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CKJ Review



CKJ REVIEW

# Optimization of guideline-directed medical therapies in patients with diabetes and chronic kidney disease

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## ABSTRACT

Diabetes is the leading cause of chronic kidney disease (CKD) and kidney failure worldwide. CKD frequently coexists with heart failure and atherosclerotic cardiovascular disease in the broader context of cardio-kidney-metabolic syndrome. Diabetes and CKD are associated with increased risk of all-cause and cardiovascular death as well as decreased quality of life. The role of metabolic and hemodynamic abnormalities has long been recognized as an important contributor to the pathogenesis and progression of CKD in diabetes, while a more recent and growing body of evidence supports activation of both systemic and local inflammation as important contributors. Current guidelines recommend therapies targeting pathomechanisms of CKD in addition to management of traditional risk factors such as hyperglycemia and hypertension. Sodium-glucose cotransporter-2 inhibitors are recommended for treatment of patients with CKD and type 2 diabetes (T2D) if eGFR is ≥20 ml/min/173 $m^2$ on a background of renin-angiotensin system inhibition. For patients with T2D, CKD, and atherosclerotic cardiovascular disease, a glucagon-like peptide-1 receptor agonist is recommended as additional risk-based therapy. A non-steroidal mineralocorticoid receptor antagonist is also recommended as additional risk-based therapy for persistent albuminuria in patients with T2D already treated with renin-angiotensin system inhibition. Implementation of guideline-directed medical therapies is challenging in the face of rapidly accumulating knowledge, high cost of medications, and lack of infrastructure for optimal healthcare delivery. Furthermore, studies of new therapies have focused on T2D and CKD. Clinical trials are now planned to inform the role of these therapies in people with type 1 diabetes (T1D) and CKD.

**Keywords:** finerenone, GLP-1 receptor agonists, pathomechanisms, risk mitigation, SGLT2 inhibitors

## INTRODUCTION

Chronic kidney disease (CKD) develops in 40% and 30% of people with type 2 diabetes (T2D) and type 1 diabetes (T1D), respectively [1, 2]. CKD is defined by sustained albuminuria [urine albumin-to-creatinine ratio (UACR) ≥30 mg/g], low estimated glomerular filtration rate (eGFR; <60 mL/min/1.73 $m^2$), or both for at least three months [3]. Patients with diabetes and CKD are at risk for progression to kidney failure and need for kidney replacement therapy, with CKD also an important amplifier of cardiovascular (CV) risk in diabetes [4]. Only about 10% of patients with T2D and CKD progress to kidney failure requiring kidney replacement therapy, with most dying from atherosclerotic cardiovascular disease (ASCVD) or heart failure (HF) prior to progressing to kidney failure [5, 6]. Importantly, both

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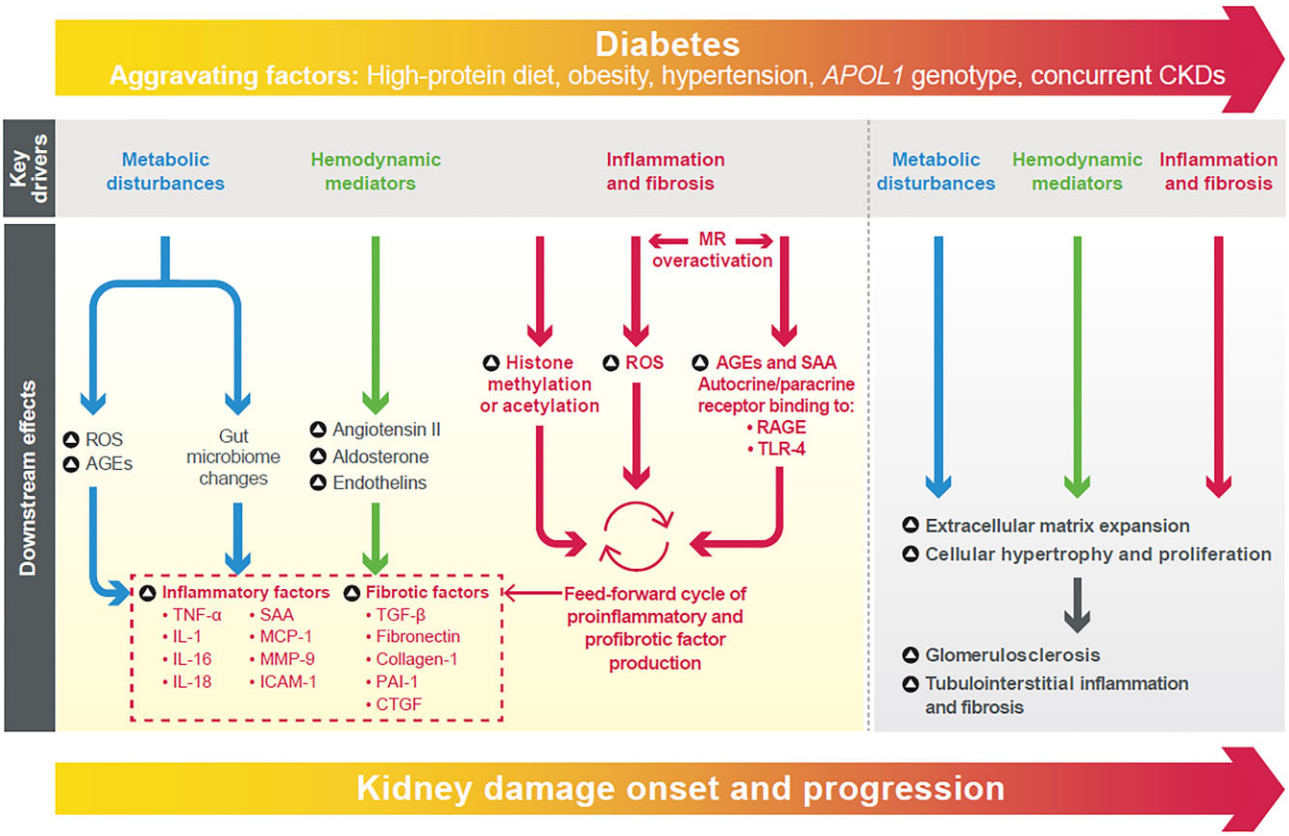


**Figure 1:** Diagram showing the interrelation of mechanistic drivers in early though advanced stages of kidney damage and disease progression in diabetes. AGE, advanced glycation end product; CKD, chronic kidney disease; CTGF, connective tissue growth factor; DKD, diabetic kidney disease; ICAM-1, intracellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chomoattractant protein-1; MMP-9, matric metalloproteinase 9; MR, mineralocorticoid receptor; PAI-1, plasminogen activator inhibitor; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species; SAA, serum amyloid A; TGF-$\beta$, transforming growth factor beta; TLR-4, toll-like preceptor-4; TNF-$\alpha$, tumor necrosis factor alpha. **From:** Tuttle KR, Agarwal R, Alpers CE *et al*. Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney Int* 2022;**102**:248–60.

albuminuria and a decline in eGFR are independent and additive risk factors for CV events, CV-related mortality, and all-cause mortality [7].

