New therapeutic horizons in CKD: The role of SGLT2 inhibitors in clinical practice

Running heading: The role of SGLT2 inhibitors in CKD

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Abstract

Chronic kidney disease (CKD) is a serious, progressive condition associated with significant patient morbidity. Hypertension control and use of renin-angiotensin system (RAS) blockers are the cornerstones of treatment for CKD. However, even with these treatment strategies, many individuals will progress towards kidney failure.

Recently, SGTL2 inhibitor clinical trials with primary renal endpoints have firmly established SGLT2 inhibition, in addition to standard of care, as an effective strategy to slow-down the progression of CKD and reduce some of its associated complications. With the emergence of this new clinical evidence supporting the use of SGLT2 inhibitors in the management of CKD in people with and without diabetes, and as licensing and guidelines for SGLT2 inhibitors are updated, there is a need to adapt CKD treatment pathways and for this class of drugs to be included as part of standard care for CKD management.

In this article, we have used consensus opinion alongside the available evidence to provide support for the healthcare community involved in CKD management, regarding the role SGLT2 inhibitors in clinical practice. By highlighting appropriate prescribing and practical considerations, we aim to encourage greater, and safe, use of SGLT2 inhibitors for people with CKD, both with and without diabetes.

Key Points

- Increased use of SGLT2 inhibitors in people with CKD has the potential to significantly modify the clinical course and improve outcomes for patients.
- Clinical trials have demonstrated that SGLT2 inhibitors are well-tolerated, with a low risk of serious adverse effects, which should not overshadow the benefits on clinical outcomes.
- Clarity around appropriate prescribing and practical considerations for the use of SGLT2 inhibitors in people with CKD with and without diabetes, is likely to encourage greater, and safer, use of SGLT2 inhibitors in appropriate target populations.

1. Introduction

Chronic Kidney Disease (CKD) is a common complication of diabetes and hypertension[1, 2], with a global prevalence estimated at approximately 9%[3]. This is likely to increase in the future due to ageing populations and an increasing prevalence of comorbidities. The severity of CKD is determined by the estimated glomerular filtration rate (eGFR), with six categories ranging from normal (> 90 ml/min/1.73m^2) to kidney failure (<15 ml/min/1.73m^2), and urinary albumin-to-creatinine ratio (UACR), with three categories: normal to mild increased (<3mg/mmol), moderate increased (3-30 mg/mmol) and severe increased (>30 mg/mmol). CKD progression is characterised by deterioration of many aspects of kidney function and can lead to anaemia, metabolic acidosis, CKD-mineral bone disorder (CKD-MBD), hyperkalaemia, and hypertension, and ultimately end-stage kidney disease (ESKD) which requires renal replacement therapy with dialysis or kidney transplantation. Individuals with CKD have an increased risk of cardiovascular (CV) morbidity and mortality manifesting as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death, and those with ESKD exhibit a markedly elevated risk[3, 4], and CV events are the leading cause of death in this population[5-7]. As such, the progressive nature of CKD and its associated clinical and economic burden underlines the importance of early intervention to prevent or delay CKD progression.

Optimisation of blood glucose, blood pressure, blood lipids and albuminuria control, and prescription of drugs that block the renin-angiotensin-aldosterone system (RAAS) pathway such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are key to managing CKD and to slowing its progression[8-12]. However, despite these treatment strategies, many patients demonstrate continued decline in kidney function, and consequently there remains an unmet need for novel renoprotective therapies.

Over the last two years, evidence has emerged to advance our understanding of therapeutic approaches to mitigate CKD progression in both people with and without diabetes, with particular

attention focused on mineralocorticoid receptor antagonists (MRAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors. Finerenone, a nonsteroidal, selective MRA, has recently demonstrated efficacy in people with CKD and type 2 diabetes (T2D); the FIDELIO-DKD trial demonstrated that randomisation to finerenone resulted in lower risks of CKD progression and CV events when compared to placebo, in individuals with CKD and T2D[13]. Finerenone is currently under review for approval by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA).

