# New Paradigms for CKD Management in Patients With T2D

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## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Identify the risks of kidney disease and their consequences in patients with type 2 diabetes (T2D).
- Appropriately screen for the presence of chronic kidney disease (CKD) in patients with T2D.
- Initiate evidence-based therapy to slow the progression of kidney disease in patients with T2D and CKD.
- Become familiar with the novel nonsteroidal mineralocorticoid receptor antagonist finerenone and its role in the treatment of patients with T2D and CKD.

### KEY TAKEAWAYS

- Chronic kidney disease (CKD) is defined by persistent abnormalities in urinary albumin excretion, estimated glomerular filtration rate (eGFR), or both. Unfortunately, CKD is widely underrecognized by clinicians and patients.
- Guideline-directed management of CKD in type 2 diabetes (T2D) involves lifestyle modifications, optimized control of modifiable risk factors, and use of therapies with evidence of cardiorenal benefit, including renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, finerenone, and long-acting glucagon-like peptide-1 receptor agonists (GLP-1 RAs).
- Finerenone is a novel, nonsteroidal mineralocorticoid receptor antagonist (MRA), which is pharmacologically and clinically distinct from steroidal MRAs and can be used as recommended in current guidelines to improve cardiorenal outcomes in patients with T2D and CKD.

### TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of CKD.

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## CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES

Chronic kidney disease (CKD) is an important diabetes-related complication.[1] CKD in diabetes can progress to kidney failure, and the need for kidney replacement therapy (dialysis or transplant) markedly amplifies cardiovascular risk and is costly to the healthcare system.[1] CKD additionally increases mortality risk, with one analysis reporting an approximate 10-fold increase in 10-year mortality risk for patients with type 2 diabetes (T2D), albuminuria, and impaired glomerular filtration rate (GFR) when compared to people with T2D without kidney disease.[2]

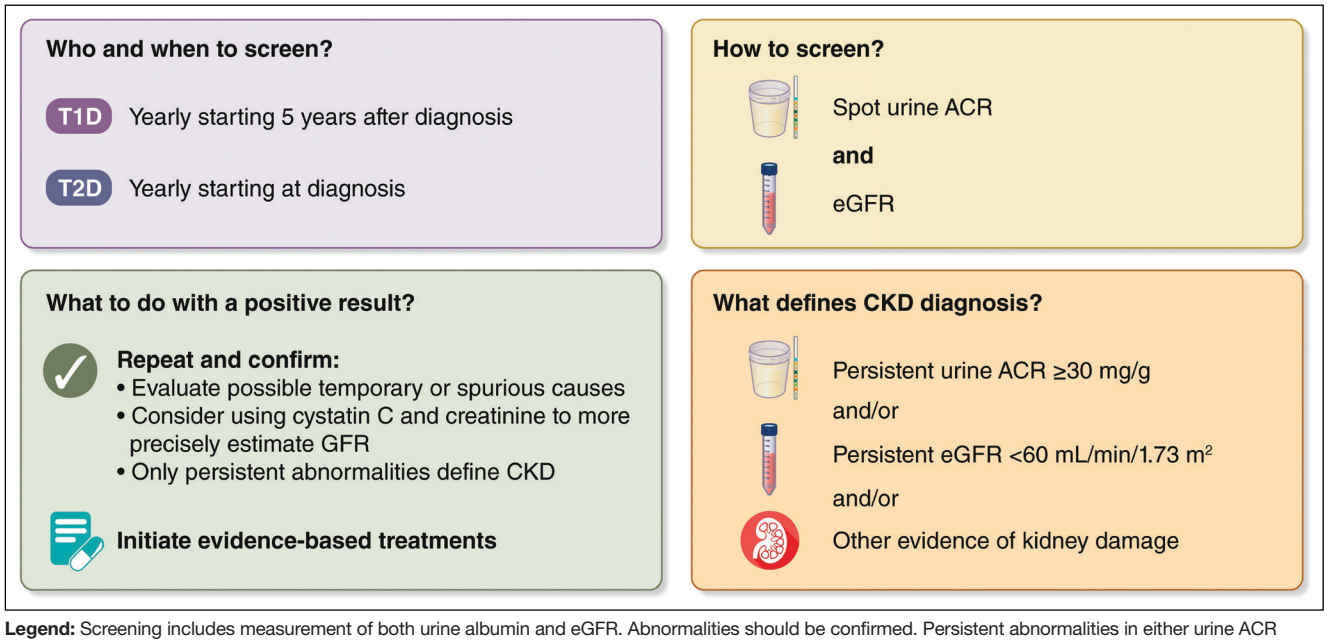
The prevalence of CKD in the United States continues to increase in parallel with the prevalence of diabetes.[3] According to estimates from the Centers for Disease Control and Prevention (CDC), approximately one-third of the estimated 37 million people living with diabetes in the United States may have CKD.[4] In most cases, CKD is initially asymptomatic and is identified and diagnosed through recommended annual laboratory screening.[5] Unfortunately, CKD awareness is quite low among clinicians and patients alike, with an estimated 90% of people with CKD unaware of their condition.[6] Early identification and management is essential, however, to slow CKD progression, mitigate cardiovascular risk, and prevent premature mortality.[1] Fortunately, recent important therapeutic advancements now provide clinicians and patients with additional therapeutic options to mitigate cardiorenal risk. Because the vast majority of people with T2D are managed in primary care settings, primary care clinicians play a critical role in the early identification and treatment of CKD in T2D.[7] Recognizing and overcoming key barriers to optimized CKD care in the primary care setting, such as suboptimal screening, lack of clinician and patient awareness, limited clinician time and resources, and suboptimal use of guideline-directed therapies, are critical to improve patient care and outcomes.[8]

