new onset diabetes after transplantation from Halden et al. (10)

Assessment	Empagliflozin			Placebo			*P value**
	Baseline	Week 24	**Change**	Baseline	Week 24	**Change**	
HbA1c (%)	6.9 (6.5, 8.2)	6.7 (6.3, 7.5)	**-0.2 (-0.6, -0.1)**	6.6 (6.1, 7.2)	6.9 (6.4, 7.4	**0.1 (-0.1, 0.4)**	***0.025***
Fasting plasma glucose (mmol/L)	8.0 (7.3, 8.6)	7.2 (6.6, 8.1)	**-0.65 (-1.2, -0.13)**	7.3 (6.5, 8.6)	7.5 (6.8, 8.4)	**0.30 (-0.45, 0.55)**	***0.27***
2-hour glucose after oral glucose tolerance test (mmol/L)	15.6 (13.3, 17.7)	14.2 (12.4, 15.6)	**-1.75 (-3.7, 0.93)**	13.3 (10.3, 17.4)	14.1 (10.5, 16.9)	**-0.40 (-1.4, 1.4)**	***Not significant, approaching 1.0***
Body weight (kg)	92.0 (81.8, 104.5)	88.8 (79.0, 100)	**-2.5 (-4, -0.05)**	84.0 (79.3, 94.0)	85.0 (79.5, 97.5)	**1.0 (0.0, 2.0)**	***0.01***
Mean 24-h systolic BP (mmHg)	136 (131, 147)	142 (126, 148)	**2 (-5, 6)**	135 (127, 146)	137 (132, 143)	**2 (-7, 6)**	***Not significant, approaching 1.0***
Mean 24-h diastolic BP (mmHg)	76 (71, 82)	76 (70, 82)	**0 (-5, 2)**	78 (74, 85)	80 (74, 86)	**1 (-3, 4)**	***Not significant, approaching 1.0***
eGFR (mL/min/1.73 m^2)	66 (57, 68)	61 (56, 67)	**-3 (-7, 0)**	59 (52, 72)	59 (52, 67)	**-1.0 (-2.8, 0.75)**	***Not significant, approaching 1.0***
Renal glucose excretion (g/24 h)	0.45 (0.20, 1.48)	46.0 (36.8, 68.6)	**45.9 (36.1, 64.3)**	0.5 (0.1, 2.3)	1.5 (0.2, 4.5)	**0.20 (0.0, 1.6)**	***<0.001***

BP= blood pressure; eGFR=estimated glomerular filtration rate; HbA1c=glycosylated haemoglobin;
* *p* values calculated from difference in change between baseline and 24 weeks among the 22 allocated empagliflozin versus the 22 allocated placebo.

At 24 weeks, there was evidence that empagliflozin reduced weight, but there was no difference in blood pressure between the study arms (Table 7b.1). Blood levels of calcineurin inhibitors and everolimus were also not significantly different between the empagliflozin and placebo arms (10). At 8 weeks of follow-up, eGFR acutely declined by an average of -4 mL/min/1.73m^2 among those allocated empagliflozin versus -1 mL/min/1.73m^2 among those allocated to placebo. By 24 weeks, this difference had reduced to -3 versus -1 mL/min/1.73m^2 (Table 7b.1).

Empagliflozin was generally well tolerated. One participant allocated empagliflozin withdrew from the trial due to urosepsis. There were three urinary tract infections in each arm, and no reported episodes of rejection (10).

7b.1.2 Quality of the evidence

Currently, the reported randomized evidence of the effects of SGLT-2 inhibitors in kidney transplant recipients is limited to less than 50 trial participants with NODAT followed for less than 6 months from a single centre. There is therefore currently insufficient data to provide specific evidence-based recommendations for safe use of SGLT-2 inhibition in this population (11). There are a number of older anti-diabetic treatments with well-known safety profiles which can be used to treat hyperglycaemia in NODAT. This section of this guideline will be updated as more randomized evidence becomes available.