Recently, focus has been increasing on the potential for SGLT2 inhibitor utilisation in CKD clinical practice, as data from cardiovascular outcomes trials (CVOTs) assessing SGLT2 inhibitors have suggested that these therapies have reno-protective effects distinct from their glucose lowering action, including the potential to reduce the rate of GFR decline and the risk of ESKD in people with type 2 diabetes (T2D)[14-22]. The recent DAPA-CKD trial demonstrated that in addition to conferring renal, heart failure (HF), and mortality benefits in people with T2D and albuminuric CKD, SGLT2 inhibitors also have a role in preventing progression of CKD in the absence of diabetes[23]. Based on the results of DAPA-CKD, dapagliflozin has recently been approved by the FDA[24], the European Commission (EC) and the Medicines and Healthcare Products Regulatory Agency (MHRA)[25], Japan's Ministry of Health, Labour and Welfare (MHLW)[26], and is currently under review in several other countries around the world.

Despite the robust clinical trial data demonstrating favourable outcomes with SGLT2 inhibitors, on top of RAS blockade, for people with CKD, with and without diabetes, and updated guidelines and licencing for use of these drugs in these individuals, real-world evidence has demonstrated that SGLT2 inhibitors are currently underutilised in CKD management, with only a third of people with T2D and at high-risk of CKD being treated with this drug class[27]. It is likely that aside from the high perceived cost of these drugs, there is a lack of awareness of the CKD indication for SGLT2 inhibitors,

which is likely to be greatest in non-diabetic CKD, for which the evidence has only recently emerged. Lack of payer knowledge and understanding of the potential clinical and health economic implications for the use of these drugs, particularly in CKD management may represent and additional barrier for the widespread uptake of these agents despite the emerging evidence of clinical trial outcome data. In addition, there is also a hesitancy to integrate these drugs due to concerns regarding potential adverse events, and confusion around which patients would/would not be suitable for this treatment. Therefore, in this article we draw upon consensus opinion and interpretation of the available evidence to provide support for healthcare professionals responsible for the management of CKD, regarding the role of SGLT2 inhibitors in clinical practice. By highlighting appropriate prescribing and practical considerations, we aim to encourage greater, and safe use of SGLT2 inhibitors in this population. Increased use of SGLT2 inhibitors in people with CKD has the potential to have significant clinical benefits for these patients.

The authors attended a virtual roundtable meeting in which the available SGLT2 inhibitor data in the CKD population was examined and the risk-benefit profile of SGLT2 inhibitors reviewed, leading to the drafting of the manuscript outline. Follow up discussion and revisions of the manuscript were conducted via email correspondence.

2. Clinical effectiveness of SGLT2 inhibitors in people with CKD

SGLT2 inhibitors block the reabsorption of glucose in the proximal tubule of the kidney, increase glucose excretion, and consequently can cause a modest reduction in blood glucose levels. In addition to their glucose-lowering properties, SGLT2 inhibitors also lead to a concomitant increase in sodium excretion with a reduction in blood pressure. This reduction in the reabsorption of sodium and glucose in the proximal tubule is thought to lead to restoration of tubuloglomerular feedback, inducing vasoconstriction of the afferent arteriole and a reduction in blood flow through the glomerulus. This is believed to reduce intraglomerular pressure and glomerular hyperfiltration which

provides renal protection[28]. These reno-protective effects were illustrated in the SGLT2 inhibitor CVOTs, by the preservation of eGFR and reduced rates of progression to ESKD, in people with diabetes (EMPA-REG, CANVAS, DECLARE-TIMI 58, and VERTIS CV)[14-20] and HF (DAPA-HF and EMPEROR-Reduced)[21, 22]. Both DAPA-HF and EMPEROR-Reduced reported a similar effect of SGLT2 inhibitors to reduce the decline in the eGFR slope. However, there were discordant results for the renal composite outcomes; in DAPA-HF the renal composite outcome was numerically lower in with dapagliflozin compared to placebo, but was not statistically significant, whilst it was significantly lower with empagliflozin compared to placebo in EMPEROR-Reduced. This may have been a result of the relatively fewer kidney events in DAPA-HF, due to the higher baseline eGFR entry criteria and the different composite outcome definition. Although, when the results of DAPA-HF and EMPEROR-Reduced were combined in a meta-analysis, the risk of major kidney outcomes was reduced by 38% (HR, 0.62; 95% CI, 0.43–0.90) with SGLT2 inhibitor use, without evidence for heterogeneity[29].