A dramatic expansion of guideline-directed medical therapy (GDMT) for CKD in diabetes is supported by high quality evidence of improving kidney, CV, and mortality outcomes in this population. Agents from the sodium-glucose cotransporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1RA), and non-steroidal mineralocorticoid receptor antagonist (ns-MRA) classes have emerged as agents capable of reducing residual risks for kidney disease and CV disease in patients with T2D and CKD on top of renin-angiotensin system (RAS) blockade [8, 9]. However, available evidence indicates that clinical uptake of GDMT is suboptimal, necessitating increased dissemination and implementation efforts [10–13].

## CONSIDERATIONS FOR A MECHANISM-BASED TREATMENT APPROACH OF CKD IN DIABETES

When considering a mechanism-based treatment approach to maximize cardio-kidney-metabolic risk reduction, it is important to consider the complex pathophysiology of CKD in diabetes and how currently available therapies address key pathomechanisms.

### Pathomechanisms of CKD in diabetes

Diabetes mellitus is associated with multiple derangements including insulin resistance, hyperinsulinemia, hyperglycemia, obesity, RAS and aldosterone overactivity, endothelial dysfunction, and maladaptive innate immune responses [14–18]. This diabetic milieu triggers multiple closely interconnected and self-perpetuating metabolic, hemodynamic, inflammatory, and fibrotic abnormalities ultimately resulting in structural and functional deterioration of the kidney (Fig. 1) [19].

The kidney provides near complete reabsorption of glucose filtered through the glomerulus. The majority (~90%) of filtered glucose reabsorption takes place in the early segment of the proximal tubule via coupling of apically located SGLT2 transporters and facilitative glucose transporters located on the basolateral membrane of tubular cells [20]. As a result of maladaptive upregulation of SGLT2 transporters in diabetes, the tubular maximum reuptake threshold for glucose in the filtrate is increased from approximately 200 mg/dl in the non-diabetic state to higher levels in diabetes [21, 22]. The ensuing increase in glucose and sodium chloride uptake in the proximal tubule reduces solute delivery to the macula densa, thus inhibiting tubuloglomerular feedback and adenosine-mediated vasoconstriction of the afferent arteriole, and possibly, vasodilation of the efferent arteriole [23]. Concurrently, local RAS activation with production of angiotensin II as well as endothelin-1

contribute to increased efferent arteriolar resistance and vasoconstriction [23]. An imbalance between pre-glomerular afferent arteriolar vasodilation and post-glomerular efferent arteriolar vasoconstriction results in glomerular hypertension and hyperfiltration [20]. Furthermore, increased glucose reabsorption in diabetes results in greater oxygen demand in the cortex and medulla [24, 25]. Advanced glycation end products (AGEs), compounds formed through the interaction of glucose and associated metabolites with proteins and amino acids, interact with the membrane-bound receptor for advanced glycation end-products (RAGE) [26]. The AGE/RAGE complex has been implicated in the activation of various signaling pathways including Janus kinase 1 and 2/Signal transducer and activators of transcription and transcription factors such as nuclear factor kappa B, thus promoting macrophage migration, production of pro-inflammatory cytokines (e.g. interleukin-6, tumor necrosis factor-$\alpha$, vascular cell adhesion molecule-1), and oxidative stress [26–31]. Ongoing exposure to the diabetic milieu causes injury or death of kidney cells through stimulation of pattern recognition receptors, including toll-like receptors and inflammasomes, resulting in activation of a resident network of mononuclear phagocytes in the kidney [32–35]. These events play a major role in progression of inflammation driving tubular and glomerular injury [18, 36–42]. A final common pathway of chronic metabolic and hemodynamic abnormalities and unrelenting inflammation is activation of multiple pro-fibrotic mediators, cells, and pathways (aldosterone, fibrotic phenotype macrophages, activation of nuclear factor kappa B and mitogen-activated protein kinase pathways, and tumor growth factor-$\beta$), culminating in fibrosis of glomerular and tubulointerstitial compartments [43].

## CLINICAL TRIAL EVIDENCE FOR KIDNEY PROTECTION WITH GUIDELINE-DIRECTED MEDICAL THERAPIES

In 2008 the US Food and Drug Administration issued a guidance requiring manufacturers to conduct dedicated cardiovascular outcome trials (CVOTs) for newly approved glucose-lowering therapies [44]. The guidance was developed in response to concerns about the CV safety of the thiazolidinedione agent rosiglitazone [45]. In response, large CVOTs were conducted for most agents within the SGLT2 inhibitor and GLP-1RA medication classes [46]. While required by the FDA to demonstrate CV safety, several CVOTs conducted with agents from the SGLT2 inhibitor and GLP-1RA classes serendipitously reported CV benefit [46]. Many CVOTs additionally reported key secondary outcome signals of benefit for kidney and HF outcomes, providing important hypothesis-generating data regarding the potential for additional organ protective benefits of therapy. Secondary outcome data from CVOTs in turn prompted follow-up kidney and HF outcome trials that have collectively transformed the standard of care for patients with CKD or HF irrespective of diabetes status [47].

The following sections provide overviews of clinical outcome data and corresponding mechanisms of action (Fig. 2) [48] supporting SGLT2 inhibitors, GLP-1RAs, and finerenone as GDMT for T2D and CKD. In addition, evidence of kidney benefit in non-T2D populations is also highlighted.

