Chronic Kidney Disease in Patients with Diabetes

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LEARNING OBJECTIVES

1. Distinguish the recommendations for the screening, diagnosis, and staging of chronic kidney disease (CKD) in individuals with diabetes.
2. Evaluate evidence and current recommendations for the use of kidney-protective agents in individuals with diabetes and CKD.
3. Design an individualized therapy plan, including lifestyle modifications and pharmacotherapy, for an individual with diabetes and CKD.
4. Develop a monitoring plan to evaluate the efficacy and safety of pharmacotherapy in the progression of CKD.

ABBREVIATIONS IN THIS CHAPTER

ADA	American Diabetes Association
AKI	Acute kidney injury
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DKD	Diabetes-related kidney disease
DPP-4	Dipeptidyl peptidase-4
ESKD	End-stage kidney disease
GLP-1	Glucagon-like peptide-1
HD	Hemodialysis
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalization for heart failure
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
PD	Peritoneal dialysis

INTRODUCTION

Epidemiology and Prevalence

Chronic kidney disease (CKD) continues to be a significant public health problem, with the most recent data indicating a prevalence of around 15% in the U.S. adult population (CDC 2021; USRDS 2021). Diabetes is the most common risk factor for CKD and is the leading cause of end-stage kidney disease (ESKD). Almost 40% of U.S. adults with diabetes have CKD, and those with diabetes and CKD are at an 8-fold higher risk of cardiovascular (CV) and all-cause mortality than those without diabetes and CKD (CDC 2022). Even though CKD is a well-known and prevalent complication associated with diabetes, only 32% of individuals with stage 3 or 4 CKD and diabetes are aware they have CKD. Because of its asymptomatic nature in earlier stages of disease and suboptimal screening rates, most patients with CKD are not aware of their diagnosis until the disease has progressed significantly. The high morbidity and mortality rates and significant costs associated with management highlight the need for increased screening for CKD and monitoring of progression in patients with diabetes to ensure the implementation of timely interventions to reduce the global burden of kidney disease.

Pathophysiology of CKD in Patients with Diabetes

Chronic metabolic changes associated with diabetes, such as hyperglycemia and hyperaminoacidemia, result in altered kidney hemodynamics and promote inflammation and fibrosis that are well-known features of the pathophysiology of CKD in patients with diabetes. Hyperglycemia is proposed to contribute to the onset and

RAS	Renin-angiotensin system
SGLT2	Sodium-glucose cotransporter-2
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UACR	Urine albumin/creatinine ratio

Table of other common abbreviations.

progression of CKD in patients with diabetes by increasing the reabsorption of glucose and sodium by sodium-glucose cotransporters in the proximal tubule of the kidney and impairing the adaptive tubuloglomerular feedback mechanism. Tubuloglomerular feedback regulates the glomerular filtration rate (GFR) according to the sodium concentration in the tubule fluid at the macula densa. In the setting of hyperglycemia, the increased reabsorption of sodium at the proximal tubule and the subsequent decrease in concentration detected at the macula densa causes dilation of the afferent arterioles, increased perfusion of the glomerulus, and hyperfiltration (Bargman 2022; Alicic 2017). The neurohormonal activation that often accompanies hyperglycemia and initial nephron losses causes an increase in circulating concentrations of angiotensin II to cause vasoconstriction of the efferent arterioles of the kidney and increases catecholamine and prostaglandin concentrations (Bargman 2022). Increased concentrations and altered responsiveness to these vasoactive hormones promote increases in pressure and flow across the glomerular membrane, and this glomerular hypertension further contributes to glomerular hyperfiltration. The initial compensatory hyperfiltration that occurs from the combination of glomerular hypertension and impaired tubuloglomerular feedback eventually becomes maladaptive with increases in glomerular protein filtration, leading to proteinuria and glomerulosclerosis with consequent destruction of nephrons. Stimulation of the renin-angiotensin-aldosterone system and subsequent overactivation of the mineralocorticoid receptor has also been proposed to play a role in the progressive inflammation and fibrosis in heart and kidney tissues that contribute to the onset and progression of CV disease (CVD) and CKD (Agarwal 2021b). Novel therapeutic agents for CKD have been developed to target the inflammatory and fibrotic processes of CKD and are discussed later in this chapter.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- The general etiology and pathophysiology of chronic kidney disease and diabetes
- Equations used in the estimation of kidney function and updates related to race
- Glycemic targets for patients with diabetes as defined by leading guidelines
- Drug knowledge of the oral pharmacologic agents used to treat diabetes

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2022. Diabetes Care 2022;45:S1-S264.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;3:S1-S150.
- Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98:S1-S115.
- Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102:S1-S123.
- Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int 2021;99:S1-S87.

Risk Factors for CKD

Box 1 summarizes nonmodifiable and modifiable risk factors for CKD. Modifiable risk factors implicated in the onset of CKD also contribute to its progression; therefore, they should be continuously evaluated and managed.

Nonmodifiable Risk Factors

The most common nonmodifiable risk factors for CKD include age, sex, ethnicity, family history of CKD, and duration of diabetes, with older age being the most common, given that kidney function naturally declines with increasing age (Harjutsalo 2014). Women have a higher prevalence of CKD than men; however, men have a higher risk of CKD progression, and the incidence of ESKD is 1.5 times higher in men than in women (Ricardo 2019). There are well-documented race and ethnicity differences in the prevalence of CKD and ESKD, with the prevalence of CKD being 2- to 3-fold higher in African Americans, Hispanics, and Asians and up to 18-fold higher in Native Americans than in non-Hispanic whites (Bhalla 2013). The risk of developing CKD also increases with the duration of diabetes. For individuals with type 1 diabetes (T1D), the incidence of CKD has been reported to peak 15–20 years after diagnosis (Harjutsalo 2014). Given that type 2 diabetes (T2D)

Box 1. Risk Factors for Onset and Progression of Diabetes-Related CKD

Modifiable risk factors

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Obesity and metabolic syndrome
- Smoking
- Exposure to nephrotoxic agents

Nonmodifiable risk factors

- Older age (> 60 yr)
- Ethnicity
- Sex
- Family history of CKD
- Longer duration of diabetes

CKD = chronic kidney disease.

Information from: Harjutsalo V, Groop PH. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:260-6; Bhalla V, Zhao B, Azar KM, et al. Racial/ethnic differences in the prevalence of proteinuric and non proteinuric diabetic kidney disease. Diabetes Care 2013;36:1215-21.

is insidious in nature and may go undetected for extended periods before an official diagnosis, the true duration of disease before CKD diagnosis is unknown. For those without CKD present upon diagnosis of T2D, early implementation of lifestyle interventions may delay the onset of complications, including CKD (Tuomilehto 2001).

