

Decision Points in the Management of Patients with Diabetic Kidney Disease

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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.
- Describe the benefits and limitations of the steroidal and nonsteroidal mineralocorticoid receptor antagonists in the treatment of patients with DKD.

KEY TAKEAWAYS

- Diabetes is second only to hypertension as a cause of chronic kidney disease (CKD).
- Urine albumin-to-creatinine ratio (UACR) is an independent and better predictor of cardiovascular mortality than estimated glomerular filtration rate (eGFR) across the full range of kidney function.
- In patients with diabetic kidney disease (DKD), comprehensive treatment that includes achieving blood pressure, blood glucose, blood lipid, and body weight goals, as well as smoking cessation, is critical.
- Treatment with a sodium-glucose cotransporter-2 inhibitor (SGLT-2i) should not be initiated in patients with an eGFR <60 mL/min/1.73 m² (ertugliflozin), <45 mL/min/1.73 m² (dapagliflozin or empagliflozin), or <30 mL/min/1.73 m² (canagliflozin).
- The addition of an SGLT-2i (ie, canagliflozin, dapagliflozin, or empagliflozin) is recommended for patients with DKD who have inadequate glycemic control with metformin.
- Finerenone is a nonsteroidal mineralocorticoid receptor antagonist shown to further improve kidney outcomes in patients with

albuminuric DKD treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

- New treatment options for cardiovascular and renal protection are becoming available for use in combination with traditional medications for blood pressure, blood glucose, and blood lipid control.

TARGET AUDIENCE

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

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OVERVIEW AND DEFINITION OF DKD

Chronic kidney disease (CKD) is common in the United States, affecting an estimated 37 million adults.¹ CKD is defined as abnormalities of kidney structure or function for more than 3 months with implications for health.² Two key criteria for CKD are albuminuria (ie, albumin excretion rate ≥ 30 mg/24 h or urine albumin-to-creatinine ratio ≥ 30 mg/g) and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m².

Among the many risk factors for CKD, diabetes is second only to hypertension.³ Diabetes is responsible for 35% of all cases of CKD,⁴ while approximately 37% of adults with diabetes have CKD.⁵ Increasing duration of diabetes increases CKD risk.⁶ Other risk factors include older age, male sex, race/ethnicity (American Indian, Hispanic, Asian/Pacific Islander), family history of CKD, obesity, and smoking.⁷ This article focuses on CKD in individuals with diabetes, ie, diabetic kidney disease (DKD).

CASE SCENARIO

58-year-old male diagnosed with type 2 diabetes (T2D) 7 years ago. Since diagnosis, his glycated hemoglobin (A1c) has been $< 7.0\%$ for only short periods. He says he feels well but complains of puffiness in both feet.

Medical history:

- T2D, low-density lipoprotein cholesterol (LDL-C) hypercholesterolemia, obesity; former smoker (quit 4 years ago)
- 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 20.7%

Cardiac: blood pressure 134/84 mm Hg; pulse 78 beats/min

Lungs: clear; respiratory rate 16 breaths/min

Eyes: mild retinopathy with occasional hemorrhages

Body mass index 33.4 kg/m²

Laboratory:

- Electrolytes normal
- Estimated glomerular filtration rate (eGFR) 48 mL/min/1.73 m² (57 mL/min/1.73 m² 11 months ago)
- A1c 8.3% (7.6% 1½ years ago)
- Cholesterol: total cholesterol 224 mg/dL, LDL-C 126 mg/dL, triglycerides 270 mg/dL, high-density lipoprotein cholesterol (HDL-C) 44 mg/dL

Current treatment:

- Metformin 1 g twice daily
- Sitagliptin 100 mg once daily
- Simvastatin 40 mg once daily

- Ramipril 10 mg once daily
- Aspirin 81 mg once daily

Should this patient be screened for CKD?

The American Diabetes Association (ADA) recommends, and the International Society of Nephrology (ISN) supports, that all children and adults with type 1 diabetes (T1D) or T2D be screened at least annually.⁸⁻¹⁰ Children should begin screening at puberty or age > 10 years, whichever is earlier, once the child has had T1D or T2D for ≥ 5 years. Adults with T1D should begin screening 5 years after diagnosis, while adults with T2D should begin screening at diagnosis.

How should this patient be screened for the presence of CKD?

Screening for CKD in children and adults involves measuring urinary albumin (morning preferred) with a spot urine to calculate the urine albumin-to-creatinine ratio (UACR).^{9,11} Albuminuria is an independent and better predictor of cardiovascular (CV) mortality than eGFR across the full range of kidney function (**FIGURE**).^{2,12} However, the eGFR also should be measured in adults since one may become abnormal before the other. Albuminuria, for example, can occur more than a decade before a noticeable decline in eGFR,^{13,14} while approximately 40% of individuals with T2D have an eGFR < 60 mL/min/1.73 m² without detectable albuminuria.^{15,16}

Should the patient be referred to a nephrologist?

