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Review

Best Practices in the Use of Sodium–Glucose Cotransporter 2 Inhibitors in Diabetes and Chronic Kidney Disease for Primary Care

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Abstract: Diabetes is the leading cause of chronic kidney disease (CKD), with nearly half of all cases of kidney failure requiring kidney replacement therapy. While attention is often focused on the profound effects kidney failure has on the quality of life, the principal cause of complications and death among patients with diabetes and CKD is cardiovascular disease (CVD). These risks are often underappreciated by both healthcare professionals and patients. Sodium–glucose cotransporter 2 (SGLT-2) inhibitors were originally developed and approved as glucose-lowering agents for treating type 2 diabetes (T2D). However, agents within the SGLT-2 inhibitor class have since demonstrated robust benefits for CKD, atherosclerotic cardiovascular disease (ASCVD), and heart failure (HF) outcomes. Specifically, dedicated kidney disease and HF outcome trials have shown markedly reduced rates of kidney failure, CVD and HF events, and death among people (with and without diabetes) with CKD. SGLT-2 inhibitors will be used by primary care clinicians, nephrologists, and cardiologists across a range of cardiovascular and kidney conditions and diabetes. Knowledge and awareness of the benefits and key safety considerations, and risk mitigation strategies for these medications is imperative for clinicians to optimize the use of these life-saving therapies.

Keywords: diabetic kidney disease; type 2 diabetes; SGLT-2 inhibitors; albuminuria

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1. Background and Introduction

Diabetes mellitus and chronic kidney disease (CKD), defined by sustained albuminuria (urine albumin-to-creatinine ratio (UACR) $\geq$ 30 mg/g), low estimated glomerular filtration rate (eGFR; <60 mL/min/1.73 m^2), or both for $\geq$90 days, commonly co-exist. Diabetic kidney disease, or CKD in diabetes without other known causes, occurs in about 30% of people with type 1 diabetes (T1D) and 40% of those with type 2 diabetes (T2D) [1]. CKD itself may be asymptomatic, but is associated with a high risk of morbidity and mortality. In the United States (US), over 37 million adults (~10.5% of the population) are estimated to live with diabetes [2]. Of these estimated 37 million adults living with diabetes, more than 90% have T2D [3]. Globally, 537 million people have diabetes, with a predicted growth in prevalence to nearly 783 million by 2045 [2,3]. As a global leading cause of CKD, diabetes accounts for nearly half of all cases of chronic kidney failure requiring kidney replacement therapy [4]. Despite the serious consequences of CKD, the low rate of awareness among

clinicians and patients is troubling. Only half of patients at high risk for progression to kidney failure even know they have the condition [5].

When a person has diabetes and CKD, their risk for CVD events is equal to someone with established CVD, but it is even greater if the CKD is stage 3B or greater [6]. Therefore, patients with T2D and CKD are most likely to die due to cardiovascular (CV) events. Only about 10% of these patients will survive to progress to kidney failure requiring kidney replacement therapy [3,7,8]. The most common causes of death overall in patients with T2D and CKD are atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF) [8]. A decline in the eGFR or the presence of albuminuria are additive risk factors for CVD events, CVD-related mortality, and all-cause mortality [9]. Even early stages of CKD in people with diabetes (stages 1–3) are associated with a dramatic increase in all-cause risk of death (3-fold) compared to people with diabetes and no CKD (hazard ratio (HR): 3.16; 95% confidence interval (CI): 3.0–3.4), and a loss of life expectancy of 16 years [10]. While the rates of most diabetes-related complications such as myocardial infarction, stroke, lower extremity amputation, and death have decreased in recent years, similar reductions have not been realized for cases of kidney failure [11].

Until recently, no class of glucose-lowering agents was considered a preferred treatment for patients with T2D and CKD. Rather, the recommended treatment approach focused on achieving individualized glycated hemoglobin A1c (HbA1c) targets, optimized blood pressure control, and the use of renin–angiotensin system (RAS) inhibitors, either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB). The historical glucocentric approach focused on intensifying treatment in response to hyperglycemia in a reactive fashion, which means the treatment is always trying to catch up to the disease progression. Further complicating this approach, people with T2D and CKD have a more limited choice of glucose-lowering agents due to safety concerns (e.g., hypoglycemia, lactic acidosis with metformin) and other untoward effects (e.g., fluid retention with thiazolidinediones) in people with reduced kidney function. Treatment burden poses another significant barrier in patients with T2D and CKD. Many people with T2D and CKD require two to four medications to achieve and maintain individualized glycemic targets, another two to three medications to manage blood pressure, and yet another one to two to treat dyslipidemia [12]. Despite treatment with a large number of medications (which often also includes numerous medications to control or treat a host of other comorbidities), they still have large residual risk for death and CKD progression [13,14].