### SGLT2 inhibitors

Following initial signals of kidney benefit from SGLT2 inhibitor CVOTs [49–51], three dedicated kidney outcome trials have been conducted with canagliflozin, dapagliflozin, and empagliflozin, respectively (Table 1) [52–54]. Notably, all three trials added SGLT2 inhibitor treatment to background RAS inhibitor therapy, with reported SGLT2 inhibitor benefits over placebo representing residual risk reduction beyond benefits provided with RAS inhibitor therapy alone. The first dedicated kidney outcome trial published was the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [52]. CREDENCE specifically enrolled participants with T2D and CKD and reported a 30% relative risk reduction for its primary kidney-specific composite outcome (Table 1) [52]. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) trials subsequently demonstrated kidney protection in populations inclusive of participants with and without diabetes, participants with baseline eGFRs down to 20 mL/min/1.73 $m^2$, and with varying degrees of albuminuria [53]. Indeed, when analyzed by subgroup, benefits observed with empagliflozin treatment in the EMPA-KIDNEY trial found no heterogeneity of effect based on background diabetes or baseline eGFR [54], findings supported by a recent meta-analysis of large SGLT2 inhibitor outcome trials [55]. Another recently published meta-analysis of large randomized controlled trials found that kidney benefits of SGLT2 inhibitor therapy were greatest in patients with preserved eGFR, thus supporting early initiation of SGLT2 inhibitors to optimize kidney outcomes [56].

Identification of the mechanisms responsible for the organ protective effects of SGLT2 inhibitors is an area of active inquiry [57]. A principal mechanism of action of SGLT inhibitors is blockade of glucose reabsorption in the proximal tubule [58], with resultant glucosuria and increased delivery and reabsorption of sodium chloride at the macula densa [19]. Increased solute reabsorption at this site increases ATP utilization and generation of adenosine that acts in a paracrine manner to increase afferent vasoconstriction, thus reducing glomerular hyperperfusion and hypertension [20, 59]. Some studies indicate possible reduction of efferent vasoconstriction [60–62]. Additional putative mechanisms of SGLT inhibitor benefits may be mediated by off-target effects in various kidney, myocardial, and endothelial cells. SGLT inhibitors have been reported to mitigate oxidative stress, activate the nutrient/energy/redox sensor complex, reduce the mammalian target of rapamycin complex 1 (mTORC1) activity, and lower intracellular glucose [57, 62–67]. SGLT2 inhibitors may also protect the kidney and heart by lowering blood pressure, weight loss, and shifting energy utilization to lipids [22, 58].

### GLP-1RAs and the dual GLP-1/GIP receptor agonist tirzepatide

GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted by intestinal enteroendocrine cells in response to glucose intake that increase postprandial insulin secretion [68–70]. Incretin hormones also play an important role in regulation of food intake and appetite, serving as an interface between metabolic processes and inflammation [68, 70, 71]. Like SGLT2 inhibitors, GLP-1RAs were initially developed as glucose-lowering therapies [72]. In addition to the established ASCVD benefits of agents within the GLP-1RA class [73], growing evidence supports their use to improve kidney disease outcomes [74]. Exploratory findings from several GLP-1RA CVOTs reported benefits on kidney disease progression and reduction of albuminuria [75–77]. Additionally, a glycemic control trial performed in participants with T2D and moderate-to-severe CKD

**Table 1: Summary: of SGLT2 inhibitor kidney outcome trials [52–54].**

| Trial | CREDENCE ($n = 4401$) | DAPA-CKD ($n = 4304$) | EMPA-KIDNEY ($n = 6609$) |
|---|---|---|---|
| Treatment | Canagliflozin vs. placebo | Dapagliflozin vs. placebo | Empagliflozin vs. placebo |
| Mean participant age (years) | 63 | 62 | 64 |
| Key inclusion criteria | • T2D<br>• eGFR 30 to <90 mL/min/1.73 $m^2$<br>• UACR >300 to 5000 mg/g<br>• Treated with RAS inhibitor for ≥4 weeks prior to randomization | • eGFR 25 to 75 mL/min/1.73 $m^2$<br>• UACR of 200 to 5000 mg/g<br>• Treated with RAS inhibitor for ≥4 weeks prior to screening | • eGFR 20 to <45 mL/min/1.73 $m^2$ regardless of albuminuria, or<br>• eGFR 45 to <90 mL/min/1.73 $m^2$ with UACR ≥200 mg/g<br>• Treated with RAS inhibitor unless deemed inappropriate by the investigator |
| Baseline diagnosis of T2D (%) | 100 | 67 | 46 |
| Median follow-up (years) | 2.6 | 2.4 | 2.0 |
| Primary outcome | | | |
| HR (95% CI) | ESKD, doubling of SCr, or renal or CV death | ≥50% decline in eGFR, ESKD, or renal or CV death | ESKD, ≥40% decline in eGFR, sustained eGFR of <10 mL/min/1.73 $m^2$, or renal or CV death |
| | 0.70<br>(0.59–0.82) | 0.61<br>(0.51–0.72) | 0.72<br>(0.64–0.82) |
| Key secondary outcomes | | | |
| Progression to ESKD; HR (95% CI) | 0.68<br>(0.54–0.86) | 0.64<br>(0.50–0.82) | N/R |
| CV death; HR (95% CI) | 0.78<br>(0.61–1.00) | 0.81<br>(0.58–1.12) | 0.84<br>(0.60–1.19) |
| All-cause mortality; HR (95% CI) | 0.83<br>(0.68–1.02) | 0.69<br>(0.53–0.88) | 0.87<br>(0.70–1.08) |

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HR, hazard ratio; N/R, data not reported; RAS, renin-angiotensin system; SCr, serum creatinine; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