The effectiveness of the dual SGLT1/SGLT2 inhibitor sotagliflozin at preventing CV events while also slowing progression of CKD in people with diabetes and CKD, with or without albuminuria, has been demonstrated in the SCORED trial. This trial included 10,584 participants that were randomised to receive sotagliflozin or placebo with a median follow-up of 16 months (the trial ended early owing to loss of funding). Treatment with sotagliflozin resulted in a statistically significant 26% reduction in the composite of deaths from CV causes, hospitalisations for HF, and urgent visits for HF compared to placebo[30]. There was also a 29% reduction in the renal composite of first occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73m^2 for ≥30 days, although this did not reach statistical significance[30].

Renal specific outcomes were studied in the multicentre, double-blind, placebo-controlled randomized trial, CREDENCE. This study assessed the effects of canagliflozin in 4,401 trial participants with the combination of T2D and CKD (eGFR 30 - 90 ml/min/1.73m^2 and UACR ≥30 mg/mmol), that were already taking maximally tolerated doses of ACEi or ARBs, with a median follow-up of 2.6 years. The trial results demonstrated a 30% relative risk reduction with canagliflozin, compared to placebo, in the primary composite endpoint of a doubling of the serum creatinine level, ESKD (dialysis, transplantation, or a sustained estimated GFR of <15 ml/min/1.73m^2), or death from renal or CV causes, in people with T2D and CKD[31]. The risk of ESKD and risks of major adverse CV events and hospitalization for HF were also reduced. The trial confirmed the safety profile of canagliflozin - with no significant differences in the incidence of adverse events or serious adverse events between the treatment and placebo groups. Although post-marketing surveillance has reported cases of Fournier's gangrene (a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention) associated with use of SGLT2 inhibitors, there were no reported cases of Fournier's gangrene in the CREDENCE trial. Rates of diabetic ketoacidosis (DKA) were low, although they were higher in the treatment group - DKA was reported in 11 participants who received canagliflozin and in one participant who received placebo[31]. Additionally, canagliflozin, compared to placebo, was associated with a reduction in the overall incidence rate of kidney-related adverse events (60.2 vs 84.0 per 1,000 patient-years), further highlighting the safety of canagliflozin[32].

The DAPA-CKD trial had a broader renal inclusion criterion than the CREDENCE trial and included people with and without T2D. The trial assessed the effects of dapagliflozin in 4,304 participants with CKD (eGFR 25 - 75 mL/min/1.73m^2 and UACR 22.6 - 565 mg/mmol) on maximally tolerated, stable doses of ACEi or ARB, unless contraindicated. Following a median follow up of 2.4 years there was a 39% relative risk reduction in the primary composite outcome of a sustained decline in eGFR of at least 50%, ESKD, and CV or renal death, in the dapagliflozin group, compared to placebo[23].

Notably, results were similar regardless of diabetes status. Randomisation to dapagliflozin also resulted in a significant 44% reduction in worsening renal function or death from kidney failure, 31% reduction in all-cause mortality and 29% reduction in HF hospitalization or CV death[23]. The trial confirmed the safety profile of dapagliflozin - with no significant differences in the incidence of adverse events or serious adverse events between the dapagliflozin and placebo groups. Fournier's gangrene was not reported in any participants who received dapagliflozin but occurred in one participant who received placebo. DKA was not reported in any participants who received dapagliflozin but was seen in two participants who received placebo. Neither DKA nor severe hypoglycaemia were observed in participants without T2D. The observed outcome benefits and safety profile of dapagliflozin appeared independent of the aetiology of nephropathy[33].

A similar CKD trial in people with and without diabetes is underway to evaluate the safety and efficacy of empagliflozin (EMPA-KIDNEY), with results expected in 2022. The data from this trial is expected to fill a crucial knowledge gap around efficacy and safety in people with lower eGFR (importantly in those with or without albuminuria and with or without T2D). The trial will evaluate eGFR ≥20-45 (who do not need to have albuminuria) as well as those with an eGFR ≥45 to <90 with UACR ≥20 mg/mmol[34].