Fortunately for patients with T2D and CKD and the clinicians that care for them, major therapeutic advancements in recent years now offer additional options to mitigate kidney and CV risk. While initially developed and marketed as glucose-lowering therapies, SGLT-2 inhibitors are now recognized as “organ” (heart and kidney)-protective therapies. Consistent and robust evidence for markedly improved clinical outcomes have established SGLT-2 inhibitors as a first-line standard-of-care therapy for individuals with T2D and CKD [15].

2. Methods

The authors searched PubMed for all relevant clinical outcome trials in the last 10 years using the following keywords: type 2 diabetes AND: chronic kidney disease; nephropathy; albuminuria; cardiovascular outcome trials; heart failure outcomes; and renoprotection. The authors also utilized clinical practice guidelines published by the American Diabetes Association (ADA), the National Kidney Foundation (NKF), Kidney Disease: Improving Global Outcomes (KDIGO), and the American Society of Nephrology (ASN), American College of Physicians, American Academy of Family Physicians (endorsed ACP), BMJ, and Australia Diabetes.

3. Results

The authors reviewed the relevant literature and provided the following summative report. The goal was to highlight current evidence supporting the kidney and CV benefits

of SGLT-2 inhibitors, highlight potential mechanisms of organ protection, and discuss important safety considerations when using SGLT-2 inhibitors for people with T2D and CKD. Finally, the authors discuss strategies to facilitate and encourage the use of SGLT-2 inhibitors to improve clinical outcomes in patients with T2D and CKD.

4. Discussion

SGLT-2 inhibitors work to lower glucose by preventing glucose and sodium reabsorption in the proximal tubule, leading to urinary glucose excretion and a reduction in blood glucose [16–18]. The US Food and Drug Administration (FDA) has approved five SGLT-2 inhibitors to date for the treatment of hyperglycemia in T2D: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin [19–23]. Based on findings from clinical trials, several agents within the class have received expanded indications (Table 1) [19–23]. Such expanded indications (depending on the agent) include reduced risks of: progression of CKD and kidney failure, heart failure hospitalization, major adverse ASCVD events, and CV or all-cause death.

Table 1. Labeled indications and dosing for currently available SGLT-2 inhibitors [19–23].

Agent	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Bexagliflozin
Indication(s)	• Adjunct to diet and exercise to improve glycemic control in adults with T2D • To reduce the risk of MACE in adults with T2D and established CVD • To reduce the risk of ESKD, doubling of SCr, CV death, and hospitalization for HF in adults with T2D and diabetic nephropathy with albuminuria	• Adjunct to diet and exercise to improve glycemic control in adults with T2D • To reduce the risk of hospitalization for HF in adults with T2D and established CVD or multiple CV risk factors • To reduce the risk of CV death and hospitalization for HF in adults with HF with reduced ejection fraction (NYHA class II-IV) • To reduce risk of sustained eGFR decline, ESKD, CV death, and hospitalization for HF in adults with CKD at risk for progression	• Adjunct to diet and exercise to improve glycemic control in adults with T2D • To reduce the risk of CV death in adults with T2D and established CVD • To reduce risk of CV death and hospitalization for HF in adults with HF	Adjunct to diet and exercise to improve glycemic control in adults with T2D	Adjunct to diet and exercise to improve glycemic control in adults with T2D
Recommended dosing	• Initiate at 100 mg once daily • May increase to 300 mg once daily for additional glycemic control (if eGFR ≥60)	***Glycemic Control in T2D*** • Initiate at 5 mg once daily • May increase to 10 mg once daily for additional glycemic control ***All Other Indications*** • Initiate at 10 mg once daily	• Initiate at 10 mg once daily • May increase to 25 mg once daily for additional glycemic control	• Initiate at 5 mg once daily • May increase to 15 mg once daily for additional glycemic control	• An amount of 20 mg once daily in the morning
Kidney dose adjustment *	• eGFR ≥ 60: No dosage adjustments required • eGFR 30 to <60: 100 mg once daily • eGFR < 30: Initiation not recommended; patients with albuminuria >300 mg/day may continue 100 mg once daily for organ protection • Contraindicated in dialysis	• eGFR < 25: Initiation not recommended; may continue 10 mg once daily to reduce the risk of eGFR decline, ESKD, CV death and HF hospitalization • Contraindicated in dialysis	• eGFR < 30: Use for glycemic control not recommended; data insufficient to provide dosing recommendations in patients with T2D and CVD • eGFR < 20: Data insufficient to provide dosing recommendation in HF • Contraindicated in dialysis	• eGFR < 45: Use not recommended • Contraindicated in dialysis	• eGFR < 30: Use not recommended • Contraindicated in dialysis