The ADA recommends that referral to a nephrologist be considered in several situations.⁹ These include 1) uncertain etiology of kidney disease; 2) difficult management issues, eg, anemia, metabolic bone disease, secondary hyperparathyroidism, resistant hypertension, or electrolyte disturbance; 3) eGFR < 30 mL/min/1.73 m²; and 4) rapidly progressing kidney disease. Since this patient's eGFR has declined from 57 mL/min/1.73 m² to 48 mL/min/1.73 m²—or 16%—over 11 months, nephrologist referral is appropriate. When making the referral, it is recommended to clearly state the reason, such as “I am referring this patient since his eGFR is < 60 mL/min/1.73 m² and has declined 16% over 11 months.”

What are the goals of treatment for this patient with DKD?

Following diagnosis of DKD, intervention to prevent further deterioration in kidney function or to at least slow disease progression is the primary goal. This requires achieving blood glucose, blood pressure, blood lipid, and body weight targets, as well as cessation of tobacco use, if appropriate.⁹⁻¹¹ Empowering individuals through ongoing education, coaching, and support provided in a coordinated manner by a mul-

tidisciplinary care team is critically important.^{10,17}

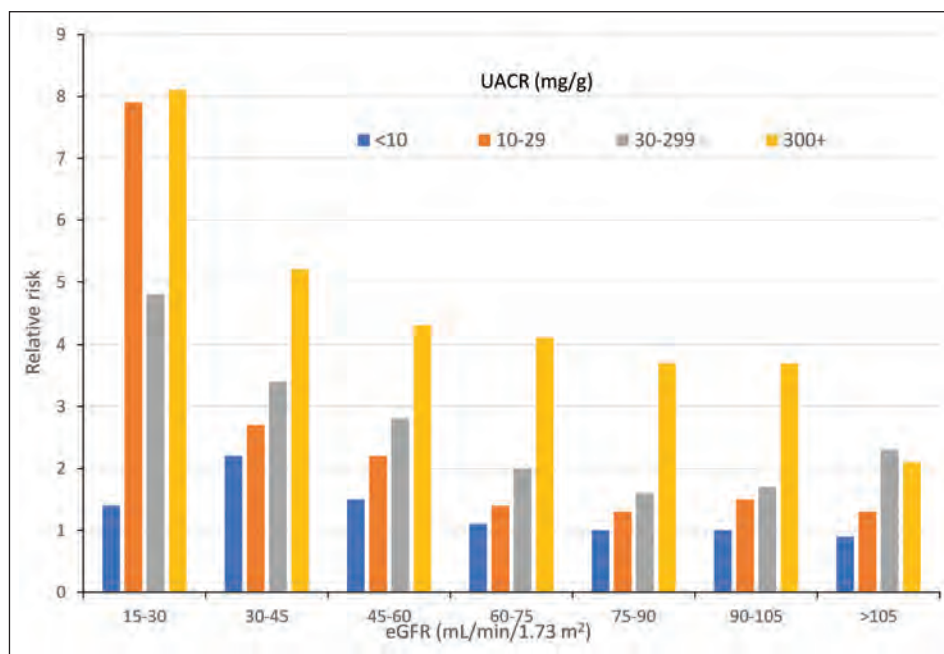
What changes should be made to the treatment plan other than medications for T2D?

Holistic patient management is of paramount importance in individuals with chronic diseases such as diabetes mellitus and CKD to achieve the glycemic, blood pressure, and other treatment targets needed to optimize health outcomes. Currently, the patient in the case scenario does not meet several of these treatment targets. Among these, his A1c of 8.3% indicates that his glucose-lowering therapy needs to be intensified (see below). Reinforcing the importance of continuing to not smoke is advisable.

The patient's 10-year ASCVD risk of 20.7% places him at high risk for a CV event. For individuals with a 10-year ASCVD risk >15%, the target blood pressure is <130/80 mm Hg, whereas it is <140/90 mm Hg for individuals with a 10-year ASCVD risk score <15%.¹⁸ Since his 10-year ASCVD risk is 20.7% and his blood pressure is >130/80 mm Hg, his dose of the angiotensin-converting enzyme inhibitor (ACEI) ramipril should be increased up to a maximum of 20 mg once daily, although this should be done cautiously due to his eGFR of <60 mL/min/1.73 m².¹⁰ His LDL-C and triglyceride levels are above recommended levels, while his HDL-C level is below recommended levels, necessitating an increase to high-intensity statin therapy.¹⁹ If he does not tolerate an increase in statin dose, adding other LDL-C-lowering therapy, eg, ezetimibe or a proprotein convertase subtilisin/kexin type 9 inhibitor, should be considered.¹⁸ If his triglyceride level remains elevated following intensified statin therapy, consideration may be given to initiating therapy to target triglycerides.