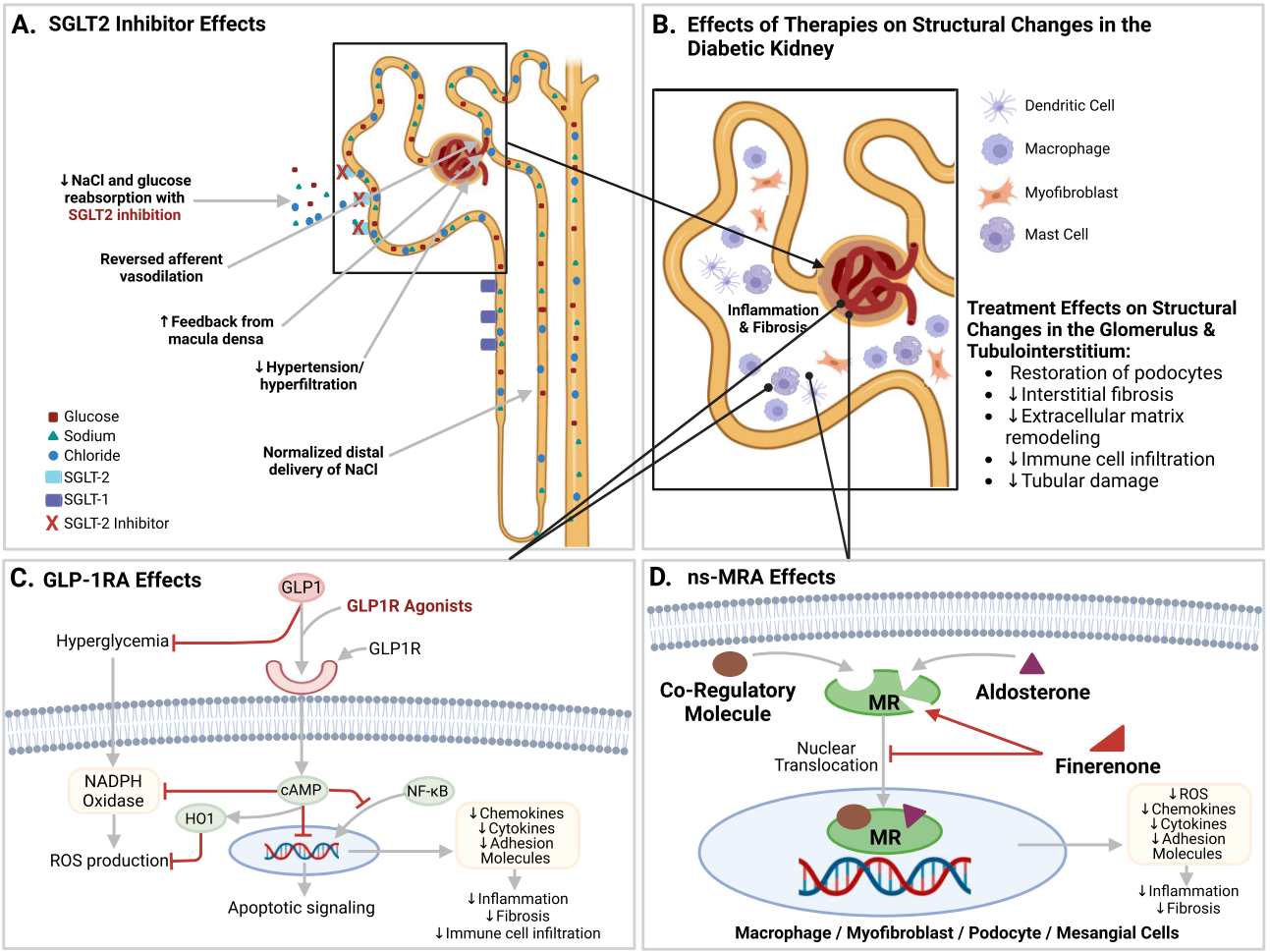


**Figure 2:** Mechanisms of kidney protection with SGLT2 inhibitors, GLP-1RAs, and a nonsteroidal MRA. **A**. Hemodynamic changes in the diabetic kidney are reversed with SGLT2 inhibition. In diabetes, the resorptive capacity for glucose in the proximal tubule is increased via upregulation of SGLT2 and SGLT1. As a result of enhanced glucose and sodium chloride uptake in the proximal tubule, solute delivery to the macula densa cells of the juxtaglomerular apparatus is diminished resulting in altered tubuloglomerular feedback. Adenosine release is subsequently decreased resulting in vasodilation of afferent arteriole, glomerular hyperfiltration, and hypertension. SGLT2 inhibition deceases glucose and sodium reabsorption, thus increasing solute delivery to the distal tubule. These effects help restore tubuloglomerular feedback with a resulting increase in production of adenosine leading to vasoconstriction of the afferent arteriole, and possibly vasodilation of the efferent arteriole, with improvement of glomerular hyperfiltration and hypertension. **B**. Structural changes observed in patients with diabetes and CKD include glomerular hypertrophy, thickening of the glomerular basement membrane, podocyte detachment and foot process effacement, expansion of glomerular mesangial cell matrix, immune cell infiltration, and interstitial fibrosis. Treatment with SGLT2 inhibitors, GLP-1RAs, and ns-MRA helps restore podocytes and decreases extracellular mesangial matrix remodeling, immune cell infiltration, tubular damage, and interstitial inflammation and fibrosis. **C**. The proposed effects of GLP-1RAs in kidney are predominantly mediated through activation of the GLP-1 receptor (GLP1R). Beneficial effects are principally related to suppression of inflammation and oxidative stress, reduced immune cell infiltration, and reduced fibrosis. Activation of the GLP1 receptorR reduces production of reactive oxygen species (ROS) via hemoxygenase 1 (HO1), and reduces production of proinflammatory chemokines, cytokines, adhesion molecules and pro-fibrotic factors via inhibition of nuclear factor-κB (NF-κB) binding. ROS production is also reduced through a non-receptor mediated reduction in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. **D**. Overactivation of the MR in diabetes has been implicated in the promotion of inflammation and fibrosis. Antagonism of the MR with a non-steroidal (finerenone) MRAs suppresses expression of pro-inflammatory and pro-fibrotic genes in macrophages, myofibroblasts, podocytes, and mesangial cells. cAMP, cyclic adenosine monophosphate; GLP1, glucagon-like peptide 1; GLP1R, glucagon-like peptide 1 receptor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HO1, haem-oxygenase 1; MR, mineralocorticoid receptor; NaCl, sodium chloride; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; SGLT-1, sodium-glucose cotransporter 1; SGLT-2, sodium-glucose cotransporter 2. **From:** Neumiller JJ, Alicic RZ, Tuttle KR. Incorporating evidence and guidelines for personalized care of diabetes and chronic kidney disease [48].

(inclusive of patients with eGFRs down to 15 mL/min/1.73 $m^2$) found a significantly slower rate of eGFR decline with dulaglutide treatment when compared with insulin glargine [78]. Pooled analyses inclusive participants from liraglutide and semaglutide CVOTs further found that GLP-1RA therapy reduced albuminuria and slowed eGFR decline compared to placebo with greatest benefit in those with baseline eGFR <60 mL/min/1.73 $m^2$ [79, 80]. While these secondary and exploratory findings are promising, the ongoing Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease trial (FLOW, NCT03819153) will determine the impact of GLP-1RA therapy on a primary kidney outcome in patients with T2D and CKD [81]. While the full results are not yet released, the FLOW trial will be stopped early due to meeting pre-specified efficacy criteria during a planned interim analysis [82]. There is additional growing interest in the potential role of the dual GLP-1/GIP receptor agonist, tirzepatide, on kidney outcomes, with a recent paper highlighting benefits on