7b.2 SUMMARY STATEMENTS

1. There is currently insufficient evidence on safety and efficacy to provide recommendations for use of SGLT-2 inhibition in people with a functioning kidney transplant

2. Any use of SGLT-2 inhibition to treat diabetes mellitus in a kidney transplant recipient should be evaluated by multi-disciplinary discussion (grade 2D)
Note: effects on glycaemic control at an eGFR <60 mL/min/1.73m^2 in people with a kidney transplant appear small and potential risk of complications from urinary tract infection should be considered.

7b.3 CLINICAL RESEARCH RECOMMENDATIONS

The generation of reliable randomized trial evidence for transplant recipients is a key research recommendation. Please refer to section 2.3.

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Section 7: Use in special populations of specific interest

7c Heart failure with preserved ejection fraction (HFpEF) and acute decompensated heart failure (irrespective of ejection fraction)

7c.1 BACKGROUND

7c.1.1 Summary of trial evidence

High-quality randomized evidence from DAPA-HF and EMPEROR-REDUCED supports the use of SGLT-2 inhibition in patients with stable symptomatic heart failure with reduced ejection fraction (HFrEF) (1, 2), and the SOLOIST-WHF trial demonstrated cardiac benefit in patients with type 2 diabetes mellitus (DM) who had been recently hospitalised with worsening heart failure, irrespective of ejection fraction (3). However, compared to HFrEF, our literature review found more limited information on whether SGLT-2 inhibition has cardiac benefits in people with heart failure with preserved ejection fraction (HFpEF).

We found information in people with HFpEF from subgroup analyses from the large placebo controlled trials, plus a series of smaller trials powered to assess effects on symptoms or measures of cardiac function. The large trials providing information on cardiac outcomes were all in people with type 2 DM and compared results in those with and without HFpEF. They included: the SOLOIST-WHF trial (3); the SCORED trial in people with type 2 DM and chronic kidney disease (CKD) (4), and two of the completed large clinical outcome trials in people with type 2 DM at high atherosclerotic cardiovascular risk (DECLARE-TIMI 58 & VERTIS CV (5, 6)).

The evidence on which to base guideline recommendations in HFpEF will change in 2021/2022 when the EMPEROR-PRESERVED and DELIVER trials report. Each of these two trials has recruited about 6000 patients with stable HFpEF (i.e. heart failure and a left ventricular ejection fraction (LVEF) >40%) with and without DM. Eligibility criteria allow for recruitment of people with estimated glomerular filtration rates (eGFRs) as low as 20 and 25 mL/min/1.73m^2, respectively (7, 8). Table 1.1 in Section 1 provides more details of eligibility criteria and pre-specified outcomes. EMPEROR-PRESERVED has announced positive results, but a formal report is awaited (9).

There is also emerging data on the use of SGLT-2 inhibition in people with acutely decompensated heart failure (10). Below, we provide a summary of the currently available randomized data for the cardiac benefits of SGLT-2 inhibition in HFpEF and in acute decompensated heart failure irrespective of LVEF. We also offer a summary statement regarding people with these conditions in the context of CKD.

Effects of SGLT-2 inhibition on cardiac outcomes in HFpEF

Table 7c.1 lists the four large SGLT-2 inhibitor trials that have provided subgroup analyses comparing results by the presence or absence of HFpEF (3, 4, 11, 12). The analyses which are most relevant to people with CKD are those provided by the SCORED and SOLOIST-WHF trials in which about 20% of the trial populations had HFpEF and median eGFR was 45 and 50 mL/min/1.73m^2, respectively. Both trials demonstrated that, compared to placebo, sotagliflozin reduced the risk of the primary outcome of total number of deaths from cardiovascular causes and hospitalisations/urgent visits for heart failure (i.e. first and subsequent events). In SCORED, overall there was a 26% relative risk reduction (hazard ratio

[HR]=0.74, 95% confidence interval [CI] 0.63-0.88), with nominally significant benefits in both patients with and without heart failure, with no suggestion of heterogeneity by baseline LVEF (4). In SOLOIST-WHF, overall there was a 33% relative risk reduction compared to placebo (0.67, 0.52-0.85), with these relative benefits evident irrespective of baseline LVEF. Risk reductions were nominally significant in both patients with HFrEF and HFpEF considered separately (3). Most participants from DECLARE-TIMI 58 and VERTIS CV had eGFRs of >60 mL/min/1.73m^2 and exploratory analyses by baseline HF are limited by incomplete baseline LVEF phenotyping. Such results are less relevant to this guideline than those from SCORED and SOLOIST-WHF (see Table 7c.1) (11, 12).