The clinical studies conducted to date that examined renal endpoints (summarised in Table 1), as well as those planned, include a broad range of patients with albuminuria and degrees of CKD based on eGFR. As such these data could be considered as potentially generalizable to the broad range patients with CKD in routine clinical practice. However, the true impact of SGLT2 inhibitors on renal outcomes in the context of every day clinical practice requires further evaluation through propensity score–matched real-world studies. One such study in which the reduced risk of renal outcomes reported in the clinical trials of SGLT2 inhibitors has also been observed in a 'real-world' setting is CVD-REAL 3. CVD-REAL 3 was a large-scale multinational, observational cohort study that included

data from 65,231 participants with T2D, and which compared outcomes following initiation of SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin) with those following initiation of other glucose-lowering drugs (dipeptidyl peptidase-4 inhibitors, insulin, glucagon-like peptide-1 receptor agonists, sulfonylurea, thiazolidinedione, metformin, metiglinides, and acarbose) in propensity-matched patient cohorts. The results of the study demonstrated that initiation of SGLT2 inhibitors was associated with a 51% decrease in relative risk of the renal composite outcome (50% decline in eGFR or ESKD) compared with other glucose-lowering drugs[35].

3. Cost effectiveness of SGLT2 inhibitors in people with CKD

Treatment of end-stage kidney disease has been associated with substantial healthcare costs and resource utilisation with approximately 2-3% of total annual healthcare expenditure in developed countries being attributable to the treatment of ESKD[36]. Additional costs and bed days associated with stage 5 CKD and macroalbuminuria, compared to stage 1 (or without) CKD, per 1000 patient years have been estimated at £435,000 and 1017 bed days, in the UK[37].

As CKD is associated with multimorbidity which requires the use of resource-intensive treatments, the management of pre-ESKD patients may also have significant costs. For these patients, costs often increase incrementally with disease severity, particularly when comparing CKD stages 4–5 with stages 2–3[38-40]. Furthermore, CKD progression also has a negative impact on health-related quality of life (HRQoL) outcomes[41].

In an assessment of the cost effectiveness of canagliflozin for treating diabetic kidney disease, using a microsimulation model that was developed using patient-level data from the CREDENCE trial, canagliflozin demonstrated considerable gains in health and lower overall costs. The clinical benefits associated with canagliflozin use, including preservation of eGFR, decrease in UACR, and reductions

in the risks of dialysis, CV events, and mortality, resulted in gains of 0.27 life-years, 0.28 quality-adjusted life-year (QALYs) and cost savings of £4,706 per patient over 10 years[42].

In a multinational cost-effectiveness analysis of CKD, which utilised data from DAPA-CKD, dapagliflozin improved patient quality of life and significantly improved clinical outcomes at a cost below established willingness-to-pay thresholds[43]. Treatment with dapagliflozin reduced rates of CKD progression, with patients spending 1.70 more years in CKD stages 2-4 versus standard therapy alone (12.06 versus 10.36 years), and increased life expectancy by an estimated 1.75 years (15.5 versus 13.8 years). Improved life expectancy and reduced incidence of adverse clinical outcomes led to lifetime incremental QALY gains of 0.82, 0.87 and 0.88 and incremental cost-effectiveness ratios of £5,940, €11,687 and €10,699 in the UK, Germany and Spain respectively[43, 44].

Whilst use of SGLT2 inhibitors in the management of CKD has demonstrated cost effectiveness based on willingness to pay thresholds, these drugs are perceived to have a relatively high acquisition cost and as such may be considered as having potential adverse budget impact implications to healthcare systems. However, it is noteworthy that the added cost of treating people with more expensive drugs has the potential to be offset by cost savings from the perspective of avoided clinical events, and consequently may result in budget impact neutrality. In the context of SGLT2 inhibitor use in CKD, this consideration requires further evaluation.

In a study estimating the budget impact of dapagliflozin for the treatment of CKD from a UK payer perspective, approximately 1.8 million patients were estimated to be eligible for treatment in the UK per year based on CKD prevalence and the DAPA-CKD inclusion criteria, and dapagliflozin was estimated to reduce total 3-year costs associated with CKD management by £3.3 million in these patients[45].

4. The role of SGLT2 inhibitors in the management of CKD with and without T2D

To date, the mainstay of treatment to delay CKD progression has been ACEi or ARBs, which are recommended in NICE clinical guideline 182 'Chronic kidney disease in adults: assessment and management'[9]. This guideline, however, was last updated in 2015 and as such, does not take into account the recent cardiovascular and renal outcome trials. The Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the European Society of Cardiology (ESC), and the Association of British Clinical Diabetologists (ABCD) – UK Kidney Association (UKKA), all recommend in their current guidelines the use of an SGLT2 inhibitor for people with T2D and eGFR ≥30 ml/min/1.73m^2, where the approved licence indication allows[8, 46, 47].