Modifiable Risk Factors

Modifiable risk factors for the onset and progression of CKD include the presence of hyperglycemia, hypertension, dyslipidemia, obesity, smoking, and exposure to nephrotoxic agents (KDIGO 2020). Optimization of glycemic management has been shown to prevent the onset and delay the progression of CKD in several landmark trials (Ismail-Beigi 2010; ADVANCE Collaborative Group 2008; UKPDS Group 1998a; DCCT Research Group 1993). In the DCCT, individuals with T1D randomized to intensive glycemic management had a 34% lower risk of developing moderately increased albuminuria (DCCT Research Group 1993). The U.K. Prospective Diabetes Study (UKPDS) showed that individuals with T2D in the intensive antihyperglycemic therapy arm had a 25% relative risk reduction in microvascular complications, which included fatal and nonfatal kidney failure (UKPDS Group 1998a).

Hypertension is another major risk factor for developing CKD (KDIGO 2020). Elevations in blood pressure have been shown to correlate with increases in albuminuria, and several studies have shown an inverse relationship between blood pressure and GFR (Harjutsalo 2014). Dyslipidemia, typically characterized by high plasma concentrations of TG and LDL, very LDL, and intermediate-density LDL as well as abnormally low HDL concentrations, is also a modifiable risk factor for CKD (Jenkins 2003). Patients who are overweight and those with obesity also have a higher risk of developing CKD, which is primarily driven by comorbid diabetes and hypertension; however, studies suggest that obesity alone can lead to the development of CKD (Whaley-Connell 2017). In addition, smoking is a known modifiable risk factor for the development of micro- and macrovascular complications of diabetes, and smoking cessation and should be encouraged as part of every treatment plan, if applicable (KDIGO 2020).

DIAGNOSIS

Chronic kidney disease is defined as abnormalities in kidney structure or function for more than 3 months (KDIGO 2013). More specifically, diabetes-related kidney disease (DKD) is a clinical diagnosis made on the basis of the presence of albuminuria (defined as two of three spot urine albumin/creatinine ratios [UACRs] greater than 30 mg/g collected within a 3- to 6-month period) and/or an estimated GFR (eGFR) less than 60 mL/minute/1.73 m^2 when diabetes is the sole cause of kidney damage (ADA 2022). Diabetes-related kidney disease and "diabetic nephropathy" are often used interchangeably when describing individuals with CKD and diabetes. However, this association is incorrect because *DKD* is a comprehensive term encompassing all kidney complications related to diabetes, whereas *diabetic nephropathy* is a progressive glomerular nephropathy secondary to diabetes and is only one component of DKD (Piccoli 2015). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the management of diabetes and CKD now recommend against the use of both terms to avoid the connotation that CKD is caused by diabetes in all cases and give preference to CKD in patients with diabetes (KDIGO 2022). In patients with T1D, CKD is typically characterized by the presence of longstanding diabetes, albuminuria without gross hematuria, a progressive decline in eGFR, and retinopathy (Piccoli 2015). People with T2D have many of these same features; however, CKD is often present at diagnosis in this population because of the presence of longstanding hyperglycemia, and retinopathy may be present (CDC 2021; Molitch 2010). In addition, patients with T1D or T2D may have reduced eGFR without overt albuminuria, a pattern that is increasingly common as the prevalence of diabetes increases overall.

Screening and Surveillance of CKD in People with Diabetes

People with diabetes should have eGFR and UACR assessed at least once yearly, starting 5 years after a diagnosis for patients with T1D and starting at diagnosis for those with T2D to ensure timely diagnosis of CKD. Patients with diabetes and CKD will require more frequent laboratory monitoring, with the recommendation being to monitor eGFR and UACR at least twice yearly to evaluate disease progression, detect superimposed kidney diseases (e.g., acute kidney injury

[AKI]), estimate risk of complications, facilitate appropriate medication dosing, and determine which patients require specialized treatment by a nephrologist (ADA 2022).

Measuring and Categorizing Albuminuria

Albuminuria and eGFR independently influence the progression rate of CKD. A normal value for UACR is defined as less than 30 mg/g (A1 albuminuria). Moderately increased albuminuria, 30–300 mg/g (A2 albuminuria), is considered abnormal or elevated; is a precursor for more advanced stages of CKD; and is a marker of vascular damage. Severely increased albuminuria is defined as a UACR greater than 300 mg/g (A3 albuminuria). Baseline albuminuria at the time of diagnosis of CKD is a strong predictor of ESKD, defined as an eGFR less than 15 mL/minute/1.73 m^2 or requiring kidney replacement therapy (KRT), with higher albuminuria concentrations and lower eGFR values predicting a faster decline in eGFR. A reduction in albuminuria with intervention is associated with slowed progression of CV and kidney complications (Heerspink 2019; Babazono 2009).

A 24-hour urine collection is considered the "gold standard" for the quantitative evaluation of albuminuria; however, improper timing or missed samples may lead to significant over- or underestimation of albuminuria. Spot UACR estimates 24-hour urine albumin excretion without the inconvenience of a 24-hour collection, making it cost-effective and efficient for diagnosis and monitoring progression (ADA 2022; KDIGO 2013). It is recommended to check a spot urine sample for the albumin/creatinine ratio, as opposed to measuring a spot urine albumin sample without simultaneous measurement of urine creatinine, given that a spot urine albumin sample alone is susceptible to false-positive and false-negative results because of variation in urine concentrations secondary to hydration status (ADA 2022). Moderately or severely increased albuminuria should be diagnosed on the basis of two of three spot UACRs in a 3- to 6-month period because exercise within 24 hours, infection, fever, congestive heart failure (HF), marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (ADA 2022).

Stages of CKD

A standardized CKD classification and staging system using GFR and degree of albuminuria was outlined by KDIGO in 2012 (KDIGO 2013). This information is summarized on the National Kidney Foundation website. Glomerular filtration rate is estimated from SCr using several validated formulas; however, KDIGO specifically recommends the CKD Epidemiology Collaboration equation over other equations. As mentioned earlier, individuals with CKD should have their kidney function assessed at least twice yearly and should be continuously reassessed throughout the continuum of disease; therefore, individuals with CKD are likely to have their stage reclassified throughout disease progression.