Weight loss for those with overweight or obesity is of demonstrated benefit in improving CV markers and glycemic control.²⁰ Lifestyle management is an important first step for weight loss; pharmacotherapy with medications approved for long-term use (ie, liraglutide, naltrexone/bupropion extended-release, orlistat, or phentermine/topiramate extended-release) is often needed.²¹ For individuals with non-dialysis-dependent DKD, dietary intervention includes

FIGURE. Cardiovascular mortality risk based on eGFR and UACR²



reducing dietary protein intake to 0.8 g/kg/d and dietary sodium to 2300 mg/d; dietary potassium should be closely monitored, particularly in individuals treated with an ACEI or angiotensin receptor blocker (ARB).⁹

Continuing preventive care is important. For example, hepatitis B vaccine is indicated for patients likely to progress to end-stage kidney disease.⁹

What precautions should be taken regarding the use of medications in DKD?

It is particularly important to assess the benefits and limitations of medications in individuals with DKD.²² Some medications can cause kidney injury, while others that are principally cleared by the kidneys can rise to toxic levels as kidney function declines. Alternatives should be considered for commonly used nephrotoxic medications, eg, nonsteroidal anti-inflammatory drugs, iodinated contrast material, and aminoglycosides. Some medications may require temporary discontinuation in individuals with eGFR <60 mL/min/1.73 m² who have a serious intercurrent illness that increases the risk of acute kidney injury. Such medications include ACEIs, ARBs, aldosterone inhibitors, direct renin inhibitors, and diuretics.²²

Medications that are principally cleared by the kidney should be used with caution, with dosing modification and close monitoring for associated toxicity. Examples of glucose-lowering medications principally cleared by the kidneys include insulin, metformin, glyburide, dipeptidyl pepti-

dase-4 inhibitors (eg, alogliptin, saxagliptin, and sitagliptin), glucagon-like peptide-1 receptor agonists (GLP-1 RAs; eg, exenatide and lixisenatide), and sodium-glucose cotransporter-2 inhibitors (SGLT-2is).^{9,10}

What changes should be made to the treatment plan for blood glucose control?

Before modifying the treatment plan, the patient's adherence with current treatment should be assessed. Once confirmed, intensification of his glucose-lowering medications will be needed since his A1c is 8.3%. Improved glycemic control to achieve A1c <7.0% reduces the risks of sustained hyperglycemia and slows the progression of DKD.²³⁻²⁶ It should be noted that less intensive control is recommended for patients with CKD who have substantial comorbidities.⁹ Reducing the doses of metformin and sitagliptin will be needed in the near future since his eGFR is approaching 45 mL/min/1.73m².²² Renal function is an important consideration, as this impacts the initiation and dosing of many glucose-lowering medications. While continuing metformin is reasonable due to its favorable tolerability profile, low cost, and complementary mechanism of action with other glucose-lowering medications, discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin is appropriate since its magnitude of glycemic lowering is modest and it does not promote weight loss or reduce CV risk.^{10,27}

In contrast, medications within the GLP-1RA and SGLT-2i classes promote weight loss and have been shown in CV outcomes trials to reduce CV risk. In addition, both GLP-1 RAs and SGLT-2is are associated with a low incidence of hypoglycemia, which is especially important to avoid in patients with CKD.^{10,27} Consequently, selected medications in both classes are recommended as second-line therapy for patients who do not achieve adequate glycemic control with metformin.^{10,27} In patients with DKD, SGLT-2i medications with proven kidney benefit are preferred over a GLP-1 RAs.^{10,27}

All of these CV outcomes trials had prespecified kidney endpoints. Of the GLP-1 RAs, dulaglutide,²⁸ liraglutide,²⁹ and semaglutide³⁰ (but not exenatide³¹ or lixisenatide³²) showed reductions in major kidney outcomes. Of the SGLT-2is, canagliflozin,³³ dapagliflozin,³⁴ and empagliflozin³⁵ (but not ertugliflozin³⁶) showed reductions in major kidney outcomes, although ertugliflozin slowed the rate of decline in eGFR.³⁶

Additional CV outcomes trials limited to patients with preexisting CKD were subsequently conducted with the SGLT-2is canagliflozin and dapagliflozin. These were the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)³⁷ and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease)³⁸ trials. A third trial

involving ertugliflozin, EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin),³⁹ is in progress. CREDENCE and DAPA-CKD demonstrated significant reductions in kidney and CV outcomes with canagliflozin and dapagliflozin, respectively. Consequently, canagliflozin and dapagliflozin are recommended by the ADA and ISN for patients with CKD who do not achieve glycemic control with metformin.^{10,27}