* eGFR values expressed in mL/min/1.73 m^2. **Abbreviations:** CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MACE, major adverse cardiovascular events; mg, milligrams; NYHA, New York Heart Association; SCr, serum creatinine; T2D, type 2 diabetes mellitus.

SGLT-2 inhibitors are efficacious glucose-lowering agents. In addition, SGLT-2 inhibition contributes to weight loss and modest reductions in systolic blood pressure [24]. While these risk factor benefits are well described, they do not fully account for the organ-protective effects of SGLT-2 inhibitors. This is evidenced by kidney and CV benefits observed in patients with CKD, where the glucose-lowering effects of SGLT-2 inhibitors are blunted (see Kidney outcome trials section below). Furthermore, several kidney and HF outcome trials have demonstrated benefits in people with CKD and in heart failure in the absence of T2D. SGLT-2 inhibitors can improve energy efficiency, reduce glomerular hyperfiltration and hypertension, increase erythropoietin and erythrocyte production, reduce oxidative stress, and reduce inflammation [25]. These proposed mechanisms may reduce fibrosis, podocyte and tubular damage, and mesangial matrix expansion in the kidney. In the heart, these effects are believed to reduce fibrosis, improve myocardial energetics, reduce myocardial remodeling, and improve left ventricular function [25]. While the mechanisms by which SGLT-2 inhibitors protect the heart and kidneys are still being explored, clinical trials support their central role in managing people with T2D, CKD, HF, and ASCVD (Figure 1) [26,27]. The following sections provide a succinct review of currently available clinical trial data (Table 2).

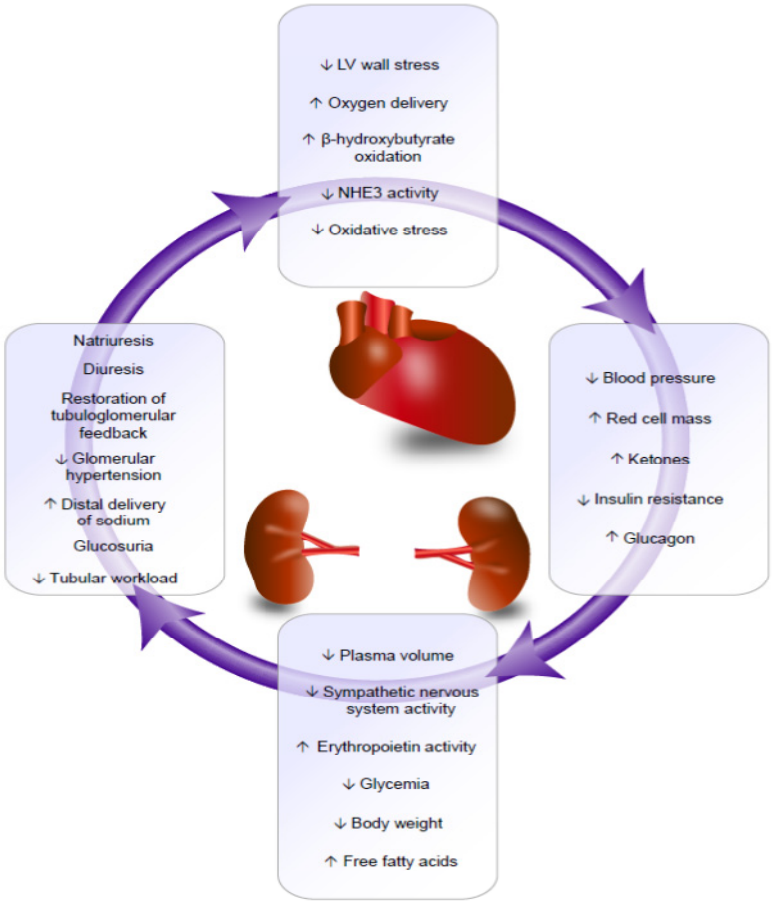

Figure 1. Mechanisms of kidney and heart protection by SGLT-2 inhibitors [26,27].