PREVENTION AND DELAYING THE PROGRESSION OF CKD

The rate of decline in GFR and progression of CKD is highly variable and depends on the individual's age as well as the management of modifiable risk factors, such as hypertension, dyslipidemia, smoking, weight loss, and/or hyperglycemia. The rate of progression of CKD in the literature varies and depends on whether the individual has T1D or T2D. Without addressing risk factors, 80% of patients with T1D will progress to severely increased albuminuria in 10–15 years, and about 50% of these individuals will develop ESKD within 10 years and 75% within 20 years (Molitch 2004). Patients with T2D may present with moderately or severely increased albuminuria shortly after diagnosis because diabetes may have been present for many years before the official diagnosis. Without intervention, 20%–40% of patients with T2D and moderately increased albuminuria will progress to severely increased albuminuria; however, only 20% of those with severely increased albuminuria will progress to ESKD.

Early implementation of interventions is key to preventing the onset and slowing the progression of CKD, as well as reducing CV risk (ADA 2022). Those with CKD are more likely to die of CV complications than kidney-related causes. Interventions should focus on optimizing glycemic management, blood pressure management, CV risk reduction, and patient engagement in nonpharmacologic recommendations. These interventions are most effective when implemented early and assessed often. Many risk factors implicated in the onset and progression of CKD overlap with those associated with increased CV risk; therefore, targeting modifiable risk factors to reduce CVD in those with CKD may prevent the progression to ESKD (KDIGO 2013).

Nonpharmacologic Recommendations

Lifestyle modifications should be included in all treatment plans for individuals with CKD. Engaging in physical activity; maintaining a healthy weight; following a healthy diet; smoking cessation, if applicable; and avoiding nephrotoxic agents are all important in slowing kidney disease progression.

Engaging in Physical Activity

Regular physical activity improves glycemic management, reduces CV risk, maintains a healthy weight, and improves overall well-being (ADA 2022; KDIGO 2013). Adults with diabetes, with and without CKD, are recommended to engage in at least 150 minutes of moderate- to vigorous-intensity aerobic activity per week, distributed over at least 3 days, with no more than 2 consecutive days without physical activity (ADA 2022). Resistance training should also be recommended for two or three sessions per week. In addition, the American Diabetes Association (ADA) recommends decreasing the time individuals spend sitting daily and interrupting prolonged sitting every 30 minutes with light activity.

Healthy Weight Management

Obesity is increasing in prevalence in the general population and among people with diabetes. Studies have shown that the risk of ESKD increases with increasing BMI (Hsu 2006). Compared with individuals who had a normal weight, a BMI of 30–34.9 kg/m^2 increased the risk of ESKD by 3.5-fold, a BMI of 35–39.9 kg/m^2 by 6-fold, and a BMI greater than 40 kg/m^2 by 7-fold (Hsu 2006). A higher BMI remained an independent predictor of ESKD after adjusting for blood pressure and diabetes. It has been proposed that obesity affects kidney hemodynamics by increasing glomerular pressure and hyperfiltration (Krikken 2009). Adiponectin has also been suggested to link obesity to podocyte damage (Sharma 2009).

Individuals with CKD are recommended to maintain a normal body weight (BMI 20–24.9 kg/m^2) (KDIGO 2013). The ADA recommends at least a 5% reduction in body weight for most patient populations with T2D who are overweight and obese to see improved glucose, lipid, and blood pressure levels and a reduction in CV risk. If safe and feasible, more intensive weight-loss goals (i.e., 15% reduction in body weight) may be appropriate to optimize these clinical benefits (ADA 2022). An overall healthy eating plan with some degree of calorie restriction in conjunction with weight-loss medications and/or metabolic surgery should be considered in selected individuals with T2D to reduce body weight, A1C, and CVD risk.

Dietary Modifications

Dietary recommendations for patients with advanced CKD have historically focused on protein restriction to reduce albuminuria and limit disease progression. However, recent evidence shows that reducing dietary protein intake to less than 0.8 g/kg/day has no clinically significant effect on the rate of eGFR decline, and a low-protein diet may promote malnutrition in individuals with CKD (Ikizler 2020; Evert 2019). The recommended dietary protein intake for patients with CKD not requiring dialysis is at least 0.8 g/kg/day, which is the same as the dietary allowance for those without CKD (ADA 2022; KDIGO 2020). Excessive dietary protein intake of over 1.3 g/kg/day has been associated with increased albuminuria, a decline in eGFR, and CVD mortality; therefore, the recommended protein intake for patients with CKD not requiring dialysis should be less than 20% of the total calorie intake and should not exceed 1.3 g/kg/day (ADA 2022; Evert 2019). Higher dietary protein intake of 1–1.2 g/kg/day can be recommended for those treated with dialysis to prevent malnutrition from the hypercatabolic state of advanced CKD (KDIGO 2020; Murray 2018; Klahr 1994). In general, as CKD progresses, sodium, potassium, and phosphorus consumption in the diet should be limited to facilitate fluid, electrolyte, and mineral balance and prevent complications associated with kidney impairment, such as worsening hypertension, volume overload, hyperkalemia, and hyperphosphatemia (Ikizler 2020).

Smoking Cessation

Smoking cessation should be recommended in all patients with diabetes to reduce the risk of CVD and CKD progression (ADA 2022; KDIGO 2020, 2013). Smoking cessation therapy should be offered to all individuals with diabetes who use tobacco products. Pharmacologic therapy in addition to behavioral counseling in a motivated patient may increase the likelihood of cessation; however, treatment selection should be evaluated in the setting of declining kidney function (ADA 2022; Formanek 2018). Varenicline requires a dose adjustment in severe kidney impairment (CrCl less than 30 mL/minute) and ESKD (Formanek 2018). Bupropion should be used with caution in CKD because of the potential for accumulation. A maximum dose of 150 mg/day of bupropion is recommended for those with a CrCl of 15–60 mL/minute, and an alternative agent may be preferred when the CrCl is less than 15 mL/minute (Nagler 2012). It is also recommended that nicotine replacement therapy, including gum, lozenge, inhaler, and patch formulations, be used with caution in severe kidney impairment because of decreased nicotine clearance; however, no specific dose adjustments are available (Formanek 2018).

Avoidance of Nephrotoxic Agents

The presence of medications that are known nephrotoxins may worsen kidney impairment; therefore, such substances should be avoided in patients at risk of and with known CKD (KDIGO 2013). Exposure to NSAIDs, including cyclooxygenase-2 inhibitors, lithium, calcineurin inhibitors, selected antimicrobial agents (e.g., aminoglycosides, amphotericin B), and radiocontrast dye, should be limited or avoided altogether, if possible. In addition, NSAIDs should not be used in combination with diuretics and renin-angiotensin system (RAS) inhibitors, even in patients without CKD, because of the risk of AKI and worsening kidney function (KDIGO 2013; Lapi 2013).