**Table 2: Summary of finerenone outcome trials [94, 95].**

| Trial | FIDELIO-DKD ($n = 5734$) | FIGARO-DKD ($n = 7437$) |
|---|---|---|
| Treatment | Finerenone vs. placebo | Finerenone vs. placebo |
| Mean participant age (years) | 66 | 64 |
| Key inclusion criteria | • T2D<br>• eGFR 25 to <60 mL/min/1.73 $m^2$ and UACR 30 to <300 mg/g, or<br>• eGFR 25 to <75 mL/min/1.73 $m^2$ and UACR 300 to 5000 mg/g<br>• Treated with RAS inhibitor at maximum tolerated dose | • T2D<br>• eGFR 25 to 90 mL/min/1.73 $m^2$ and UACR 30 to <300 mg/g, or<br>• eGFR >60 mL/min/1.73 $m^2$ and UACR 300 to 5000 mg/g<br>• Treated with RAS inhibitor at maximum tolerated dose |
| Mean baseline A1C (%) | 7.7 | 7.7 |
| Median follow-up (years) | 2.6 | 3.4 |
| Primary outcome | | |
| HR (95% CI) | Kidney failure, ≥40% decline in eGFR, or renal death<br>0.82<br>(0.73–0.93) | CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF<br>0.87<br>(0.76–0.98) |
| Key secondary outcomes | | |
| Key secondary composite; HR (95% CI) | CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF<br>0.86<br>(0.75–0.99) | Kidney failure, ≥40% decline in eGFR, or renal death<br>0.87<br>(0.76–1.01) |
| Progression to ESKD; HR (95% CI) | 0.86<br>(0.67–1.10) | 0.64<br>(0.41–0.995) |
| CV death; HR (95% CI) | 0.86<br>(0.68–1.08) | 0.90<br>(0.74–1.09) |
| All-cause mortality; HR (95% CI) | 0.90<br>(0.75–1.07) | 0.89<br>(0.77–1.04) |

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; MI, myocardial infarction; RAS, renin-angiotensin system; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

both albuminuria and eGFR decline in the SURPASS-4 trial [83]. A Study of Tirzepatide (LY3298176) in Participants with Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes (TREASURE-CKD; NCT05536804) is an ongoing 52-week trial examining the effect of tirzepatide on kidney oxygenation in addition to multiple secondary clinical outcomes inclusive of eGFR and UACR changes.

In major T2D clinical trials, GLP-1RAs demonstrated glucose-lowering effects, along with reductions in blood pressure and body weight, that were preserved in advanced CKD [84–86]. The relative impact of glycated hemoglobin (A1C), systolic blood pressure, and body weight change on kidney outcomes was assessed in a mediation analysis of CVOTs with liraglutide and semaglutide [87]. The analysis showed that lower glycemia and reduced blood pressure only moderately mediated (10–25%) development of macroalbuminuria, doubling of serum creatinine, decline in eGFR to <45 mL/min/1.73 $m^2$, and progression to kidney failure, supporting direct GLP-1RA effects on the kidney [87]. Indeed, mechanistic studies demonstrate that GLP-1RAs suppress oxidative stress, inhibit activation and infiltration of inflammatory cells into the heart and kidney, and reduce activation of proinflammatory cytokines and profibrotic factors [88–93].

## Ns-MRA (finerenone)

The efficacy and safety of finerenone were characterized through two primary outcome trials: the Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) trial and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial (Table 2) [94, 95]. Clinical benefits reported with these two trials resulted in the approval of finerenone by the United States Food and Drug Administration to reduce the risks for CKD progression, kidney failure, and CV events in patients with T2D and CKD [96]. As detailed in Table 2, FIDELIO-DKD and FIGARO-DKD reported relative risk reductions of 18% and 13% for their primary composite kidney and CV outcomes, respectively [94, 95]. The benefits of finerenone were observed when added to optimized background RAS inhibitor therapy. Collectively these trials enrolled participants with T2D and CKD with a range of baseline eGFR and UACR values, with the pooled FIDELITY analysis of data from FIDELIO-DKD and FIGARO-DKD reporting benefits on composite kidney and CV outcomes across a range of baseline eGFR and albuminuria levels [97], and irrespective of prevalent ASCVD [98]. While a study is underway to investigate finerenone's potential benefit as add-on to background SGLT2 inhibitor therapy (ClinicalTrials.gov Identifier: NCT05254002), *post hoc* findings suggest that finerenone may provide additive kidney protection when used in combination with other GDMT [99, 100].

Overactivation of the mineralocorticoid receptor (MR) is associated with inflammation and fibrosis in the kidney. Moreover, aldosterone breakthrough with increased plasma aldosterone may occur in patients on RAS inhibitor therapy, which may exacerbate MR overactivation and contribute to kidney damage. As such, the MR has emerged as an important therapeutic target in T2D and CKD [101, 102]. MRs are located in distal tubules, the

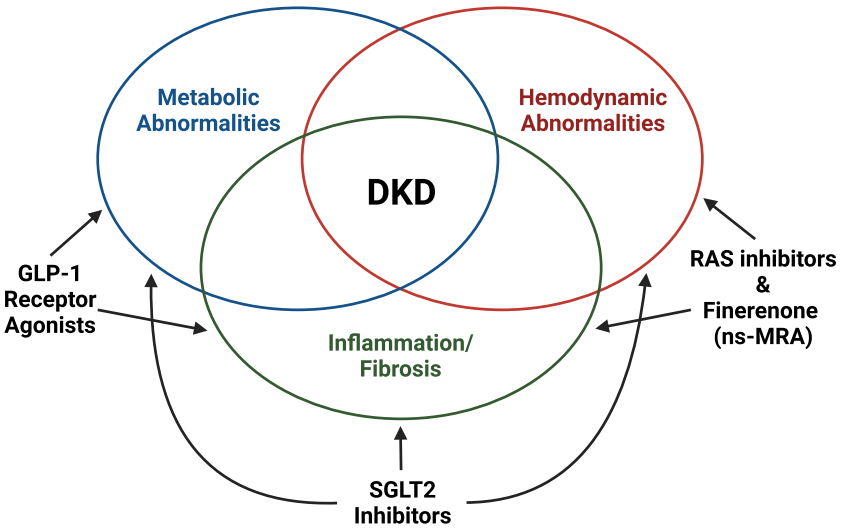


**Figure 3:** Proposed mechanisms of kidney protection for guideline-directed medical therapies. Current guideline-directed medical therapies, inclusive of RAS inhibitors, SGLT2 inhibitors, GLP-1RAs, and the ns-MRA finerenone address multiple pathophysiological drivers of DKD. DKD, diabetic kidney disease; GLP-1, glucagon-like peptide-1; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2. Created with Biorender.com.

collecting duct, podocytes, fibroblasts, and mesangial cells [103]. Finerenone, a ns-MRA, selectively binds to the MR as a 'bulky' antagonist [101]. Once bound, the finerenone-MR complex transits to the nucleus and downregulates pro-inflammatory and profibrotic gene transcription, in turn inhibiting transcriptional cofactor recruitment involved in hypertrophic, proinflammatory, and profibrotic gene regulation [104]. In pre-clinical studies, finerenone demonstrated albuminuria reduction, regression of cardiac hypertrophy, and lower markers of inflammation and fibrosis [105–108].