4.1. Cardiovascular Outcome Trials

Cardiovascular outcome trials (CVOTs) have been published for empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin [28–31]. The EMPA-REG OUTCOME trial with empagliflozin was the first reported CVOT to demonstrate the safety of an SGLT-2 inhibitor, and the first to show the clear benefit of a particular glucose-lowering agent for protection against MACE in people with T2D and established ASCVD [32]. The trial's primary outcome was a composite of death from CV disease, non-fatal MI, and non-fatal

stroke. The primary outcome occurred in 10.5% of patients in the intervention group compared to 12.1% of patients in the placebo group (HR: 0.86; 95% CI: 0.74–0.99; $p = 0.04$ for superiority) [32]. The CANVAS Program (canagliflozin) and DECLARE-TIMI 58 (dapagliflozin) trials reported benefits of treatment on CV outcomes [29,30] The VERTIS trial (ertugliflozin) demonstrated CV safety but failed to demonstrate superiority for its primary 3-point MACE outcome (HR: 0.97; 95% CI: 0.85–1.11) [31]. These CVOT findings have resulted in expanded ASCVD indications for canagliflozin and empagliflozin (Table 1). While findings of ASCVD benefits with agents from the SGLT-2 inhibitor class foundationally changed the treatment landscape for people with T2D, these landmark CVOTs also included key secondary outcomes of interest, including the progression of CKD and HF hospitalization.

4.2. Kidney Outcome Trials

In a follow-up to hypothesis-generating findings of kidney benefit in CVOTs, several dedicated kidney outcome trials have been completed with SGLT-2 inhibitors (Table 3) [33–35]. The first kidney outcome trial reported was the CREDENCE trial with canagliflozin [33]. CREDENCE demonstrated a superiority of canagliflozin treatment when added to standard-of-care background (optimized RAS inhibitor therapy) for the primary composite kidney outcome inclusive of end-stage kidney disease (ESKD), a doubling of serum creatinine, or CV or kidney disease death (HR: 0.70; 95% CI: 0.59–0.82) [33]. DAPA-CKD—which assessed the impact of dapagliflozin treatment on a composite kidney outcome (sustained decline in eGFR of $\geq$50%, progression to ESKD, or death from CV or kidney causes)—was tested in patients with CKD with or without diabetes [34]. When compared to placebo, dapagliflozin treatment reduced the relative risk for the composite kidney outcome by nearly 40% (HR: 0.61; 95% CI: 0.50–0.72). The number needed to treat was only 19 to prevent CKD progression or a kidney failure event over a median treatment period of 2.4 years [34]. CV-related death and hospitalization for HF was also substantially reduced, confirming both kidney and heart protection in patients regardless of diabetes status [34]. In further support of the findings from CREDENCE and DAPA-CKD, the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) with empagliflozin likewise reported robust benefits of SGLT-2 inhibitor therapy in patients with CKD (inclusive of patients with and without diabetes) [35]. EMPA-KIDNEY reported benefits of treatment on a primary composite endpoint of CKD progression or CV death when compared to placebo (13.1% vs. 16.9%; HR: 0.72; 95% CI: 0.64–0.82) [35]. All three kidney disease outcome trials were stopped early because of the overwhelming efficacy showing clear, positive benefits for CKD with or without T2D. Therefore, CKD indications were added to the US labels for these agents (Table 1).