Kidney-Protective Agents in Patients with Diabetes and CKD

Certain classes of antihypertensive and antihyperglycemic agents have been shown to prevent the progression of kidney disease in large clinical outcomes trials of patients with CKD. This benefit appears to be independent of the blood pressure– and blood glucose–lowering effects of these agents. Advances in novel therapeutic agents have recently shown benefit in the management of CKD with promising effects on rates of both kidney and CV events.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Substantial, irrefutable evidence supports RAS inhibition as initial blood pressure–lowering therapy to prevent the progression of CKD in patients with CKD and hypertension, irrespective of diabetes status (KDIGO 2013). The neurohormonal overactivation that is characteristic of CKD contributes to

kidney decline through glomerular hypertension, proteinuria, and subsequent nephron loss. Thus, the longstanding standard of care to mitigate the harmful effects of RAS overstimulation has been inhibition with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), which have a pronounced vasodilatory effect and reduce proteinuria in this population.

Many landmark trials have shown the benefit of ACEI or ARB therapy on clinical kidney-related outcomes in patients with DKD and elevated blood pressure (Brenner 2001; Lewis 2001). The RENAAL trial studied the effect of ARB therapy on 1513 participants 31–70 years of age with T2D and a UACR of at least 300 mg/g and SCr of 1.3–3.0 mg/dL (1.5–3.0 mg/dL for male participants weighing more than 60 kg). Participants were randomized to losartan 50 mg daily, titrated to 100 mg daily after 4 weeks according to the blood pressure reading immediately before the next dose, or placebo (Brenner 2001). The primary outcome, assessed in a time-to-event analysis, was a composite of a doubling of SCr, ESKD, or all-cause death. After a mean follow-up of 3.4 years, the primary outcome occurred in significantly fewer patients in the losartan group than in the placebo group, which was driven by significant reductions in the doubling of SCr and ESKD. No significant difference in all-cause death was observed between the groups. The effect of losartan on the primary outcome was unchanged when adjusted for blood pressure, suggesting that kidney outcomes improved irrespective of losartan's blood pressure–lowering effect. A post hoc analysis showed that the degree of albuminuria at baseline and 6 months after therapy strongly predicted kidney outcomes, suggesting the albuminuria-reducing effect of losartan was largely responsible for its kidney-protective benefit (de Zeeuw 2004). Of note, 93.5% of participants in RENAAL were using antihypertensive therapy at baseline, though hypertension diagnosis was not formally recorded, showing the necessity to avoid extrapolating these findings to normotensive patients with T2D and CKD not receiving antihypertensive therapy. In addition, 71% of participants in the losartan group were receiving the 100-mg dose by trial end, suggesting these positive results were reflective of high-dose ARB therapy.

The IDNT study reiterated the benefit of RAS inhibition in patients at higher risk of DKD progression compared with RENAAL (Lewis 2001). The study enrolled 1715 participants 30–70 years of age with a documented diagnosis of T2D, hypertension, and proteinuria (UACR 900 mg/g or greater) and an SCr of 1–3.0 mg/dL in women and 1.2–3.0 mg/dL in men. Participants were assigned to irbesartan 75 mg daily titrated to 300 mg daily, amlodipine 2.5 mg daily titrated to 10 mg daily, or placebo. Over a mean follow-up of 2.6 years, the primary composite of doubling of SCr, ESKD, and all-cause death was significantly reduced with irbesartan compared with amlodipine and placebo, and this effect persisted between groups independently of differences in blood pressure. These results were primarily driven by a significant reduction in the doubling of SCr with irbesartan relative to amlodipine and placebo. Although the mean dose at study end was not reported, like in the RENAAL trial, the IDNT study protocol used maximally tolerated ARB therapy to achieve the outcomes reported.

A 2006 Cochrane review went on to solidify the role of ACEIs and ARBs in preventing CKD progression in patients with diabetes (Strippoli 2006). This systematic review included 49 randomized controlled trials of 12,067 people with diabetes (T1D and T2D) and CKD at all stages. Thirty-eight trials compared ACEIs with placebo, four trials compared ARBs with placebo, and seven trials compared ACEIs with ARBs. With respect to all-cause death, there was no significant difference with ACEIs or ARBs compared with placebo; however, a subgroup analysis showed that studies using maximally tolerated ACEI dosing compared with placebo or no treatment had a significant reduction in mortality, whereas this benefit was not seen in studies using one-half or less than one-half of the maximally tolerated dosing. Mortality rates in head-to-head comparison trials with ACEIs and ARBs were similar between groups. Rates of ESKD with ACEIs and ARBs were significantly lower than with placebo or no treatment. No data were available to directly compare the rates of ESKD between ACEIs and ARBs.

Angiotensin-converting enzyme inhibitors and ARBs continue to be first-line antihypertensive therapy for patients with albuminuric CKD to prevent disease progression (ADA 2022; KDIGO 2021). The KDIGO 2021 guidelines for the management of blood pressure in CKD recommend initiating an ACEI or ARB for patients with diabetes, high blood pressure, CKD, and moderately (UACR 30–300 mg/g) and severely (UACR greater than 300 mg/g) increased albuminuria (KDIGO 2021). In addition, KDIGO states that it is reasonable to use an ACEI or ARB in patients with high blood pressure, CKD, and no albuminuria, irrespective of diabetes status (KDIGO 2021); however, of importance, there is limited evidence from kidney outcomes trials showing additional nephroprotection with these agents beyond what is anticipated from blood pressure lowering (Halimi 2012). Despite the lack of robust evidence in this area, the KDIGO guidelines for the management of diabetes and CKD continue to recommend consideration of an ACEI or an ARB for patients with diabetes, albuminuria, and normal blood pressure (KDIGO 2022).

The 2022 ADA Standards of Care strongly recommend ACEIs or ARBs as first-line antihypertensive therapy for patients with diabetes, eGFR less than 60 mL/minute/1.73 m^2, and UACR of at least 300 mg/g, given their robust evidence in preventing CKD progression in this population (ADA 2022). The recommendation for ACEIs or ARBs as first-line antihypertensive therapy in patients with diabetes, eGFR less than 60 mL/minute/1.73 m^2, and UACR of 30 to less than 300 mg/g is not as strong as for those with severely increased albuminuria because prospective trials with RAS inhibition in this population have shown reduced progression to severely

increased albuminuria and CV events but not reduced progression to ESKD (ADA 2022; HOPE Study Investigators 2000).