Table 7c.1: Subgroup analyses by baseline evidence of HFpEF from the large placebo-controlled SGLT-2 inhibitor trials (3, 4, 11, 12)

Trial	Population	Average eGFR, mL/min/1.73m^2	HFpEF definition & number (%)	Outcome: Subgroup: hazard ratio (95% CI)	
SCORED	Type 2 DM & CKD	Median: 45	HF & LVEF 40-50% 581/10584 (5%) HF & LVEF ≥50% 1667/10584 (16%)	Primary outcome of total no. of CV deaths, HHF/urgent treatment for HF:	
				HF+ LVEF	0.75 (0.62-0.91)
				HF+ LVEF <40%	0.95 (0.78-1.28)
				HF+LVEF 40-50%	0.50 (0.32-0.77)
				HF+ LVEF ≥50%	0.72 (0.52-0.99)
				No HF	0.75 (0.57-0.99)
				All	0.74 (0.63-0.88)
SOLOIST-WHF	Type 2 DM & recent hospitalisation for worsening HF	Median: 50	LVEF ≥50% 256/1222 (21%)	Primary outcome of total no. of CV deaths, HHF/urgent treatment for HF:	
				HFrEF	0.72 (0.56–0.94)
				HFpEF	0.48 (0.27-0.86)
				ALL	0.67 (0.52-0.85)
DECLARE-TIMI 58	Type 2 DM & established or risk factors for ASCVD	Mean (SD): 85 (16)	1316/17160 (7.7%) with HF without HFrEF (i.e. HFpEF [LVEF ≥45%] and unknown LVEF combined)	First HHF:	
				HFrEF	0.64 (0.43-0.95)
				HF without HFrEF	0.76 (0.62-0.92)
				No HF	0.77 (0.60-0.97)
VERTIS CV	Type 2 DM & established ASCVD	Mean (SD): 76 (21)	Not applicable: Study considered those with LVEF >45% irrespective of the presence of HF	First HHF:	
				HF	0.63 (0.44-0.90)
				HFrEF	0.48 (0.30-0.76)
				No HF	0.79 (0.54-1.15)
				ALL	0.70 (0.54-0.90)
				LVEF <45% with or without HF	0.86 (0.58-1.29)

ASCVD=atherosclerotic cardiovascular disease; DM=diabetes mellitus; CKD=chronic kidney disease; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HHF=hospitalisation for heart failure; HFpEF-heart failure with preserved ejection fraction; LVEF=left ventricular ejection fraction; SD=standard deviation. A post-hoc analysis of patients from the CANVAS trial is not included in this table as LVEF was not phenotyped at baseline. Instead LVEF was sought for fatal or hospitalisation for heart failure events, categorising LVEF ≥50% as HFpEF. Overall, SGLT-2 inhibition with canagliflozin reduced risk of fatal or hospitalisation for HF versus placebo by 30% (HR=0.70, 0.55-0.89), with results driven by benefit in among those with reduced or unknown LVEF, with more uncertainty about benefit in those with an LVEF ≥50% (13).

Effects of SGLT-2 inhibition on exercise tolerance, patient-reported clinical symptom scores, natriuretic peptides and other measures of cardiac function in HFpEF

The EMPERIAL-PRESERVED trial recruited 315 people with HFpEF, 161 (51%) of whom had type 2 DM. Median eGFR was 57 mL/min/1.73m^2 and median LVEF 53%. The trial's key assessments found no differences in results of 6-minute walk tests and clinical symptoms

scores between those allocated empagliflozin versus placebo (14). The EMPERIAL-PRESERVED and EMBRACE-HF trials also found that, compared to placebo, SGLT-2 inhibition did not reduce natriuretic peptide levels in HFpEF (14, 15). Other trials have also found no effect of SGLT-2 inhibition on N-terminal pro-brain natriuretic peptide (NT-pro-BNP) in HFpEF when compared to alternative oral hypoglycaemic agents (16, 17). EMBRACE-HF also assessed the effects of SGLT-2 inhibition on pulmonary artery diastolic pressure (PADP) and diastolic resistance in 65 people with heart failure. Overall, empagliflozin reduced PADP by -1.7 mmHg at 12 weeks versus placebo (-1.7 mmHg [95%CI 0.3, 3.2]), but effects among the subset of participants with HFpEF (defined as LVEF >40%) were less certain -0.83 mmHg (-2.62, 0.97) (15).