Currently, canagliflozin is approved to treat CKD in individuals with T2D, whilst dapagliflozin is approved for CKD management in both those with and without T2D. Taking into consideration the inclusion criteria in DAPA-CKD[48] and the current label indication for dapagliflozin in the management of CKD[48], our consensus opinion is that people with CKD, with eGFR ≥15 ml/min/1.73m^2, irrespective of albumin status, should be considered for treatment with dapagliflozin, independent of diabetes status. Based on the inclusion criteria in CREDENCE[31] and the current label indication for canagliflozin in the management of CKD[49], canagliflozin may be considered in the management of CKD in people with T2D with eGFR ≥30 ml/min/1.73m^2 and albuminuria (UACR > 30 mg/mmol). Due to their complementary mechanism of action, a combination of SGLT2 inhibitors and single agent RAAS blockade should be adopted in clinical practice, for most patients.

In people treated with an SGLT2 inhibitor for both CKD and T2D, additional glucose-lowering treatment may be necessary if GFR falls persistently below 45 mL/min/1.73m^2, due to reduced

glucose-lowering at this level of renal function as the CKD outcome benefits are independent of glucose lowering, baseline HbA1 or eGFR levels.

5. Appropriate prescribing of an SGLT2 inhibitor in CKD patients

SGLT2 inhibitors have a wide range of clinical outcome benefits across multiple chronic conditions in particular T2D, HF and CKD, resulting in a growing appreciation in the utility of these agents in the field of cardiorenal metabolic medicine. As such the prescription of these agents may be undertaken by a number of healthcare professionals including specialists within the fields of diabetes, cardiology, and nephrology. However since a large proportion of people with cardiorenal metabolic disease are managed in primary care it is essential that primary care physicians are also fully aware of the issues relating to the appropriate prescribing of these agents across the different therapy indications.

Selecting appropriate people with CKD for SGLT2 inhibitor treatment is critical for maximising the risk-benefit profile associated with this treatment class. Based on the DAPA-CKD data, as well as recent clinical guidance and the label indication, we have developed a checklist that serves as a tool to mitigate the risk of side effects while giving confidence to practitioners to safely prescribe these drugs (Figure 1). The checklist follows a traffic light system that recommends that people in the green section should be considered for treatment with an SGLT2 inhibitor, on top of RAS blockade. This group includes treatment with dapagliflozin for people with CKD with or without T2D with eGFR ≥15 ml/min/1.73m^2 and treatment with canagliflozin for people with CKD with T2D and albuminuria and with eGFR ≥30 ml/min/1.73m^2.

While an SGLT2 inhibitor may be prescribed for CKD patients with prior amputation, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue, such prescribing should be under caution (amber section of the checklist) as the association between SGLT2 inhibitors and

amputation remains unclear; whilst canagliflozin was associated with an increased risk for lower limb amputation in CANVAS[15] there was not a significantly higher rate of amputation compared with placebo in CREDENCE[31], and a real-world study in the USA reported that the risk of amputation in patients treated with SGLT2 inhibitors was not higher compared with other diabetes drugs[50]. In addition, we also recommended that caution be applied in prescribing SGLT2 inhibitors to individuals with a history of organ transplantation; despite case studies that have highlighted the safe and effective use of SGLT2 inhibitors by transplant recipients[51-56], there remains a lack of formal trial evidence, as this patient group was not included in DAPA-CKD.

As the most common adverse effects associated with use of SGLT2 inhibitors include genital mycotic infections and volume-related effects, use of SGLT2 inhibitors should be with caution in people with CKD with a significant history of recurrent mycotic genital tract infection as well as in those at risk for volume-related adverse effects (dizziness and hypotension), such as the elderly, those with moderate renal dysfunction, and those taking concomitant diuretic therapy, as these side effects may be more likely to develop in these individuals if prescribed SGLT2 inhibitor therapy

We do not recommend initiating SGLT2 inhibitor use at this time (red section of checklist), if eGFR is less than 15 mL/min/1.73m^2. However, if a patient has already been receiving an SGLT2 inhibitor for a period of time and then eGFR declines below 15 mL/min/1.73m^2, then SGLT2 inhibitor treatment should be continued. People with autosomal dominant polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis, those receiving cytotoxic therapy, immunosuppressive therapy, or other immunotherapy as well as CKD patients receiving dialysis, or that are pregnant or breast-feeding should not be considered for SGLT2 inhibitor treatment as there is limited experience in these population groups. In addition, despite guidance around the use of SGLT2 inhibitors to improve metabolic control in type 1 diabetes[57], this drug class has not been studied for the treatment of CKD in people with concomitant type 1 diabetes, and as such is not currently recommended in this

population. In addition, there is significantly greater rates of DKA in association with SGLT2 inhibitor use in people with type 1 diabetes. Due to the serious consequences associated with DKA, patients that experience DKA whilst taking an SGLT2 inhibitor should have it permanently withheld.