Both the KDIGO and ADA guidelines note that small elevations in SCr (less than 30% from baseline) during RAS initiation have no effect on mortality or kidney disease progression and should not be confused with AKI (ADA 2022; KDIGO 2021). Both guidelines explicitly recommend continuing ACEI or ARB therapy unless the SCr increases by more than 30% within 4 weeks of treatment initiation or dose increase, or the patient develops associated hyperkalemia. In addition, ADA and KDIGO highlight the lack of evidence with the use of RAS inhibitors at suboptimal doses. Both specifically recommend the use of ACEIs or ARBs at maximally tolerated doses because all clinical outcomes trials showing reduced kidney disease progression implemented titration protocols to target maximum doses and did not use low doses of these agents. Despite both classes being well established to prevent DKD progression, combination therapy with ACEIs and ARBs has had no benefits on CV or kidney outcomes and has been associated with increased rates of hyperkalemia (Fried 2013; ONTARGET Investigators 2008). Thus, concomitant use of ACEI and ARB therapy should be avoided (ADA 2022; KDIGO 2021).

Sodium-Glucose Cotransporter-2 Inhibitors

Recently, an extensive amount of literature has been published to support the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors to improve clinical outcomes in patients with T2D and CKD, despite the agents' lower antihyperglycemic efficacy in people with a reduced eGFR. The SGLT2 inhibitors lower the threshold for glucose reabsorption by inhibiting SGLT2 in the proximal convoluted tubule, the primary site of glucose reabsorption, thus facilitating glucosuria and reducing blood glucose concentrations (van Bommel 2017). The proposed mechanism of SGLT2 inhibitors for kidney protection is mainly by restoration of impaired tubuloglomerular feedback and reduced hyperfiltration. It is hypothesized that the inhibition of glucose and sodium reuptake in a 1:1 ratio at the proximal tubule leads to increased sodium excretion detected at the macula densa, which facilitates vasoconstriction of the afferent arteriole and reduced intraglomerular pressure through tubuloglomerular feedback. Although vasoconstriction of the afferent arteriole induces a transient decline in eGFR during the first weeks of treatment with SGLT2 inhibitors, eGFR gradually returns to baseline and stabilizes while reducing glomerular hyperfiltration to have long-term kidney-protective effects. Similar to the initiation of an ACEI or ARB, the transient eGFR decline with SGLT2 inhibitor initiation should be expected and is usually not an indication to discontinue therapy (KDIGO 2020).

The kidney-protective benefits of SGLT2 inhibitors were first recognized in the FDA-mandated CV outcomes trials (CVOTs) for newer antihyperglycemic therapies. In patients with T2D and established or at high risk of atherosclerotic CVD (ASCVD), including those deemed at high risk because of their concomitant CKD, empagliflozin and canagliflozin significantly reduced the risk of the primary outcome of major adverse CV events (MACE), defined as a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or CV death, and empagliflozin significantly decreased the risk of the individual component of CV death (Neal 2017; Zinman 2015). Dapagliflozin and ertugliflozin were noninferior but not superior to placebo for the MACE primary outcome in their respective CVOTs (Cannon 2020; Wiviott 2019). Although an initial concern for AKI secondary to volume depletion existed with the SGLT2 inhibitors, an unexpected finding from CVOTs for all four currently available agents was a significant reduction in the risk of secondary or exploratory composite kidney outcomes with their use (Cherney 2021; Wiviott 2019; Neal 2017; Wanner 2016). Table 1 summarizes the design, patient population, and primary and secondary kidney-related end points from the CVOTs for the available SGLT2 inhibitors.

Findings from the CVOTs of patients with T2D set the stage for more recent kidney outcomes studies to assess the effect of SGLT2 inhibitors on a primary kidney end point (Table 2). The CREDENCE trial randomized 4401 adults 30 and older with T2D and CKD treated with maximally tolerated ACEI or ARB therapy to canagliflozin 100 mg daily or placebo (Perkovic 2019). After a median follow-up of 2.6 years, the primary composite outcome of doubling of SCr, ESKD, or death from kidney or CV causes was significantly reduced in the canagliflozin group compared with the placebo group, which was primarily driven by a reduction in the doubling of SCr and ESKD. Subgroup analyses showed more pronounced benefit in participants with a baseline eGFR less than 60 mL/minute/1.73 m^2 and those with a UACR greater than 1000 mg/g for both the primary and secondary kidney-specific composite end points. Results of the CREDENCE trial led to updated prescribing information for canagliflozin, allowing its initiation in CKD stage 3B (eGFR 30–44 mL/minute/1.73 m^2) and permitting its continuation as eGFR declines until dialysis or transplantation if severely increased albuminuria is present to reduce the risk of ESKD, doubling of SCr, CV death, and hospitalization for HF (HHF).

The DAPA-CKD trial randomized 4304 adults 18 and older with CKD with or without T2D using maximally tolerated ACEI or ARB therapy to dapagliflozin 10 mg daily or placebo (Heerspink 2020). After a median follow-up of 2.4 years, the primary composite outcome of a sustained at least 50% decrease in eGFR from baseline, ESKD, or death from kidney or CV causes occurred in significantly fewer participants in the dapagliflozin group. This result was primarily driven by a reduction in a sustained at least 50% decrease in eGFR from baseline and ESKD. The effect of dapagliflozin compared with placebo on the primary outcome was consistent in patients both with and without T2D. Subgroup analyses further showed consistent benefit for the primary end point in participants with

Table 1. Summary of Kidney-Related End Points from CVOTs Evaluating SGLT2 Inhibitors in Patients with T2D