4.3. Heart Failure Outcome Trials

A series of dedicated HF outcome trials have solidified SGLT-2 inhibitors as a first-line standard-of-care treatment for HF, irrespective of diabetes status [36]. Four dedicated HF outcome trials have been completed with dapagliflozin and empagliflozin, demonstrating the benefits of these agents in both reduced-ejection-fraction HF (HFrEF) and HF with preserved ejection fraction (HFpEF), respectively [37–40]. The DAPA-HF trial reported a 26% risk of reduction in worsening HF or CV-related death (HR: 0.74; 95% CI: 0.65–0.85) in patients with HFrEF, and the DELIVER trial reported an 18% risk of reduction in worsening HF or CV death (HR: 0.82; 95% CI: 0.73–0.92), which are benefits largely driven by benefits on worsening HF [37,38]. Both trials enrolled participants with baseline HF with or without diabetes, with a benefit of dapagliflozin treatment observed irrespective of diabetes status in both trials. Similarly, both the Empagliflozin in Heart Failure (EMPEROR—Reduced) and (EMPEROR—Preserved) trials showed that treatment with empagliflozin decreased the risk of CV death or hospitalization for worsening HF in participants with HFrEF and HFpEF, respectively, regardless of the presence of diabetes [39,40]. Furthermore, the eGFR annual decline was significantly reduced in the empagliflozin groups [40]. A recently

published meta-analysis of large HF outcome trials confirms the benefit of SGLT-2 inhibitor therapy to reduce the risk for CV death and HF hospitalization in a broad range of patients with HF [41]. As a result, dapagliflozin and empagliflozin are indicated for HF, irrespective of ejection fraction or diabetes (Table 1).

Table 2. Summary of SGLT-2 inhibitor outcome trials in people with T2D.

Agent *	CV MACE	CV Death	Kidney Disease Progression	HF Hospitalizations	Study/Refs.
canagliflozin	Reduced	No effect	Reduced (Primary Outcome)	Reduced (Secondary Outcome)	[29,33]
dapagliflozin	No effect	No effect	Reduced (Primary Outcome)	Reduced (Primary Outcome)	[30,34,37,38]
empagliflozin	Reduced	Reduced	Reduced (Primary Outcome)	Reduced (Primary Outcome)	[28,32,39,40]
ertugliflozin	No effect	No effect	No effect	Reduced (Secondary Outcome)	[31]

* Outcome data are not yet available for bexagliflozin. Abbreviations: CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events.

Table 3. Summary of key kidney outcome trials with sodium–glucose cotransporter 2 inhibitors [33–35].

Trial	CREDENCE (n = 4401)	DAPA-CKD (n = 4304)	EMPA-KIDNEY (n = 6609)
Treatment	Canagliflozin vs. Placebo	Dapagliflozin vs. Placebo	Empagliflozin vs. Placebo
Key Inclusion Criteria	• T2D • eGFR 30 to <90 mL/min/1.73 m^2 • UACR > 300 to 5000 mg/g • Treated with RAS inhibitor for ≥4 weeks prior to randomization	• eGFR 25 to 75 mL/min/1.73 m^2 • UACR of 200 to 5000 mg/g • Treated with RAS inhibitor for ≥ 4 weeks prior to screening	• eGFR 20 to <45 mL/min/1.73 m^2, regardless of UACR; OR eGFR ≥ 45 to <90 mL/min/1.73 m^2 with UACR ≥ 200 mg/g • Treated with background RAS inhibitor
Mean Participant Age (Years)	63	62	64
Baseline Diagnosis of T2D (%)	100	67	46
Median Follow-Up (Years)	2.6	2.4	2.0
Primary Composite Outcome			
HR (95% CI)	**ESKD, doubling of SCr, or renal or CV death** 0.70 (0.59–0.82)	**≥50% decline in eGFR, ESKD, or renal or CV death** 0.61 (0.51–0.72)	**ESKD, sustained eGFR < 10 mL/min/1.73 m^2, sustained ≥40% decrease in eGFR, or renal or CV death** 0.72 (0.64–0.82)

Abbreviations: A1C, glycated hemoglobin A1c; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; RAS, renin–angiotensin system; SCr, serum creatinine; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

5. Guideline Recommendations for Use of SGLT-2 Inhibitors

In consideration of the glucose-lowering and organ-protective benefits of SGLT-2 inhibitors, this class of medication has taken a prominent position within current diabetes, CKD, and CVD guidelines (Table 4) [15,42–44]. A recently published consensus statement by the American Diabetes Association (ADA)/Kidney Disease: Improving Global Outcomes (KDIGO) on the management of CKD in diabetes recommends first-line treatment with an SGLT-2 inhibitor with proven kidney or CV benefits in patients with T2D,

CKD, and an eGFR $\geq$ 20 mL/min/1.73 m^2 [45]. Once initiated, SGLT-2 inhibitor therapy is recommended to be continued at lower eGFR levels until the patient progresses to dialysis [45].