6. Practical considerations

Although the data from trials of SGLT2 inhibitors in patients with CKD demonstrate a good safety profile, when prescribing an SGLT2 inhibitor in routine clinical practice it is important to be aware of the adverse events that have previously been associated with SGLT2 inhibitors such as genital fungal infections, volume-related events (including low blood pressure, fainting, and dehydration), and DKA[58] and have strategies in place to mitigate these risks. Education and guidance to support healthcare professionals, that may be unfamiliar with SGLT2 inhibitors, to understand and manage these risks is important. Guidance similar to that provided by the ABCD and Diabetes UK[59], which provides essential information on SGLT2 inhibitors for non-diabetes specialists, including the main advantages and the important risks of which healthcare professionals should be aware, would be considered a useful resource.

Of the adverse events, genital fungal infections appear to be the most prevalent and consistent event reported in the clinical trials. However, the majority of these infections are mild to moderate and can be easily treated with topical antifungals. The importance of good personal hygiene should be discussed with patients prescribed SGLT2 inhibitors to prevent/reduce the risk of infection. Whilst there were reports of increases in urinary tract infections in people who received an SGLT2 inhibitor in some earlier studies, this has not been a consistent finding across the clinical trials, and it remains uncertain whether this is a true side effect of the drug class. As T2D is an independent risk factor for urinary infection[60, 61], this may confound the role of SGLT2 inhibitors causing these infections.

Due to its mechanism of action, an SGLT2 inhibitor may induce diuresis and natriuresis, raising concerns around potential volume depletion adverse events. In addition, there have been previous concerns for potential renal adverse events to occur in association with SGLT2 inhibitor use. Clinical trial data in people with and without diabetes have in general demonstrated numerically fewer adverse events and cases of acute kidney injury associated with SGLT2 inhibitor use compared to placebo. However, there was a small excess of volume depletion adverse events recorded in relation to SGLT2 inhibitor use in the DAPA-CKD study; 5.9% of individuals in the dapagliflozin group were noted to experience symptoms of volume depletion, compared to 4.2% of those in the placebo group (P=0.01). In routine clinical practice, we advocate assessment of patient volume status when both initiating an SGLT2 inhibitor and while monitoring a patient routinely being managed with an SGLT2 inhibitor. Preference should be given to maintaining stable RAAS inhibitor doses and reducing other antihypertensives if blood pressure tends toward lower target range. Whilst reducing doses of other antihypertensives may be appropriate in the context of concerns around hypertension, diuretic dosing may be reduced in order to mitigate potential concerns around volume depletion.

Recent clinical studies have shown that SGLT2 inhibitors exhibit fluid homeostatic action and inhibit the upregulation of RAAS[62, 63]. In addition, the key mechanism of the fluid homeostasis by SGLT2 inhibitors is sufficient fluid and food intake, because restricted fluid and food intake during SGLT2 inhibition induces negative fluid balance and the reduction of body fluid volume[64]. As such, we recommend that patients are educated regarding symptoms of dehydration and are provided with advice around ‘sick-day rules’, whereby their prescribed SGLT2 inhibitor should be temporarily withheld during any acute dehydrating illness until they are eating and drinking again normally. Patients should additionally be advised to report any signs and symptoms of volume depletion (postural dizziness, fatigue, confusion, muscle cramps, chest pain, abdominal pain, postural hypotension, or palpitations) to a healthcare professional. If volume depletion occurs, SGLT2 inhibitor treatment should be temporarily withheld until the volume depletion is corrected. Patients

should be monitored, particularly in the first week of therapy, if a drop in blood pressure could pose a risk, such as patients with a history of CV disease, hypotension, or elderly patients.