Trial	Design	Population	Outcomes (95% CI)
EMPA-REG OUTCOME (Wanner 2016; Zinman 2015)	Empagliflozin 10–25 mg daily vs. PBO n=7020 3.1 yr	T2D (A1C 7%–10%), age ≥ 18 yr with established CVD eGFR ≥ 30 mL/min/1.73 m^2 eGFR (mL/min/1.73 m^2): 45 to < 60, 17.8%; 30 to < 45, 7.7% UACR (mg/g): 30–300, 28.7%; > 300, 11.0%	3-pt MACE, HR 0.86 (0.74–0.99) CV death, HR 0.62 (0.49–0.77) All-cause mortality, HR 0.68 (0.57–0.82) Kidney composite (progression to macroalbuminuria, doubling of SCr with eGFR ≤ 45 mL/min/1.73 m^2, KRT initiation, or death from kidney causes), HR 0.61 (0.53–0.70) Incident albuminuria, HR 0.95 (0.87–1.04)
CANVAS Program (Neal 2017)	Canagliflozin 100–300 mg daily[2] vs. PBO n=10,142 2.4 yr	T2D (A1C 7%–10.5%), age ≥ 30 yr with established CVD or ≥ 50 yr with ≥ 2 CVD risk factors; eGFR ≥ 30 mL/min/1.73 m^2 Mean eGFR: 76.5 mL/min/1.73 m^2 Median UACR: 12.3 mg/g	3-pt MACE, HR 0.86 (0.75–0.97) Kidney composite (sustained ≥ 40% eGFR decrease, KRT initiation, or death from kidney causes), HR 0.60 (0.47–0.77) Progression of albuminuria, HR 0.73 (0.67–0.79)
DECLARE-TIMI 58 (Wiviott 2019)	Dapagliflozin 10 mg daily vs. PBO n=17,160 4.2 yr	T2D (A1C 6.5% to < 12%), age ≥ 40 yr with established CVD or men ≥ 55 yr or women ≥ 60 yr with ≥ 1 CVD risk factor(s); CrCl ≥ 60 mL/min Mean eGFR: 85.2 mL/min/1.73 m^2	3-pt MACE, 0.93 (0.84–1.03) CV death + HHF, 0.83 (0.73–0.95) Kidney composite (sustained ≥ 40% eGFR decrease to < 60 mL/min/1.73 m^2, ESKD, or death from kidney causes), HR 0.53 (0.43–0.66)
VERTIS CV (Cherney 2021; Cannon 2020)	Ertugliflozin 5–15 mg daily vs. PBO n=8246 3.5 yr	T2D (A1C 7%–10.5%), age ≥ 40 yr with established CVD; eGFR ≥ 30 mL/min/1.73 m^2 Mean eGFR: 76.0 mL/min/1.73 m^2 Median UACR 19 mg/g	3-point MACE, HR 0.97 (0.85–1.11) Exploratory kidney composite (sustained ≥ 40% eGFR reduction, KRT initiation, or death from kidney causes), HR 0.66 (0.50–0.88)

CKD = chronic kidney disease; CV = cardiovascular; CVD = CV disease; CVOT = CV outcomes trials; ESKD = end-stage kidney disease; HHF = hospitalization for heart failure; KRT = kidney replacement therapy; MACE = major adverse CV events; PBO = placebo; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes; UACR = urine albumin/creatinine ratio.

Information from: Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28; Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34; Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57; Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57; Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35; Cherney DZI, Charbonnel B, Cosentino F, et al. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomized VERTIS CV trial. Diabetologia 2021;64:1256-67.

an eGFR less than and greater than 45 mL/minute/1.73 m^2 and those with a UACR below and above 1000 mg/g. Of note, the risk of all-cause mortality was significantly lower in patients randomized to dapagliflozin. The DAPA-CKD trial led to the revision of dapagliflozin's prescribing information to permit its initiation in patients with CKD (eGFR at least 25 mL/minute/1.73 m^2), irrespective of T2D status, and allow its continuation as eGFR declines to reduce the risk of eGFR decline, ESKD, CV death, and HHF.

The EMPA-KIDNEY study is evaluating the effects of empagliflozin on kidney outcomes in patients with advanced CKD with and without albuminuria and irrespective of diabetes status (EMPA-KIDNEY Collaborative Group 2022). Investigators randomized 6609 adults 18 and older with CKD (eGFR 20 to less than 45 mL/minute/1.73 m^2 or eGFR 45 to less than 90 mL/minute/1.73 m^2 with a UACR of 200 mg/g or greater) with or without T2D to empagliflozin 10 mg daily or placebo. The primary outcome being evaluated is a composite of kidney disease progression or CV death, and results are anticipated to be positive because the trial was recently terminated early at the recommendation of the Independent Data Monitoring Committee, given the overwhelming benefit of empagliflozin during a prespecified interim analysis (Boehringer Ingelheim 2022). The EMPA-KIDNEY trial will help

Table 2. Kidney Outcomes Trials of SGLT2 Inhibitors Among Patients with CKD

Trial	CREDENCE (Perkovic 2019)	DAPA-CKD (Heerspink 2020)	EMPA-KIDNEY (EMPA-KIDNEY Collaborative Group 2022)
Intervention	Canagliflozin 100 mg daily vs. PBO	Dapagliflozin 10 mg daily vs. PBO	Empagliflozin 10 mg daily vs. PBO
Size (n)	4401	4304	6609
Median follow-up	2.6 yr	2.4 yr	N/A
Patient Population			
Kidney parameters	eGFR 30 to < 90 mL/min/1.73 m^2 and UACR > 300–5000 mg/g	eGFR 25–75 mL/min/1.73 m^2 and UACR 200–5000 mg/g	eGFR 45 to < 90 mL/min/1.73 m^2 and UACR ≥ 200 mg/g, or eGFR 20 to < 45 mL/min/1.73 m^2
Diabetes status	T2D; A1C 6.5%–12%	Included patients with and without T2D	
Concurrent disease management	Stable, maximum tolerated daily dose of ACEI or ARB for ≥ 4 wk before randomization	Stable, maximum tolerated daily dose of ACEI or ARB for ≥ 4 wk before screening, unless documented intolerance or contraindication	Stable, maximum tolerated daily dose of ACEI or ARB, unless documented intolerance, contraindication, or lack of indication
Primary end point	Composite of doubling of SCr, ESKD, or death from kidney or CV causes	Composite of sustained ≥ 50% eGFR decrease, ESKD, or death from kidney or CV causes	Composite of kidney disease progression (sustained ≥ 40% eGFR decrease or eGFR < 10 mL/min/1.73 m^2, ESKD or death from kidney causes) or CV death
Baseline characteristics	Mean age: 63.0 yr Mean A1C: 8.3% 50.4% with CVD Mean eGFR: 56.2 mL/min/1.73 m^2 Median UACR: 927 mg/g 99.9% on ACEI or ARB	Mean age: 61.8 yr 67.5% with T2D 37.4% with CVD Mean eGFR 43.1 mL/min/1.73 m^2 Median UACR: 949 mg/g 98.1% on ACEI or ARB	Mean age: 63.8 yr 44% with T2D, 1% with T1D Mean eGFR 37.5 mL/min/1.73 m^2 Median UACR: 412 mg/g 87% on ACEI or ARB with UACR ≥ 200 mg/g at baseline 81% on ACEI or ARB with UACR < 200 mg/g at baseline
Outcomes (95% CI)			
Primary end point	HR 0.70 (0.59–0.82)	HR 0.61 (0.51–0.72)	N/A
ESKD	HR 0.68 (0.54–0.86)	HR 0.64 (0.50–0.82)	N/A
CV death	HR 0.78 (0.61–1.00)	HR 0.81 (0.58–1.12)	N/A
All-cause mortality	HR 0.83 (0.68–1.02)	HR 0.69 (0.53–0.88)	N/A

CKD = chronic kidney disease; CV = cardiovascular; CVD = CV disease; ESKD = end-stage kidney disease; N/A = not applicable; PBO = placebo; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes; UACR = urine albumin/creatinine ratio.