The effect of dapagliflozin versus placebo in people with type 2 DM and diastolic dysfunction has been assessed in the IDDIA trial. Results suggested dapagliflozin significantly reduced estimated left filling pressure during exercise compared to placebo (absolute mean difference 1.4 cm/s [95%CI 0.59, 2.22]), but no significant differences in other cardiac indices such as e' velocity, E/e' ratio, left ventricular mass index or left atrial volume were evident (18).

Acute decompensated heart failure (irrespective of LVEF)

The EMPA-RESPONSE-AHF trial randomized 80 patients admitted with decompensated heart failure to empagliflozin versus placebo on top of standard care (10). About one-third of participants had type 2 DM and the median eGFR was 55 mL/min/1.73m^2 (patients with an eGFR <30 mL/min/1.73m^2 were excluded). Allocation to empagliflozin did not affect the key assessments of dyspnoea, NT-proBNP, or length of stay, but was shown to be safe and caused more urine output than placebo over 4 days (e.g. net fluid loss on empagliflozin: -2163±1896 mL versus placebo: -1007±1049 mL on day 1). The trial also generated a hypothesis that SGLT-2 inhibition may reduce subsequent risk of readmission at 60 days, death or worsening of heart failure.

7c.1.2 Quality of the evidence

Those with CKD and HFpEF or acutely decompensated heart failure remain an under-investigated population deserving more research. The current lack of high-quality evidence for the use of SGLT-2 inhibition within this context limits current recommendations for use and is reflected in the summary statement in section 7c.2.

7c.2 SUMMARY STATEMENTS

There is currently insufficient evidence to provide further recommendations for use of SGLT-2 inhibition in people with CKD with co-existent HFpEF or acutely decompensated heart failure. See section 2 & 3 for recommendations for use in other forms of heart failure or to modify cardiovascular risk.

This summary statement will be reviewed when the results of EMPEROR-PRESERVED and DELIVER are published (7, 8).

7c.3 CLINICAL RESEARCH RECOMMENDATIONS

Please refer to section 2.3

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Methodological appendix:
Systematic literature review design and results

SYSTEMATIC SEARCH DESIGN

The systematic search was designed using a multi-stage process to maximise sensitivity to small trials (irrespective of recruitment of individuals with kidney disease) and to permit the inclusion of additional populations of interest in future iterations of the clinical guideline. To achieve this, database search queries and inclusion criteria were designed to be broad and sensitive to give a comprehensive summary of the relevant literature.

Searches were designed primarily to identify randomized controlled trials (RCTs) (1). However, where relevant, meta-analyses of trials and pooled analyses of such trials were identified from systematic searches. Stages of systematic search were:

1. Database search and exclusion of non-relevant article types through abstract review
2. Identification of all trials randomizing participants to SGLT-2 inhibition by full-text review
3. Identification of specific randomized trials of interest based on pre-defined inclusion criteria by full-text review
4. Identification of relevant meta-analyses from the systematic search
5. Provision of literature to working groups

Trials of interest

Pre-determined trials of interest identified for this guideline map to the guideline sections as follows:

- Large, placebo-controlled RCTs (comprising evidence for sections 2, 3, and 5 of the guideline)
- RCTs conducted in patients with type 1 diabetes mellitus (DM) (mapping to section 7a of the guideline)
- RCTs conducted in kidney transplant recipients (mapping to section 7b of the guideline)
- RCTs conducted in patients with heart failure with preserved ejection fraction (HFpEF, mapping to section 7c of the guideline)

Trials meeting primary eligibility criteria but not meeting criteria for studies of interest were documented and stored, creating a repository of relevant trials that can be interrogated in future iterations of the guideline for the use of SGLT-2 inhibitors.

Inclusion and exclusion criteria

Inclusion of identified records was mapped to broad inclusion and exclusion criteria as summarised in Appendix Table 1. Inclusion criteria for studies of interest are detailed in Appendix Table 2.