## DIAGNOSIS AND CLASSIFICATION OF CKD

CKD is defined by a persistent estimated GFR (eGFR) <60 mL/min/1.73 m$^2$, persistently elevated urine albumin excretion (albumin-to-creatinine ratio [ACR] ≥30 mg/g), or both, for >3 months.[9] Annual screening is recommended in people with T2D starting at the time of diagnosis and beginning 5 years after a diagnosis of type 1 diabetes (T1D) (**FIGURE 1**).[5] Screening for both low eGFR and albuminuria is important to identify at-risk individuals, yet evidence indicates that less than half of people with T2D are screened for albuminuria annually in the primary care setting.[10]

Kidney Disease: Improving Global Outcomes (KDIGO), a consensus recommendation from an international group of experts, has developed a "heat map" for CKD staging, which also guides decisions related to frequency of monitoring, treatment, and nephrology referral, which can be accessed here: https://pubmed.ncbi.nlm.nih.gov/36189689/#&gid=article-figures&pid=figure-2-uid-1.[5] The American Diabetes Association[1] (ADA) recommends referral to nephrology for patients with rapidly progressing CKD and/or in those with an eGFR

**FIGURE 1. CKD screening and diagnosis for people living with diabetes[5]**




**Legend:** Screening includes measurement of both urine albumin and eGFR. Abnormalities should be confirmed. Persistent abnormalities in either urine ACR or EGFR (or both) diagnose CKD and should lead to immediate initiation of evidence-based treatments.

<30 mL/min/1.73 m$^2$. Likewise, referral to nephrology is recommended when there is uncertainty about kidney disease etiology or when difficult management issues arise (eg, anemia, metabolic bone disease, secondary hyperparathyroidism).[1]

### CKD risk factors and pathophysiology

The 2 most important risk factors for CKD in diabetes are uncontrolled hyperglycemia and/or blood pressure, with the ADA noting that optimization of glycemic and blood pressure control is the only proven strategy for the primary prevention of CKD in diabetes.[1] The CDC notes a family history of CKD, hyperlipidemia, obesity, and smoking as additional risk factors for the development of CKD in diabetes.[4] As discussed in the text that follows, proactive management of modifiable risk factors is considered a foundation of CKD management in T2D.

The pathophysiology of CKD in diabetes is complex and involves a combination of metabolic, hemodynamic, inflammatory, and fibrotic changes associated with the diabetic state.[11] These factors lead to structural and functional changes in the kidney characteristic of diabetic kidney disease.[11] Notably, overactivation of the mineralocorticoid receptor (MR) is now recognized as an important driver of inflammation and fibrosis in the kidney.[12]

### Guideline-directed therapy in patients with T2D and CKD

Guideline-directed management of CKD in T2D involves a holistic approach that includes lifestyle interventions, optimized management of key modifiable risk factors (eg, lack of glycemic control, high blood pressure, elevated lipid levels), and use of therapies with evidence of cardiorenal benefit that address key pathophysiologic drivers of CKD.[1,5,13] A "4-pillars" approach for the management of CKD in patients with T2D has been proposed in the literature: treatment with a renin-angiotensin system (RAS) inhibitor, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, finerenone, and a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), all built on a foundation of key lifestyle interventions and metabolic management.[14] This approach is supported by the current ADA/KDIGO algorithm for management of patients with diabetes and CKD, which recommends intensification of these and other therapies to reduce cardiorenal and metabolic risk. A holistic approach for improving outcomes in patients with diabetes and CKD can be accessed here: https://pubmed.ncbi.nlm.nih.gov/36189689/#&gid=article-figures&pid=figure-3-uid-2.5[5]