Information from: Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306; Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46; EMPA-KIDNEY Collaborative Group. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. Nephrol Dial Transplant 2022;37:1317-29.

answer the long-awaited question of whether SGLT2 inhibitors benefit patients with non-albuminuric CKD because 48% of study participants had a baseline UACR less than 300 mg/g (EMPA-KIDNEY Collaborative Group 2022).

Findings from the CV and kidney outcomes trials with SGLT2 inhibitors have reshaped clinical guidelines for the treatment of patients with T2D and CKD. In addition, the results from DAPA-CKD and EMPA-KIDNEY will likely affect

the updated recommendations for CKD management, irrespective of diabetes status.

The 2022 ADA Standards of Care in Diabetes no longer designate metformin as initial therapy in T2D; rather, first-line therapy depends on a patient's comorbidities, patient-centered treatment factors (e.g., cost and access), and patient treatment needs and usually includes metformin and comprehensive lifestyle modifications (ADA 2022). Specifically, SGLT2 inhibitors are recommended for patients with T2D and CKD, regardless of baseline A1C or individualized A1C target, given their ability to slow CKD progression and reduce the risk of CV events independently of their blood glucose-lowering effect, as long as eGFR thresholds for initiation are met. The ADA prefers the use of SGLT2 inhibitors that have evidence for reducing CKD progression in kidney outcomes trials for people with an eGFR of at least 20 mL/minute/1.73 m^2 and a UACR of at least 200 mg/g, and SGLT2 inhibitors with proven CVD benefit can be considered to reduce CV risk in people with T2D and non-albuminuric CKD (eGFR of at least 20 mL/minute/1.73 m^2 without albuminuria) or severely increased albuminuria (UACR of at least 300 mg/g) without reduced eGFR.

The updated KDIGO guidelines for managing diabetes in people with CKD have repositioned their recommendations for SGLT2 inhibitors from the glycemic management to their comprehensive care section to reflect the irrefutable evidence that these agents should be a standard of care in the management of CKD irrespective of their glycemic effects (KDIGO 2022). These guidelines recommend SGLT2 inhibitors as first-line therapy for people with T2D with CKD and an eGFR of at least 20 mL/minute/1.73 m^2 to reduce CKD progression and CV events, and they prioritize the selection of an agent with documented kidney or CV benefits and with consideration of baseline eGFR for treatment initiation. This recommendation is made without a requirement for the presence of albuminuria, reflecting the positive findings from the EMPA-KIDNEY trial that included people with non-albuminuric CKD. Once initiated, SGLT2 inhibitors may be continued as eGFR declines below the threshold for initiation unless they are no longer tolerated, or KRT is initiated (KDIGO 2022).

Glucagon-like Peptide-1 Receptor Agonists

Emerging evidence supports the role of glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of patients with diabetes and CKD. Glucagon-like peptide-1 receptor agonists work by activating GLP-1 receptors in the pancreas to stimulate insulin secretion and inhibit glucagon production in a glucose-dependent manner. The GLP-1 receptor agonists also act at the GLP-1 receptors in the brain and gut to increase satiety and delay gastric emptying. The mechanism for the benefit of GLP-1 receptor agonists in CKD is not well understood but is proposed to be because of direct and indirect mechanisms (Sloan 2019). Beneficial indirect effects of GLP-1 receptor agonists on surrogate markers and clinical outcomes of kidney disease may be attributable to improvements in glucose management, weight loss, and blood pressure reduction. Proposed direct mechanisms for kidney benefit include GLP-1–mediated inhibition of the sodium-hydrogen exchanger 3 in the proximal tubule causing improved delivery of sodium to the macula densa, restoration of tubuloglomerular feedback, and subsequent reduction in intraglomerular pressure and glomerular hyperfiltration (Muskiet 2017; Packer 2017).

The most robust data for the benefit of GLP-1 receptor agonists on kidney disease outcomes were derived from the CVOTs of patients with T2D. Outcomes trials conducted with liraglutide, subcutaneous semaglutide, and dulaglutide in patients with T2D and established ASCVD, CKD, or a combination of these comorbidities significantly reduced the primary composite MACE end point (Gerstein 2019a, 2019b; Marso 2016a, 2016b). These agents (liraglutide, subcutaneous semaglutide, and dulaglutide) also significantly decreased the risk of the secondary composite kidney outcomes in these trials, all of which were driven by a reduction in new macroalbuminuria. The EXSCEL and ELIXA trials did not show benefit with the use of weekly exenatide and lixisenatide, respectively, compared with placebo for the primary MACE end point (Holman 2017; Pfeffer 2015). Although the lack of effect on CV events with exenatide and lixisenatide may be related to differences in their pharmacologic properties, the study design, or the severity of disease in the populations studied, post hoc analyses of the EXSCEL and ELIXA trials suggest exenatide and lixisenatide retain a beneficial effect on surrogate kidney outcomes, specifically rates of new-onset macroalbuminuria (Bethel 2020; Muskiet 2018). Table 3 summarizes the design, patient population, and primary and secondary kidney-related end points from the CVOTs for available GLP-1 receptor agonists with evidence of CKD benefit.