Risk of bias

Risk of bias of primary studies of interest (comprising large placebo-controlled randomized controlled trials) was assessed using the Cochrane Risk of Bias 2 tool (2). All studies were reviewed by two reviewers (AW, AR, AK) independently and in duplicate.

Appendix table 1: Primary eligibility criteria

Inclusion criteria	Exclusion criteria
• Parallel-group randomized trials	• Phase 1 studies
• Conducted in adult participants	• Pharmacokinetic/pharmacodynamics studies
• Randomizing to SGLT-2 inhibition	• Enrolling participants aged <18 years
	• Non-English language studies
	• Trials randomizing to SGLT-2 inhibition with no non-SGLT-2 inhibitor comparator

Appendix table 2: Inclusion criteria for specific studies of interest

Large-placebo controlled randomized trials
• Randomizing patients to SGLT-2 inhibition or Placebo
• Enrolling at least 1000 participants and at least 500 participants to each arm
• Randomizing to SGLT-2 inhibition
Type 1 DM
• Randomizing participants with type 1 DM
Kidney transplant recipients
• Randomizing renal transplant recipients
HFpEF
• Randomizing participants with heart failure
• Reporting ejection fraction for participants by allocation
• Including participants with both heart failure and with ejection fraction >50%

Database search strategy

The Medline and Embase databases were searched on 16th February 2021 via OVID. The database search was designed to identify a) RCTs (identified using validated search filters obtained from the Cochrane Handbook of Systematic Reviews), and b) studies in SGLT-2 inhibition. The full search criteria are detailed in Appendix Tables 3 & 4.

Appendix Table 3: Search strategy for Embase (Via OVID).

	Embase search strategy
1	Randomized controlled trial/
2	Controlled clinical study/
3	random$.ti,ab.
4	randomization/
5	intermethod comparison/
6	placebo.ti,ab.
7	(compare or compared or comparison).ti.
8	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9	(open adj label).ti,ab.
10	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11	double blind procedure/
12	parallel group$1.ti,ab.

13	(crossover or cross over).ti,ab.
14	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
15	(assigned or allocated).ti,ab.
16	(controlled adj7 (study or design or trial)).ti,ab.
17	(volunteer or volunteers).ti,ab.
18	human experiment/
19	trial.ti.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
22	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
23	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.
24	(Systematic review not (trial or study)).ti.
25	(nonrandom$ not random$).ti,ab.
26	"Random field$".ti,ab.
27	(random cluster adj3 sampl$).ti,ab.
28	(review.ab. and review.pt.) not trial.ti.
29	"we searched".ab. and (review.ti. or review.pt.)
30	"update review".ab.
31	(databases adj4 searched).ab.
32	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
33	Animal experiment/ not (human experiment/ or human/)
34	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	20 not 34
36	exp Sodium-Glucose Transporter 2 Inhibitors/
37	sglt2.tw.
38	sglt-2.tw.
39	exp Sodium-Glucose Transporter 2/
40	sodium-glucose transporter$.tw.
41	sodium-glucose co-transporter$.tw.
42	sodium-glucose cotransporter$.tw.
43	(canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or luseogliflozin$ or remogliflozin$ or sergliflozin$ or sotagliflozin$ or tofogliflozin$).tw.
44	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45	35 and 44

Searches 1-35 comprise the sensitive Embase RCT filter derived from the Cochrane Handbook of Systematic Reviews of Interventions (1).

Appendix Table 4: Search strategy for Medline (Via OVID)

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	clinical trials as topic.sh.
6	randomly.ab.
7	trial.ti.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp animals/ not humans.sh.
10	8 not 9
11	exp Sodium-Glucose Transporter 2 Inhibitors/
12	sglt2.tw.
13	sglt-2.tw.
14	exp Sodium-Glucose Transporter 2/
15	sodium-glucose transporter$.tw.
16	sodium-glucose co-transporter$.tw.
17	sodium-glucose cotransporter$.tw.
18	(canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or luseogliflozin$ or remogliflozin$ or sergliflozin$ or sotagliflozin$ or tofogliflozin$).tw.
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	10 and 19

Searches 1-10 comprise the highly-sensitive Medline RCT filter derived from the Cochrane Handbook of Systematic Reviews of Interventions (1).