Table 4. SGLT-2 inhibitor guideline recommendations for CKD and CVD in T2D [15,42–44].

Professional Group Recommendations	SGLT-2 Inhibitor Recommended: CKD	SGLT-2 Inhibitor Recommended: ASCVD	SGLT-2 Inhibitor Recommended: HF	SGLT-2 Inhibitor Recommendation Independent of Metformin
European Society of Cardiology/European Association for the Study of Diabetes Guidelines 2019	YES *	YES	YES	YES If patients drug-naïve for glucose-lowering agents
American Diabetes Association Standards of Care in Diabetes 2023	YES **	YES If GFR adequate based on drug approval label	YES If GFR adequate based on drug approval label	YES
Kidney Disease Improving Global Outcomes Diabetes and CKD Guideline 2022	YES **	YES If GFR adequate based on drug approval label	YES If GFR adequate based on drug approval label	YES
American Heart Association Scientific Statement on Cardiorenal Protection in Diabetes and CKD 2020	YES *** If GFR adequate based on drug approval label	YES If GFR adequate based on drug approval label	YES If GFR adequate based on drug approval label	No comment

* eGFR 30 to <90 mL/min/1.73 m^2. ** eGFR $\geq$ 20 mL/min/1.73 m^2. *** eGFR $\geq$ 30 or $\geq$45 mL/min/1.73 m^2 depending upon agent; for canagliflozin: eGFR 30–45 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio > 300 mg/g.

6. SGLT-2 Inhibitors: Safety Considerations and Risk Mitigation Strategies

Important known side effects of SGLT-2 inhibitors include euglycemic ketoacidosis, genital mycotic infections, and volume depletion. For those patients with a prior history of these side effects, particularly if recent or recurrent, the balance of benefits and harms of SGLT-2 inhibitors should be discussed with these patients. This will allow for shared decision-making that can improve the safety and adherence to these therapies.

Euglycemic diabetic ketoacidosis (DKA) may occur in patients taking SGLT-2 inhibitors due to increased fatty acid oxidation and glucagon release along with decreased insulin secretion [46,47]. Patients with diabetes who are taking insulin are at the greatest risk of ketoacidosis. To reduce the DKA risk in T2D, it is important to maintain insulin treatment and pause SGLT-2 inhibitor treatment during periods of acute illness or other significant stressors. Patients with signs or symptoms of ketoacidosis, such as nausea, vomiting, and abdominal pain, should be instructed to discontinue SGLT-2 inhibitor therapy and seek immediate medical attention. Blood or urine ketone monitoring may be used for early detection of ketosis. One of the suggested strategies for addressing euglycemic ketoacidosis is the education of patients and clinicians on early recognition, and the implementation of the "STOP DKA" protocol (stop SGLT-2 inhibitor, test for ketones, maintain fluid and carbohydrate intake, use maintenance and supplemental insulin) [45]. Currently, SGLT-2 inhibitors are not indicated for use in the US, nor in the UK for people with T1D.

SGLT-2 inhibition is associated with an acute decline in eGFR of 3–5 mL/min/1.73 m^2 ("eGFR dip") due to a functional decline in glomerular hyperfiltration. Generally, kidney function stabilizes within several weeks. Importantly, this dip is not a reason for SGLT-2 inhibitor discontinuation [48–50], with patients experiencing relatively large initial dips

in eGFR (e.g., >10%), deriving clinical kidney benefit [51]. SGLT-2 inhibitors can also cause volume depletion due to their diuretic effect. Stopping or reducing doses of other diuretics is generally not necessary upon SGLT-2 inhibitor initiation. Indeed, an analysis from the EMPA-REG OUTCOME trial found that SGLT-2 inhibitor therapy prevented CKD progression in patients with T2D and cardiovascular disease irrespective of common background medications that alter renal hemodynamics (e.g., RAS inhibitors, calcium channel blockers, diuretics) without increasing the risk for acute adverse kidney events [52]. However, the clinical monitoring of eGFR and electrolytes is prudent to inform dose titration and/or to adjustment of other antihypertensive or diuretic agents. Further, to minimize the risk of volume depletion, SGLT-2 inhibitor treatment should be paused during periods of acute illness or other stressors [53]. Genital mycotic infections occur more often in SGLT-2 inhibitor users (2–4% in men and 3–7% in women, versus <2% in non-users in both sexes) [54]. A recent report advised that the daily rinsing of the genital area after voiding and before bedtime significantly lessened the risk of genital mycotic infections (6/125 versus 51/125, $p = 0.015$) and also increased adherence to SGLT-2 inhibitor treatment over a three-year period [55]. A less common but severe side effect is Fournier's gangrene. This is a rare (1 in 10,000 patients), but serious, illness that was reported a post-market approval to the FDA [56]. It is unclear how much of this risk is attributable to SGLT-2 inhibitor treatment versus increased rates of skin infections in diabetes in general [55].