As SGLT2 inhibitors reduce blood glucose levels, there is an associated decline in insulin secretion leading to increased glucagon production. Insulinopenia and increased glucagon increases the risk for ketoacidosis (including euglycemic ketoacidosis) in the presence of other precipitating factors[65]. Ketoacidosis is rare in people without diabetes, although it can be observed in pregnancy or following alcoholic binges, or starvation. Most of the clinical trials involving people with diabetes have observed a slight increase of DKA cases in the SGLT2 inhibitor group compared to placebo, and anecdotally cases of DKA appear to be more frequent in routine clinical practice: the majority in patients with type 1 diabetes, secondary diabetes, or T2D with other risk factors for ketoacidosis. DKA is an acute metabolic complication of diabetes and in the context of SGLT2 inhibitor use may be either euglycemic or associated with hypoglycaemia. It is a serious medical emergency and without urgent treatment, it can result in coma or death. Patients should be educated to recognise the signs and symptoms of DKA, such as excessive thirst, frequent urination, dehydration, nausea, vomiting, abdominal pain, shortness of breath, unusual sleepiness or tiredness, and confusion, and seek immediate medical attention whereby their ketone levels can be checked, and appropriate treatment can be introduced. SGLT2 inhibitors should be discontinued in patients that exhibit signs and symptoms of DKA, even if blood glucose is not particularly high (euglycemic DKA). The SGLT2 inhibitor should rarely be restarted in individuals who have had DKA confirmed.

There has previously been some concern around the GFR ‘dip’ which can occur following introduction of an SGLT2 inhibitor, and early observational reports have suggested an increase in the risk of acute kidney injury with these therapies[66]. However, the dip in eGFR observed soon after SGLT2 inhibitor initiation likely reflects their protective mechanism of action and should not be a barrier to their use. Overall, long-term kidney benefit has been observed, despite an initial decline in

eGFR. Data from the clinical trials has demonstrated that the initial drop in eGFR following initiation of an SGLT2 inhibitor is followed by a stabilisation of long-term kidney function decline. For example, data from CREDENCE demonstrated that at week three after randomisation, the mean acute change in eGFR was –7% and 0.3% in the canagliflozin and placebo groups, respectively, and an acute drop in eGFR >10% was observed in significantly more individuals in the canagliflozin (45%) compared to the placebo (21%) group. However, after week three (termed the 'chronic phase'), long-term eGFR trajectories, as well as overall and kidney safety profiles, in those treated with canagliflozin were similar across eGFR decline categories, with the data suggesting that an acute decrease in eGFR up to 30% can be tolerated after treatment initiation with canagliflozin[67]. Furthermore, a systematic review and meta-analysis has demonstrated that SGLT2 inhibitors reduce the risk of acute kidney injury by 36%[68]. Based on this evidence, our advice is that no additional renal monitoring is required after initiating SGLT2 inhibitor treatment, above what would normally be done as routine, unless the individual becomes unwell. Likewise, there is no requirement for any additional lab monitoring beyond routine clinical practice, following SGLT2 inhibitor initiation.

7. Conclusion

To date, there have been limited treatment options to slow CKD progression, with a lack of new treatments that show clinical benefits for people with CKD since the RAAS inhibitor trials published over twenty years ago. This has left a substantial residual risk for kidney failure to occur. Recently, both finerenone and SGLT2 inhibitors have demonstrated significant renal benefits in the clinical trials recruiting CKD patients. Currently, two SGLT2 inhibitors have been approved for CKD patients (canagliflozin for CKD with T2D, and dapagliflozin for CKD both with and without T2D), whilst finerenone is being considered by the regulators. In the future, should finerenone also receive approval, it is likely that both drug classes will be used (as they work via distinct mechanisms) in conjunction with an inhibitor of RAAS. In the meantime, adding an SGLT2 inhibitor to standard of

care in CKD represents an opportunity to significantly modify the clinical course and improve symptoms and outcomes for patients.