### Lifestyle modifications and management of key modifiable risk factors

Cardiorenal risk reduction in T2D begins with implementation of healthy behaviors and optimized metabolic management.[1,5,13] ADA and KDIGO stress the importance of medical nutrition therapy (MNT) and consumption of balanced diets low in refined carbohydrates and sodium. A summary of key dietary recommendations from KDIGO is provided in **TABLE 1**.[5] Weight loss is encouraged for individuals with overweight or obesity, and these patients should avoid sedentary lifestyles by engaging in the recommended ≥150 minutes/week of moderate to intense/rigorous physical activity.[5] Optimized glycemic control (achievement of an individualized glycated hemoglobin [A1c] target ranging from 6.5% to <8.0%), treatment to a blood pressure of <130/80 mm Hg (if it can be safely attained), initiation of moderate- to high-intensity statin therapy, and smoking cessation support (if applicable) are all recommended components of a holistic cardiorenal risk reduction strategy.[5]

**TABLE 1. Key dietary recommendations from KDIGO for patients with diabetes and CKD[5]**

- Protein intake of 0.8 g protein/kg body weight/day for those not treated with dialysis
- Sodium intake <2 g per day
- Diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts and lower in processed meats, refined carbohydrates, and sweetened beverages

## RAS INHIBITORS

Glomerular hyperfiltration occurs in up to 40% of people with T2D and has long been recognized as a driver of CKD development and progression.[11] Glomerular hyperfiltration is driven in part by systemic hypertension and obesity, thus highlighting the importance of weight and blood pressure management in the setting of T2D and CKD.[11] RAS inhibitors directly target glomerular hyperfiltration and were the first agents approved to slow CKD progression in diabetes.[15] ADA and KDIGO recommend treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) at the highest tolerated dose in patients with diabetes who have hypertension and albuminuria.[5] Additionally, ADA and KDIGO note that patients with albuminuria rarely have normal blood pressure and that the evidence for treatment with RAS inhibitors in such patients is less strong.[5] RAS inhibitor therapy does increase risk for hyperkalemia and, therefore, electrolyte monitoring is recommended. Despite being a standard of care for more than 3 decades, RAS inhibitors unfortunately remain underutilized in patients with T2D and CKD.[16] Even in patients receiving RAS inhibitor therapy, considerable residual kidney and cardiovascular risk remain due to the complex pathophysiology of diabetic kidney disease.[17]

## SGLT2 INHIBITORS

SGLT2 inhibitors, originally developed and approved as glucose-lowering agents for the treatment of T2D, are now recognized as standard of care cardiorenal risk-reducing medications.[18] Large cardiovascular outcome trials (CVOTs) with SGLT2 inhibitors initially established the cardiovascular benefits of several agents within the class, in addition to reporting secondary outcome findings suggesting CKD and heart failure benefits with treatment.[19-21] Dedicated kidney outcome trials were subsequently conducted with canagliflozin, dapagliflozin, and empagliflozin.[22-24] All 3 kidney outcome trials were stopped early during planned interim analyses because of overwhelming efficacy for the primary kidney composite outcome. Notably, the benefits of SGLT2 inhibitor therapy reported in these trials were realized on top of background optimized RAS inhibitor therapy.[22-24] A recently published systematic review and meta-analysis of large placebo-controlled SGLT2 inhibitor trials reported a 37% risk reduction for kidney disease progression in participants randomized to SGLT2 inhibitor therapy (relative risk [RR] 0.63; 95% CI: 0.58-0.69).[25]

SGLT2 inhibitors are believed to mitigate cardiorenal risk through several mechanisms.[18] SGLT2 inhibitors improve multiple metabolic risk factors by lowering glucose levels, weight, and blood pressure. Because the cardiorenal benefits of SGLT2 inhibition are preserved in patients with low eGFR (in whom the glucose-lowering, weight loss, and blood pressure-lowering effects of SGLT2 inhibitors are negligible), the kidney and heart benefits of SGLT2 inhibitor therapy are not dependent solely on their beneficial effects on traditional metabolic risk factors.[18] Indeed, SGLT2 inhibition normalizes glomerular hemodynamics through restoration of tubuloglomerular feedback in the kidney, and evolving evidence suggests SGLT2 inhibitors may also have anti-inflammatory and antifibrotic effects in the kidney and heart.[18]