Primary Care Guidelines

While many specialists endorse and follow the above guidelines for care for people with diabetes, important primary care societies also provide recommendations for these patients. Some guidelines have not been updated recently enough to reflect the data. The American College of Physicians and the American Academy of Family Physicians follow the ACP guidelines published in 2017 [57]. The Diabetes Australia guidelines were published in 2020 and recognize the benefits of SGLT-2 inhibitors but list them as Class C [58]. The BMJ guidelines were published in 2021 and recommend the use of SGLT-2 inhibitors in people with CVD or renal disease or both [59]. It is important that these guidelines also be updated more regularly to reflect current trial patient outcomes.

7. Strategies and Considerations to Optimize Uptake of SGLT-2 Inhibitors

The clinical benefits of SGLT-2 inhibition can only be realized with appropriate use of these guideline-directed medical therapies. The first step is increasing awareness and identification of CKD. Health care professionals should screen for CKD by eGFR and albuminuria testing annually in persons with diabetes and others at high risk (e.g., hypertension, family history, CV disease). It is important to remember that an early response to kidney damage and glomerular injury is a hyperfiltration of the remaining functional glomeruli. Therefore, this makes low eGFR a late finding during CKD, and albuminuria may detect CKD earlier before eGFR decline. Once identified, the need for treatment may seem straightforward, but changing practice patterns is challenging. We have known about the benefits of ACEis and ARBs for over twenty years. However, even recently, the implementation of this standard-of-care for diabetes and CKD was striking low, in the range of 20 to 40% [27,60]. The need for a wider use of SGLT-2 inhibitors highlights the urgent need for better CKD screening and detection. Further, widespread patient education and engagement regarding the benefits of receiving RAS inhibitors and SGLT-2 inhibitors is needed. This can be accomplished via focused discussion and information dispersed in clinical settings, targeted information for high-risk groups, and public media platforms. In one such example, the NKF and CVS Kidney Care have partnered on a campaign to promote kidney health and screening for CKD [61]. Primary care clinicians are central in this effort to improve (CKD and CVD) outcomes for people with diabetes. Active early engagement from primary care and timely intervention can have a profound impact on the quality of life, morbidity, and mortality of these patients.

Key messages for providers to promote optimized use of SGLT-2 inhibitors in people with T2D and CKD:

1. Diabetes is the leading cause of CKD and kidney failure worldwide.
2. Few people at high risk of kidney failure know that they have CKD.
3. CVD is the leading cause of death in people with diabetes and CKD.
4. SGLT-2 inhibitors reduce the risks of progression to kidney failure, HF, ASCVD, and death.

8. Conclusions

Diabetes is the leading cause of CKD and kidney failure worldwide with high risks of ASCVD, HF, and death. CKD is a silent disease for most people and the targeted screening of eGFR and albuminuria is needed to identify it in people with diabetes and others at high risk (e.g., hypertension, family history, CV disease). SGLT-2 inhibitors improve glucose control and also significantly reduce CKD and CVD risks, irrespective of glycemic control or use of other glucose-lowering agents. SGLT-2 inhibitors will be also utilized in treatment beyond hyperglycemia. These agents are now first-line therapies for ASCVD, HF, and CKD, irrespective of diabetes status. Primary care clinicians should become comfortable with prescribing these agents along with cardiologists, nephrologists, and endocrinologists. A strong knowledge of benefits, side effects, and risk mitigation is needed to deliver optimal care of patients who take SGLT-2 inhibitors. Primary care providers have a responsibility to screen for CKD and implement SGLT-2 inhibitors in patients likely to benefit.

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