## CURRENT RECOMMENDATIONS FOR THE CARE OF PATIENTS WITH DIABETES AND CKD

The current armamentarium of GDMTs allows for a holistic and personalized approach to treatment, with the goal of providing kidney and heart protection, improving survival, and optimizing quality of life [19]. Currently available GDMTs target different pathways implicated in the development and progression of DKD (Fig. 3). Given early evidence of additive benefit when using GDMT in combination, a '4 pillar' strategy has been proposed to maximize risk reduction in patients with cardio-kidney-metabolic conditions [109]. Accordingly, current US and European clinical practice guidelines and advisories recommend a patient-centered, risk-based treatment approach using GDMT to optimize cardio-kidney-metabolic outcomes [8, 9, 110–115].

### Foundation: healthy lifestyle and management of traditional risk factors

Contemporary guidelines for the management of CKD in diabetes emphasize a foundation of healthy lifestyle interventions, self-management education, and optimized management of traditional risk factors for diabetes-related complications (blood glucose, blood pressure, and lipids) for all patients with diabetes (e.g. T2D and T1D) [8, 9]. Key considerations related to nutrition management include adoption of a generally healthy and balanced diet, avoiding excessive sodium intake, and maintaining appropriate protein intake (approximately 0.8 g/kg per day). Physical activity is likewise encouraged, with moderate-intensity physical activity for a cumulative duration of 150 minutes per week, or a level appropriate given CV or physical conditions [8, 9]. Encouraging cessation of tobacco smoking and achieving and maintaining weight management goals are also recommended components of holistic care (Fig. 4) [8, 9].

### First-line GDMT

First-line GDMT focuses starts with optimization of glucose, blood pressure, and lipid management to reduce kidney and heart disease risk [8, 9]. As emphasized in Fig. 4, KDIGO and the ADA recommend key first-line drug therapies in patients with diabetes and CKD [8, 9]. RAS inhibitors have been a standard of care in patients with diabetes, hypertension, and albuminuria (UACR $\geq$30 mg/g) for nearly three decades following establishment that RAS inhibition reduces risk of progression to kidney failure in this population [116–118]. RAS inhibitor therapy is recommended to be given at the maximum indicated or tolerated dose [8, 9]. In addition to their systemic antihypertensive effects, RAS inhibitors reduce angiotensin II-induced post-glomerular (efferent) arteriolar vasoconstriction and glomerular hyperfiltration [6]. Furthermore, there is ongoing effort to understand molecular mechanisms contributing to anti-inflammatory effects associated with RAS inhibition [119]. Initiation of moderate- to high-intensity statin therapy, as appropriate per the individuals CV risk factors, is additionally recommended in patients with diabetes (T1D and T2D) and CKD to reduce ASCVD risk [8, 9]. ADA/KDIGO additionally highlights SGLT2 inhibitors as a standard-of-care, first-line therapy in patients with T2D and CKD based on robust clinical benefits in this population (Table 1) [52–54]. Specifically, initiation of an SGLT2 inhibitor with proven kidney and heart benefit is recommended for patients with T2D, CKD, and an eGFR $\geq$20 mL/min/1.73 $m^2$ irrespective of baseline albuminuria [8, 9]. It is recommended that SGLT2 inhibitors be continued even at lower eGFR levels (if already incorporated into the regimen) and discontinued once the patient progresses to kidney failure requiring dialysis or kidney transplant. Table 3 provides a summary of current labeled indications and dosing for SGLT2 inhibitors approved for

Table 3: SGLT2 inhibitors: indications and recommended dosing [120–123].

| Agent | Canagliflozin | Dapagliflozin | Empagliflozin | Ertugliflozin |
|---|---|---|---|---|
| Indication(s) | • Adjunct to diet and exercise to improve glycemic control in adults with T2D<br>• To reduce the risk of MACE in adults with T2D and established CV disease<br>• 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<br>• To reduce the risk of hospitalization for HF in adults with T2D and established CV disease or multiple CV risk factors<br>• To reduce the risk of CV death, hospitalization for HF, and urgent HF visits in adults with HF.<br>• 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<br>• To reduce the risk of CV death in adults with T2D and established CV disease<br>• 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 |
| Recommended dosing | • Initiate at 100 mg once daily<br>• May increase to 300 mg once daily for additional glycemic control (if eGFR ≥60) | *Glycemic control in T2D*<br>• Initiate at 5 mg once daily<br>• May increase to 10 mg once daily for additional glycemic control<br>*All other indications*<br>• Initiate at 10 mg once daily | • Initiate at 10 mg once daily<br>• May increase to 25 mg once daily for additional glycemic control | • Initiate at 5 mg once daily<br>• May increase to 15 mg once daily for additional glycemic control |
| Kidney dose adjustment[a] | • eGFR ≥60: No dosage adjustments required<br>• eGFR 30 to <60: 100 mg once daily<br>• eGFR <30: Initiation not recommended; patients with albuminuria >300 mg/day may continue 100 mg once daily for organ protection | • eGFR ≥45: No dosage adjustments required<br>• eGFR 25 to <45: 10 mg once daily<br>• eGFR <25: Initiation not recommended; may continue 10 mg once daily to reduce the risk of eGFR decline, ESKD, CV death, and HF hospitalization | • eGFR <30: Use for glycemic control not recommended; data insufficient to provide dosing recommendations in patients with T2D and established CV disease<br>• eGFR <20: Data insufficient to provide dosing recommendation in HF | • eGFR <45: Use not recommended |

[a] eGFR values expressed in mL/min/1.73 $m^2$

CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF: heart failure; MACE, major adverse cardiovascular events; mg, milligrams; SCr, serum creatinine; T2D, type 2 diabetes mellitus.