Based on the established cardiorenal benefits of SGLT2 inhibitors in patients with T2D and CKD, they are considered first-line therapy in combination with metformin.[5] Specifically, ADA and KDIGO recommend use of an SGLT2 inhibitor with proven cardiorenal benefit in patients with an eGFR ≥20 mL/min/1.73 $m^2$, which is recommended for continuation (if tolerated) until initiation of dialysis or transplant.[5] In addition to being contraindicated in patients on dialysis, SGLT2 inhibitors do not carry indications for use in people with type 1 diabetes (T1D) because of an increased risk for ketoacidosis.[5] The most common adverse effect of SGLT2 inhibitor therapy is female genital mycotic infections. It is recommended that patients be counseled about the importance of hygiene and keeping the genital area clean and dry to minimize risk.[5]

## GLP-1 RAs

ADA and KDIGO preferentially recommend use of a long-acting GLP-1 RA with proven cardiovascular benefit in patients with T2D and CKD who do not achieve their individualized glycemic targets despite recommended first-line treatment with metformin plus an SGLT2 inhibitor, or in patients unable to take these drugs.[5] This recommendation is supported by the preserved glucose-lowering efficacy of long-acting GLP-1 RAs in advanced CKD, their established cardiovascular benefits, and preliminary evidence of kidney benefit from secondary CVOTs with liraglutide, dulaglutide, and injectable semaglutide.[26] The most common adverse effects with GLP-1 RA therapy are nausea and vomiting, which can be minimized with careful dose titration.[5] Long-acting GLP-1 RAs are not recommended for use in patients at risk for thyroid C-cell tumors (eg, multiple endocrine neoplasia) or in people with a history of pancreatic cancer because of the theoretical risks extrapolated from preclinical trials.[5] GLP-1 RAs should also be used with caution in people with a history of pancreatitis.[5] While the kidney benefits of agents from the GLP-1 RA class are less well established when compared with RAS inhibitors, SGLT2 inhibitors, and finerenone (discussed later), an ongoing dedicated kidney outcomes trial with injectable semaglutide in patients with T2D and CKD is specifically testing the impact of GLP-1 RA therapy on CKD progression.[27] The trial is expected to be completed in 2024.[27]

## MRAs

As previously noted, overstimulation of the MR promotes inflammation and fibrosis in the kidney and thus has emerged as an important therapeutic target in patients with T2D and CKD.[12] Indeed, use of MRAs alone or as an add-on to RAS inhibitor therapy has been associated with antiproteinuric effects in patients with CKD.[28] Use of traditional steroidal MRAs (eg, spironolactone, eplerenone) in the setting of T2D and CKD has been limited, however, because of concerns about treatment-related hyperkalemia, GFR decline, and antiandrogenic side effects (eg, gynecomastia).[12,29]

Unlike traditional steroidal MRAs that have not demonstrated cardiorenal benefits in patients with T2D and CKD, the novel nonsteroidal MRA finerenone has recently emerged as a guideline-directed therapy in this population.[5] Finerenone was approved by the US Food and Drug Administration (FDA) in 2021 specifically to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adults with T2D and CKD.[30] Finerenone uniquely binds to the MR, acting as a bulky, passive antagonist, and has unique pharmacokinetic and pharmacodynamic properties that likely account for its unique clinical effects when compared to steroidal MRAs (**TABLE 2**).[30-34] Two large outcome trials supported the approval

**TABLE 2. Comparison and contrast of mineralocorticoid receptor antagonists (MRAs)[30-34]**

| Agent | MRA type[a] | Pharmacokinetics | Potency/ selectivity | Key adverse effects[b] | FDA-approved indications |
|---|---|---|---|---|---|
| Spironolactone | Steroidal | • Prodrug<br>• Half-life: 1.4 h<br>• Multiple active metabolites with long half-lives | Potent/unselective | • Hyperkalemia<br>• Hypotension<br>• Electrolyte and metabolic abnormalities<br>• Gynecomastia | • Hypertension<br>• HFrEF<br>• Edema<br>• Primary hyperaldosteronism |
| Eplerenone | Steroidal | • Half-life: 4-6 h<br>• No active metabolites | Less potent/more selective than spironolactone | • Hyperkalemia<br>• Dizziness<br>• Electrolyte abnormalities | • Hypertension<br>• HFrEF post-MI |
| Finerenone | Nonsteroidal | • Half-life: 2-3 h<br>• No active metabolites | Potent/selective | • Hyperkalemia[c]<br>• Hypotension<br>• Hyponatremia | • To improve kidney and CV outcomes in T2D and CKD |

[a]Nonsteroidal MRAs are associated with fewer antiandrogenic side effects (eg, gynecomastia) when compared with steroidal MRAs.