Of key importance in CREDENCE³⁷ and DAPA-CKD³⁸ is that there were no significant differences in rates of amputation or fracture between SGLT-2i therapy and placebo. These findings are consistent with the results of a recent meta-analysis of 10 trials reporting the incidence of CV or kidney outcomes with SGLT-2i therapy.⁴⁰ Diabetic ketoacidosis (DKA) was observed with canagliflozin in CREDENCE³⁷ but not with dapagliflozin in DAPA-CKD.³⁸ In the meta-analysis, the rate of DKA was significantly higher with SGLT-2i therapy vs placebo, although the incidence was <0.2% and it occurred only in individuals with T2D.⁴⁰ Urinary tract infection was not reported in the meta-analysis. Overall, the incidence of serious adverse events was significantly lower with SGLT-2is vs placebo (risk ratio [RR] 0.68; 95% confidence interval [CI]: 0.60-0.77), with modest heterogeneity (RR 0.93; 95% CI: 0.90-0.95).⁴⁰

Another consideration when using SGLT-2i therapy in patients with DKD is dosing based on kidney function. Treatment should not be initiated in patients with eGFR <60 mL/min/1.73 m² (ertugliflozin⁴¹), <45 mL/min/1.73 m² (dapagliflozin⁴² or empagliflozin⁴³), or <30 mL/min/1.73 m² (canagliflozin⁴⁴).

Do the mineralocorticoid receptor antagonists have a role in the treatment of patients with DKD?

Medications that inhibit the renin-angiotensin-aldosterone system (RAAS) are recommended in most patients with CKD. RAAS inhibitor therapy involving an ACEI or ARB slows the progression of albuminuria; however, the aldosterone level increases in 50% of patients within 1 year.⁴⁵ The addition of the mineralocorticoid receptor antagonist (MRA) spironolactone or eplerenone to an ACEI or ARB results in further reduction in albuminuria as well as blood pressure.⁴⁶⁻⁴⁹ However, hyperkalemia due to the steroidal properties of spironolactone and eplerenone is common, particularly in patients with stage ≥3 CKD (ie, eGFR <60 mL/min/1.73 m²).^{50,51} In addition, acute reversible reduction in eGFR when added to background therapy with an ACEI or ARB or diuretic, particularly among patients with eGFR <45 mL/min/1.73 m², has limited the use of steroidal MRAs in CKD.⁵²

Finerenone is a nonsteroidal MRA with the potential to cause less potassium retention than steroidal MRAs.⁵³ The

phase 3 randomized clinical trials FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) were recently completed. Both trials are limited to patients with T2D and albuminuric CKD treated with an ACEI or ARB.^{54,55} FIGARO-DKD included more patients with earlier-stage CKD and T2D. In FIDELIO-DKD, the primary composite endpoint was time to first occurrence of kidney failure, sustained decrease $\geq 40\%$ in eGFR, or renal death.⁵⁴ In FIGARO-DKD, the primary composite endpoint was time to first occurrence of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or heart failure hospitalization (hHF).

In FIDELIO-DKD, the annual rate of the primary event over a median follow-up of 2.6 years was 7.59 vs 9.08 events/100 patient-years with finerenone vs placebo, respectively (hazard ratio [HR] 0.82; 95% CI: 0.73-0.93; $P=0.001$). Finerenone also resulted in significant improvement in the secondary renal composite endpoint (sustained doubling of serum creatinine for ≥ 4 weeks or renal death) (HR 0.76; 95% CI: 0.65-0.90). Other key CV outcomes were reduced with finerenone as well, including CV death, nonfatal MI, nonfatal stroke, and hHF. The frequency of adverse events was generally similar in the finerenone and placebo groups, although the incidence of hyperkalemia-related treatment discontinuation was higher with finerenone than placebo (2.3% vs 0.9%). A prespecified exploratory analysis showed that the incidence of new-onset atrial fibrillation or atrial flutter was significantly lower in the finerenone vs placebo group (3.2% vs 4.5%; relative risk 0.7; 95% CI: 0.53-0.94; $P=0.016$).⁵⁶

Preliminary results from FIGARO-DKD showed that finerenone significantly reduced the primary composite endpoint.⁵⁷

As of July 9, 2021, the FDA has approved finerenone to reduce the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks, and hospitalization for HF in adults with DKD. ●

CASE SCENARIO (CONT'D)

Intensified comprehensive treatment is needed for this patient to help him achieve and maintain glycemic, blood pressure, blood lipid, and body weight targets, as well as minimize the chance that he resumes smoking. Sitagliptin should be discontinued and an SGLT-2i with demonstrated kidney benefits initiated. RAAS inhibitor therapy is essential to improve kidney outcomes. He should receive support from a multidisciplinary care team that includes coaching to improve nutrition and physical exercise.

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