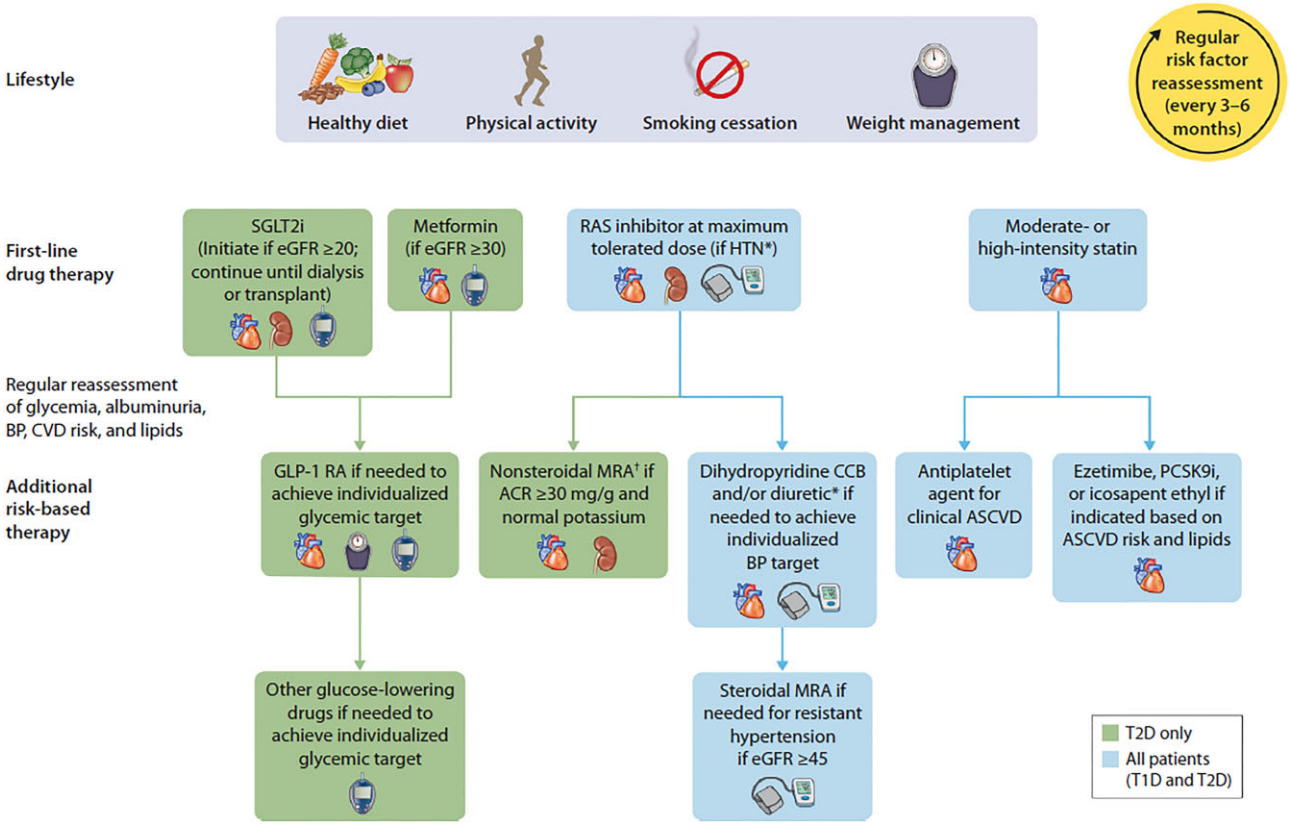


**Figure 4:** Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease (CKD). Icons presented indicate the following benefits: blood pressure (BP) cuff, BP-lowering; glucometer, glucose-lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. Estimated glomerular filtration rate (eGFR) is presented in units of ml/min/1.73 $m^2$. *Angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (at maximal tolerated doses) should be first-line therapy for hypertension (HTN) when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) with proven clinical kidney and cardiovascular benefits. ACR, albumin-to-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GLP-1 RA, GLP-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. **From:** de Boer IH, Khunti K, Sadusky T *et al*. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes. *Kidney Int* 2022;**102**:974–89.

the treatment of T2D [120–123]. Considering that the glucose-lowering efficacy of SGLT2 inhibitors is diminished as eGFR declines, ADA/KDIGO include metformin as an optional first-line therapy if needed for glycemic control in those with an eGFR ≥30 mL/min/1.73 $m^2$ [8, 9].

## Additional risk-based therapies

Moving beyond first-line therapies, ADA and KDIGO recommend regular reassessment of glycemia, blood pressure, lipids, albuminuria, eGFR, and CV risk factors to guide intensification of therapies for patients with diabetes and CKD [8, 9]. For people with T2D and CKD, GLP-1RAs and finerenone are specifically highlighted as additional risk-based therapies [8, 9]. Unlike SGLT2 inhibitors, the glucose-lowering effects of GLP-1RAs are preserved in advanced CKD with efficacy and safety established down to an eGFR of 15 mL/min/1.73 $m^2$ [8, 9, 78]. Based on secondary outcomes from CVOTs and glycemic-lowering trials suggesting kidney benefit, mechanistic studies, and their established CV benefits, ADA and KDIGO preferentially recommend use of a long-acting GLP-1RA with evidence of CV benefit in patients not meet glycemic goals despite first-line therapies [8, 9]. While the Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled with Metformin Monotherapy (DURATION-8) trial did not enroll participants with CKD, the study demonstrated that a GLP-1RA (exenatide once weekly) used in combination with a SGLT2 inhibitor (dapagliflozin) is safe and that the combination resulted in superior glycemia lowering, and clinically relevant weight and blood pressure reduction, compared with either agent used alone over two years of treatment [124].

Residual albuminuria following treatment with an SGLT2 inhibitor is associated with risk for both kidney and cardiovascular events [125], with antagonism of the MR offering an additional approach to reduce risks [126]. Based on the FIDELIO-DKD and FIGARO-DKD trials (Table 2), finerenone is recommended by ADA and KDIGO in patients with T2D and CKD with persistent albuminuria (UACR ≥30 mg/g) despite maximally tolerated RAS inhibitor therapy with or without an SGLT2 inhibitor [8, 9].