[b]Occurring more frequently than placebo.

[c]Mean increases in potassium with treatment were less with finerenone when compared with spironolactone (0.04-0.30 vs 0.45 mEq/L, respectively; $P < .01$) in the phase II minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS).

**Abbreviations:** CV, cardiovascular; h, hours; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction.

of finerenone to improve cardiorenal outcomes in patients with T2D and CKD.[35,36] In the FIDELIO-DKD trial, finerenone treatment was associated with a reduced risk for the primary composite outcome that included progression to kidney failure, sustained eGFR decline of ≥40% from baseline, or death from kidney-related causes when compared with placebo (hazard ratio [HR]: 0.82; 95% CI: 0.73-0.93; $P = .001$).[35] The primary outcome in the FIGARO-DKD trial was a cardiovascular composite outcome that included nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular-related death.[36] When compared with placebo, finerenone treatment resulted in a 13% risk reduction for the primary outcome (HR: 0.87; 95% CI: 0.76-0.98; $P = .03$).[36] As was true for kidney outcomes trials with agents from the SGLT2 inhibitor class, these benefits were observed on top of maximum tolerated background RAS inhibitor therapy.[35,36] In consideration of these data, ADA and KDIGO recommend finerenone for patients with T2D, an eGFR ≥25 mL/min/1.73 m$^2$, normal serum potassium concentration, and albuminuria (albumin-creatinine ratio [ACR] ≥30 mg/g) despite treatment with a maximum tolerated dose of RAS inhibitor.[5] Key finerenone product information is summarized in **TABLE 3**.[30]

## CONCLUSION

Recent advancements in the management of CKD in T2D now offer clinicians and patients additional tools to slow kidney disease progression and mitigate cardiovascular risk. Use of ancillary medications to further mitigate risk, such as statins, antiplatelet agents, and additional therapies to manage comorbidities and other CKD complications (eg, anemia, metabolic bone disease, metabolic acidosis), is also crucial to the holistic care of patients with T2D and CKD. Primary care clinicians will play a critical role in addressing current gaps in patient care through improved screening and identification of CKD and early optimization of guideline-directed therapies. ●

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## TABLE 3. Key finerenone product information[29]

| | | |
|---|---|---|
| **Indication** | | To reduce the risk of sustained eGFR decline, ESKD, CV death, nonfatal MI, and hospitalization for HF in adult patients with CKD associated with T2D |
| **Availability** | | • 10-mg tablets<br>• 20-mg tablets |
| **Recommended dosing** | **Starting dose**[a] | • eGFR ≥60 mL/min/1.73 $m^2$: 20 mg once daily<br>• eGFR ≥25 to <60 mL/min/1.73 $m^2$: 10 mg once daily<br>• eGFR <25 mL/min/1.73 $m^2$: Initiation not recommended |
| | **Dose adjustments** | If current dose is 10 mg once daily<br>• Serum potassium ≤4.8 mEq/L: Increase dose to 20 mg once daily[b]<br>• Serum potassium >4.8 to 5.5 mEq/L: Maintain at 10 mg once daily<br>• Serum potassium >5.5 mEq/L: Hold finerenone; consider restarting at 10 mg daily once serum potassium ≤5.0 mEq/L<br>If current dose is 20 mg once daily<br>• Serum potassium ≤4.8 mEq/L: Maintain at 20 mg once daily<br>• Serum potassium >4.8 to 5.5 mEq/L: Maintain at 20 mg once daily<br>• Serum potassium >5.5 mEq/L: Hold finerenone; restart at 10 mg daily once serum potassium ≤5.0 mEq/L |
| **Common adverse effects**[c] | | • Hyperkalemia<br>• Hypotension<br>• Hyponatremia |
| **Contraindications** | | • Concomitant use with strong CYP3A4 inhibitors (eg, itraconazole)<br>• Patients with adrenal insufficiency |

[a]Finerenone not recommended for initiation if serum potassium >5.0 mEq/L.

[b]If eGFR has decreased by >30% compared with previous measurement, maintain at 10 mg once daily.

[c]Occurring in ≥1% of participants and more frequently than placebo.

**Abbreviations:** ESKD, end-stage kidney disease.


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