Stage 1 – abstract and title screening

Citations including abstracts and relevant record details were downloaded and stored in a dedicated database. Duplicate studies were digitally identified and excluded. Remaining records were screened for relevance using the title and abstract against the primary eligibility criteria (Table 1) by a single reviewer (AJR). Excluded records were categorised based on the reason for exclusion.

Stages 2 and 3 – full-text identification of relevant trials

Remaining records not excluded through abstract and title screening were exported to an excel spreadsheet to facilitate rapid review by participating reviewers (AJR, WH, SB, AR, AK, AW). The Excel spreadsheet was piloted by all reviewers prior to use. Records were divided between reviewers such that each record was reviewed by two reviewers independently and in duplicate. Records were reviewed for relevance against the primary eligibility criteria (Appendix Table 1). Where studies were included, they were categorised against the inclusion criteria for studies of interest (Appendix Table 2). Any disagreements between reviewers regarding inclusion of a record, or categorisation of records against the inclusion criteria for studies of interest, were resolved by a third reviewer independently (WH).

For all included studies of interest, multiple records of the same trial were reconciled by reference to study acronym, where present, or trial registration database number (e.g. National Clinical Trials (NCT) database number).

Stage 4 – identification of relevant meta-analyses

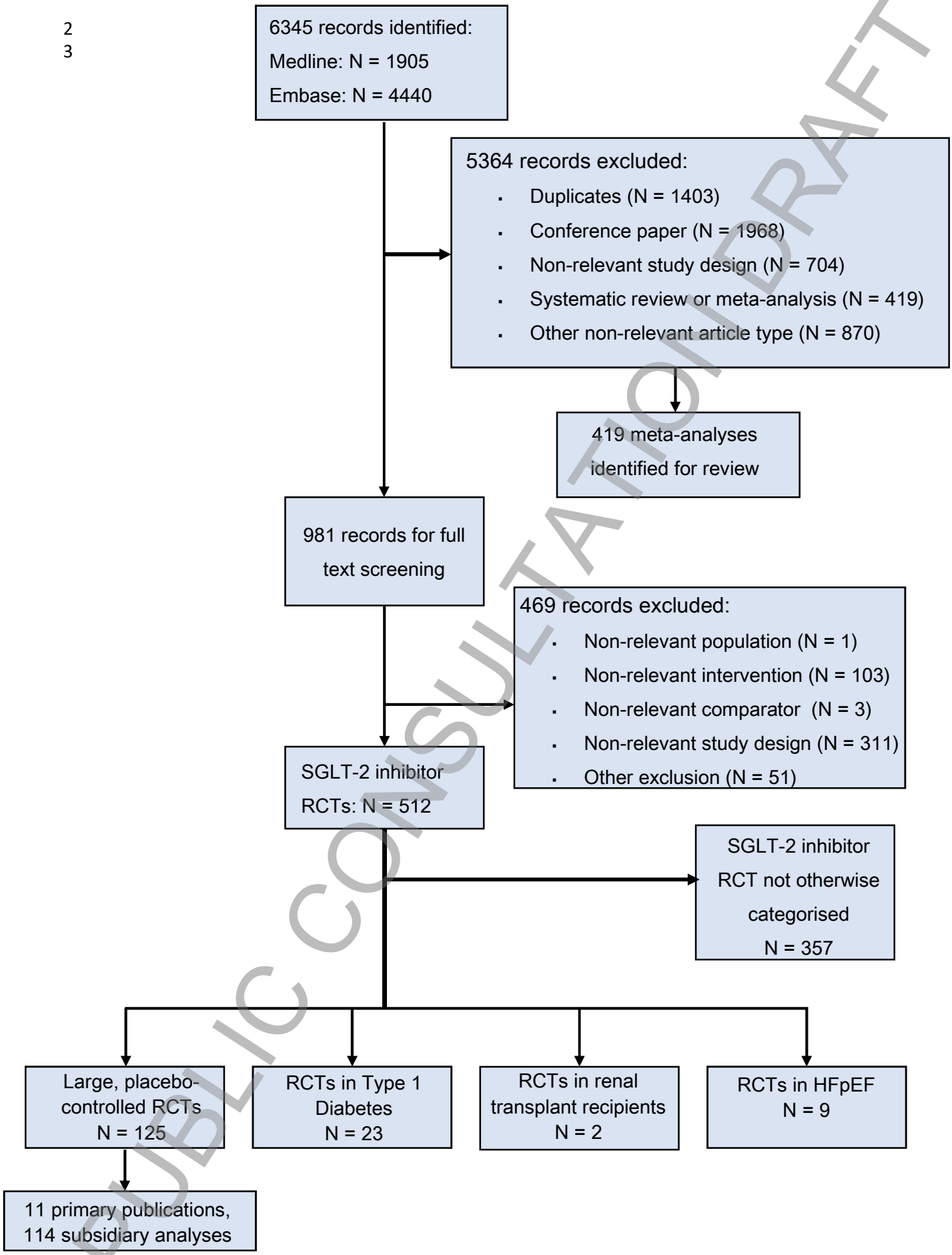
Meta-analyses identified at the abstract/title screening stage or at full-text review stage were screened for relevance by a single reviewer. Meta-analyses were considered relevant if they provided data on the following domains:

- Chronic kidney disease (CKD)
- Diabetic ketoacidosis
- Type 1 DM
- Acute kidney injury (AKI)
- Genital mycotic infections
- Frailty/ multimorbidity
- Amputation
- HFpEF
- Bone fracture
- Transplant

Stage 5 – provision of literature to working groups

Listings of all the relevant publications were distributed to the guideline working groups to inform meeting materials and discussion. From review of the relevant literature, evidence-based guidelines were proposed and agreed upon by consensus discussion.

APPENDIX FIGURE 1: SUMMARY OF SYSTEMATIC SEARCH RESULTS



APPENDIX FIGURE 2: RISK OF BIAS ASSESSMENT

D1: randomization process; D2: deviations from the intended interventions; D3: missing outcome data; D4: measurement of the outcome; D5: selection of the reported result.

APPENDIX I REFERENCES

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Appendix II: Revision history

Version number	Date	Details
-	21JUL2021	Draft for UKKA Clinical Practice Guideline Committee Review
-	10AUG2021	Draft for Public Consultation
1.0	TBC	First final released version

Appendix III: Working group membership affiliations

Name	Role and affiliations
Andrew Frankel	Nephrologist, Imperial College Healthcare NHS Trust (co-chair)
Will Herrington	Associate Professor at the Medical Research Council Population Health Research Unit at the University of Oxford, Oxford, UK; Honorary Consultant Nephrologist, Oxford Kidney Unit, Oxford (co-chair)
Angela Watt	Patient representative
Michael Watson	Patient representative
John Roberts	Patient representative
David Webb	Academic diabetologist, College of Life Sciences, University of Leicester
Chris Carvalho	General practitioner & CSG clinical lead, London City & Hackney
Patrick Holmes	General practitioner, Darlington, UK Primary Care Diabetes Society
Donald Fraser	Academic nephrologist, Wales Kidney Research Unit, Cardiff University, Cardiff, UK
James Burton	Academic nephrologist, University of Leicester, Leicester, UK
Sunil Bhandari	Nephrologist, Hull University Teaching Hospitals NHS Trust and Hull York Medical School, Hull, UK
Eirini Lioudaki	Nephrologist, Kings College Hospital NHS Trust
Mohsen el Kossi	Nephrologist, Doncaster Royal Infirmary, Doncaster UK
Alex Riding	Nephrology trainee, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
Alexa Wonnacott	Nephrology trainee, Wales Kidney Research Unit, Cardiff University, Cardiff, UK
Apexa Kuverji	Nephrology trainee, John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester, Leicester, UK
Alistair J. Roddick	Academic Clinical Fellow in Nephrology, Oxford Deanery (systematic reviewer)
Matt Holloway	Pharmacist, East Kent Hospitals University NHS Foundation Trust
Natalie Staplin	Senior Statistician, Medical Research Council Population Health Research Unit at the University of Oxford, Oxford, UK
Sarah Crimp	Administrative support, UK Kidney Association