## Patient education and risk mitigation

When initiating GDMTs in patients with diabetes and CKD, it is imperative to provide initial patient education and

**Table 4: Recommended: monitoring and risk mitigation strategies for guideline directed medical therapies [8, 96, 110].**

| Medication class | Consideration | Monitoring and/or risk mitigation strategies |
|---|---|---|
| SGLT2 inhibitors | • Genital mycotic infections | • Counsel on importance of genital hygiene |
| | • Hypoglycemia | • Adjust background glucose-lowering agents (e.g. insulin and/or insulin secretagogues) as appropriate |
| | • Volume depletion | • Monitor for symptoms of hypovolemia and consider proactive diuretic dose reduction in high risk patients<br>• Hold SGLT2 inhibitors during acute illness and/or prolonged fasting |
| | • Ketoacidosis | • Educate about signs/symptoms to facilitate early recognition (e.g. abdominal pain, nausea/vomiting, lethargy)<br>• Monitor blood or urine ketones<br>• Institute a sick day protocol (e.g. STICH protocol: **ST**op SGLT2 inhibitor, **I**nsulin administration, **C**arbohydrate consumption, **H**ydration)<br>• Maintain at least low-dose insulin in insulin-requiring individuals |
| GLP-1RAs | • Nausea/vomiting/diarrhea | • Start at lowest recommended dose and titrate slowly based on patient tolerability and response<br>• Educate on tolerability and strategies to minimize intolerance (e.g. eat slowly, eat smaller portions) |
| | • Hypoglycemia | • Adjust background glucose-lowering agents (e.g. insulin and/or insulin secretagogues) as appropriate |
| ns-MRA (finerenone) | • Hyperkalemia | • Monitor potassium levels prior to initiation, 4 weeks after initiation, 4 weeks after a dose adjustment and throughout treatment to inform dose adjustments |

GLP-1RAs, glucagon-like peptide-1 receptor agonists; ns-MRA, non-steroidal mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter-2.

appropriate follow-up concerning potential side effects and associated risk mitigation strategies [8, 9]. Table 4 provides a summary of key counseling points recommended by ADA/KDIGO to mitigate potential risks of therapy and promote medication safety with SGLT2 inhibitors, GLP-1RAs, and the ns-MRA finerenone [8, 9, 96, 110].

## OPTIMIZING UTILIZATION OF GDMT IN CKD: ADDRESSING CURRENT GAPS IN CARE

Despite recent advances and an established standard-of-care for patients with T2D and CKD [8, 9], real-world evidence shows that uptake and utilization of GDMTs is low [10–13]. For example, a recent analysis from the Center for Kidney Disease Research, Education and Hope (CURE-CKD) Registry found that in a sample of over 39 000 adults with T2D and CKD receiving care within two large health systems, only approximately 40% of patients received persistent (≥90 days) RAS inhibitor therapy for the period spanning 2019–2020 [13]. Furthermore, only 5% and 6.3% of patients received persistent treatment with a SGLT2 inhibitor or GLP-1RA, respectively [13]. Major clinical practice guidelines and advisories the importance of utilizing integrated multidisciplinary care teams to deliver coordinated, high-quality care for patients with cardio-kidney-metabolic conditions [8, 9, 114, 115, 127]. However, a variety of barriers to optimized management of cardio-kidney-metabolic conditions exist, including siloed specialty care, disparities in access to care and GDMT, lack of knowledge and understanding of current standards of care by members of the care team, and economic disincentives [128]. Development of novel, effective, and translatable cardio-kidney-metabolic care models are needed to address current disparities and suboptimal utilization of GDMTs [128].

An area of large unmet need is therapeutic advancement for CKD in T1D [129]. In contrast to the rapid development of new therapies to mitigate risks of kidney failure, CVD events, and death in T2D, prevention of kidney and CV complications in T1D remains largely unchanged, simply relying on intensive management of glycemia and blood pressure [130]. However, studies have been performed with SGLT2 inhibitors in participants with T1D [131–138]. Analyses of hemodynamic effects of SGLT2 inhibition in T1D demonstrated similar changes in eGFR and UACR to those observed in T2D [139, 140]. Indeed, pooled analysis of the Tandem1 and Tandem2 trials with sotagliflozin demonstrated a reduction in UACR by 24% in patients with a baseline UACR ≥30 mg/g [141]. Similarly, findings from the EASE-2 and EASE-3 trials with empagliflozin reported reductions in UACR compared to placebo in adults with T1D and baseline UACR ≥30 mg/g [142]. However, because of the increased risk of severe hypoglycemia and ketoacidosis observed in T1D studies with SGLT2 inhibitors, these agents are not currently approved for use in T1D in the USA or European Union [143]. GLP-1RAs have similarly been studied for glycemic control and weight loss in T1D, but their long-term effect on kidney and CV risk has not yet been evaluated [144–146]. Three upcoming trials will study new therapies for T1D and CKD. The REMODEL-T1D trial will evaluate the efficacy and safety of semaglutide for albuminuria as well as kidney oxygenation and fibrosis [147]. A Study to Learn How Well the Study Treatment Finerenone Works and How Safe it is in People With Long-term Decrease in the Kidneys' Ability to Work Properly (Chronic Kidney Disease) Together With Type 1 Diabetes (FINE-ONE, NCT05901831) will investigate the efficacy and safety of finerenone for albuminuria reduction as a bridging biomarker based on the T2D studies [148]. The effectiveness and safety of sotagliflozin in slowing kidney function decline in persons with type 1 diabetes and moderate to severe diabetic

kidney disease: The SUGAR-N-SALT Trial will test an SGLT2 inhibitor versus placebo for preservation of eGFR.

## CONCLUSIONS

Clinical practice guidelines for CKD in diabetes recommend a holistic approach where GDMT is layered on a foundation of healthy lifestyle and management of traditional risk factors, including optimization of glycemia and blood pressure. RAS inhibitors and moderate- to high-intensity statin therapy are recommended first-line therapies in all patients with diabetes and CKD. For patients with T2D, a SGLT2 inhibitor with proven kidney and heart benefits is recommended first-line plus metformin, if needed, to meet individualized glycemic goals. Consideration of additional kidney and heart protective therapies in the form of GLP-1RAs and/or finerenone are recommended for patients with T2D and CKD based on individualized risks. Unfortunately, despite the recent advancements to improve cardio-kidney-metabolic outcomes in patients with T2D and CKD, utilization and access to such lifesaving therapies is suboptimal. Widespread dissemination of current evidence-based treatments as well as development and validation of care models focusing on GDMT optimization to improve care and outcomes for CKD in diabetes are urgently needed. Furthermore, studies of new therapies to-date have focused on T2D and CKD. Importantly, clinical trials are now planned to inform the role of these therapies for people with T1D and CKD. Ongoing clinical trials and implementation science approaches are essential to optimize care that saves kidneys, hearts, and lives in all people with diabetes.

## CONFLICT OF INTEREST STATEMENT

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## DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

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