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Tables

Table 1. Summary of renal outcomes in the SGLT2 inhibitor clinical trials

Trial	Year	SGLT2 inhibitor	N	Median follow-up (years)	T2D (%)	eGFR (mL/min/1.73 m^2)	Albuminuria (mg/mmol)	Renal endpoint	HR (95% CI)	p-value
EMPA-REG[18]	2016	Empagliflozin	7,020	3.1	100	eGFR >30 Mean: 74 45–59 (17.8%) 30–44 (7.7%)	<3 (60.3%) 3–30 (28.7%) >30 (11%)	Renal composite: ESKD, doubling of creatinine, death from renal causes	0.54 (0.40 - 0.75)	<0.001
CANVAS[15]	2017	Canagliflozin	10,142	2.4	100	eGFR >30 Mean: 77	<3 (69.8%) 3–30 (22.6%) >30 (7.6%)	Renal composite: sustained 40% reduction in eGFR, need for RRT or death from renal causes	0.60 (0.47 - 0.77)	<0.01
DECLARE-TIMI 58[16]	2019	Dapagliflozin	17,160	4.2	100	Mean: 85 ≥90 (47.6%) 60–90 (45.1%) <60 (7.4%)	<3 (69.1%) 3-30 (23.9%) >30 (6.9%)	Renal composite: eGFR decline of ≥40% to <60 mL/min/1.73 m^2, ESKD, or death from renal causes	0.53 (0.43 - 0.66)	<0.0001
DAPA-HF[21]	2019	Dapagliflozin	4,744	1.5	45	eGFR >30 Mean: 66 <60 (40.6%)	Not reported	Renal composite: eGFR decline of ≥50%, ESKD, or death from renal causes	0.71 (0.44 – 1.16)	NA*
CREDENCE[31]	2019	Canagliflozin	4,401	2.6	100	eGFR >30 Mean: 56	30–500	Renal composite: ESKD, doubling of creatinine, death from renal causes	0.66 (0.53 - 0.81)	<0.001
VERTIS CV[17]	2020	Ertugliflozin	8,246	3.5	100	eGFR >30 Mean: 76 60–89 (53%) 30–59 (22%)	<3 (60%) >3 (40%)	Renal composite: ESKD, doubling of creatinine, death from renal causes	0.81 (0.63 - 1.04)	0.08
EMPEROR-REDUCED[22]	2020	Empagliflozin	3,730	1.3	50	Mean: 62 eGFR <60 (48%)	Not reported	Renal composite: RRT, transplant, sustained eGFR reduction of 40% or more, eGFR <15 mL/min/1.73 m^2	0.50 (0.32 - 0.77)	Not reported
DAPA-CKD[23]	2020	Dapagliflozin	4,304	2.4	67.5	Mean: 43 ≥60 (10%) 45–<60 (31%) 30–<45 (44.1%) <30 (14.5%)	Range 20–500 >100 (48.3%)	Renal composite: eGFR decline of ≥50%, ESKD or death from renal causes	0.56 (0.45 - 0.68)	<0.001
SCORED[30]	2021	Sotagliflozin	10,584	1.3	100	Median: 45 <30 (7%) 30–45 (44%) ≥45 (48%)	<3 (35%) 3–<30 (33%) ≥30 (32%)	Renal composite: ≥50% decrease in eGFR, RRT, renal transplantation, sustained eGFR of <15 mL/min/1.73 m^2 for ≥30 days	0.71 (0.46 - 1.08)	Not reported

CI: confidence interval; eGFR:, estimated glomerular filtration rate; ESKD: end-stage kidney disease; HR: hazard ratio; NA: *Not applicable; RRT: renal replacement therapy; SGLT2i: sodium–glucose cotransporter 2 inhibitor; T2D: type 2 diabetes*

**P values were reported only for endpoints that were included in the hierarchical-testing strategy.*

Figures

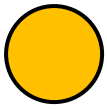
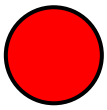
	Consider prescribing an SGLT2i for CKD patients with *ANY* the following
	• eGFR ≥15 with or without T2D (dapagliflozin) • eGFR ≥30 with T2D and albuminuria (canagliflozin)
	Possibly consider prescribing with caution an SGLT2i for CKD patients (with or without T2D) with *ANY* of the following
	• Prior amputation, severe peripheral neuropathy, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue infections • History of organ transplantation • History of recurrent mycotic genital tract infection • At risk of significant volume depletion
	Do not consider prescribing an SGLT2i for CKD (with or without T2D) with *ANY* of the following
	• eGFR<15 ml/min/1.73m^2 • Receiving dialysis • Polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis • Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy • Type 1 diabetes mellitus • Previous DKA • Pregnancy or breast-feeding

Figure 1. Checklist for appropriate prescribing of SGLT2i in CKD

ANCA: anti-neutrophil cytoplasmic antibody; CKD: chronic kidney disease; DKA: diabetic ketoacidosis; eGFR: estimated glomerular filtration rate; SGLT2i: sodium–glucose cotransporter 2 inhibitor; T2D: type 2 diabetes