The results of CVOTs conducted with the GLP-1 receptor agonists show promising results in their ability to prevent new-onset macroalbuminuria. Although no study evaluating these agents has shown improvement in clinical outcomes of CKD, such as reductions in ESKD or death from kidney disease, these studies were not powered to detect a difference in these secondary kidney outcomes. To date, no published studies have evaluated the effect of GLP-1 receptor agonists on a primary kidney outcome; however, the FLOW trial is ongoing to address this gap in evidence. The FLOW trial is randomizing adults 18 and older with T2D and CKD (eGFR 50–75 mL/minute/1.73 m^2 and UACR greater than 300 to less than 5000 mg/g or eGFR 25 to less than 50 mL/minute/1.73 m^2 and UACR greater than 100 to less than 5000 mg/g) taking a maximally tolerated ACEI or ARB to semaglutide or placebo (Novo Nordisk 2022). The trial will be appropriately powered to detect a difference in the primary composite outcome of a persistent 50% or greater eGFR decline, ESKD, or death from kidney or CV causes and is expected to be complete in 2024.

Together, the results of the FLOW trial and CVOTs with the GLP-1 receptor agonists will further elucidate their place in

Table 3. Summary of CVOTs Evaluating GLP-1 Receptor Agonists in Patients with T2D with Positive Secondary Kidney Outcomes

Trial	Design	Population	Outcomes (95% CI)
ELIXA (Muskiet 2018; Pfeffer 2015)	Lixisenatide 10 mcg daily titrated after 2 wk to 20 mcg daily vs. PBO n=6068 2.1 yr	T2D (A1C 5.5%–11%), age ≥ 30 yr and ACS < 180 days before screening; eGFR ≥ 30 mL/min/1.73 m^2 Mean eGFR: 76 mL/min/1.73 m^2 eGFR category (mL/min/1.73 m^2): 30–60: 23.1% 15–30: 0.1% Microalbuminuria: 19%, macroalbuminuria: 7%	4-pt MACE,[a] HR 1.02 (0.89–1.17) New-onset macroalbuminuria, adjusted HR 0.81 (0.66–0.991) UACR reduction by baseline albuminuria status: Normoalbuminuria, −1.69% (−11.69 to 8.30; p=0.7398) Microalbuminuria, −21.10% (−42.25 to 0.04; p=0.0502) Macroalbuminuria, −39.18% (−68.53 to −9.84; p=0.0070)
LEADER (Mann 2017; Marso 2016a)	Liraglutide 0.6 mg daily titrated every 7 days to 1.2 mg daily, then 1.8 mg daily vs. PBO n=9340 3.8 yr	T2D (A1C ≥ 7%), age ≥ 50 yr with established CVD, CKD, or chronic HF (NYHA class II or III), or ≥ 60 yr with ≥ 1 CVD risk factor; eGFR ≥ 30 mL/min/1.73 m^2 but included 222 participants with eGFR 15–30 mL/min/1.73 m^2 Mean eGFR: 80 mL/min/1.73 m^2 eGFR category (mL/min/1.73 m^2): 30 to < 60: 20.7% < 30: 2.4% Microalbuminuria: 26.3%, macroalbuminuria: 10.5%	3-pt MACE, HR 0.87 (0.78–0.97) CV death, HR 0.78 (0.66–0.93) All-cause mortality, HR 0.85 (0.74–0.97) Kidney composite (new macroalbuminuria, doubling of SCr with eGFR ≤ 45 mL/min/1.73 m^2, need for continuous KRT, or death from kidney causes), HR 0.78 (0.67–0.92) New macroalbuminuria, HR 0.74 (0.60–0.91)
SUSTAIN-6 (Marso 2016b)	Semaglutide (subcutaneous) 0.25 mg weekly titrated every 4 wk to 0.5–1 mg weekly vs. PBO n=3297 2.1 yr	T2D (A1C ≥ 7%), age ≥ 50 yr with established CVD, CKD, or chronic HF (NYHA class II or III), or ≥ 60 yr with ≥ 1 CVD risk factor Mean eGFR: ~75 mL/min/1.73 m^2 eGFR category (mL/min/1.73 m^2): 30 to < 60: 25.2% 15 to < 30: 2.9% < 15: 0.4%	3-pt MACE, HR 0.74 (0.58–0.95) Nonfatal stroke, HR 0.61 (0.38–0.99) Kidney composite (new macroalbuminuria, doubling of SCr with eGFR < 45 mL/min/1.73 m^2, need for continuous KRT, or death from kidney causes), HR 0.64 (0.46–0.88) New macroalbuminuria, HR 0.54 (0.37–0.77)
EXSCEL (Bethel 2020; Holman 2017)	Exenatide extended release 2 mg weekly vs. PBO n=14,752 3.2 yr	T2D (A1C 6.5%–10%), recruitment to attain 70% with and 30% without CVD; eGFR ≥ 30 mL/min/1.73 m^2 Median eGFR: 76 mL/min/1.73 m^2 eGFR category (mL/min/1.73 m^2): 30 to < 60: 21.5% < 30: 0.1% Microalbuminuria: 12.6% macroalbuminuria: 3.3%	3-pt MACE, HR 0.91 (0.83–1.00) Kidney composite 1 (≥ 40% eGFR decline, KRT, or death from kidney causes), adjusted HR 0.87 (0.73–1.04) Kidney composite 2 (new macroalbuminuria + kidney composite 1), adjusted HR 0.85 (0.74–0.98)
REWIND (Gerstein 2019a, 2019b)	Dulaglutide 1.5 mg weekly vs. PBO n=9901 5.4 yr	T2D (A1C ≤ 9.5%), age ≥ 50 yr with established CVD, or ≥ 55 yr with subclinical CVD or CKD, or ≥ 60 yr with ≥ 2 CVD risk factors; eGFR ≥ 15 mL/min/1.73 m^2 Mean eGFR: 76.9 mL/min/1.73 m^2 eGFR category (mL/min/1.73 m^2): < 60: 22.2% Macroalbuminuria: 7.9%	3-pt MACE, HR 0.88 (0.79–0.99) Nonfatal stroke, HR 0.76 (0.61–0.95) Kidney composite (new macroalbuminuria, sustained ≥ 30% eGFR decrease, or chronic KRT), HR 0.85 (0.77–0.93) New macroalbuminuria, HR 0.77 (0.68–0.87)

(*continued*)

Table 3. Summary of CVOTs Evaluating GLP-1 Receptor Agonists in Patients with T2D with Positive Secondary Kidney Outcomes (*continued*)

[a]Primary outcome expanded MACE to include hospitalization for unstable angina.

ACS = acute coronary syndrome; CKD = chronic kidney disease; CV = cardiovascular; CVD = CV disease; CVOT = CV outcomes trials; ESKD = end-stage kidney disease; GLP-1 = glucagon-like peptide-1; HF = heart failure; MACE = major adverse CV events; NYHA = New York Heart Association; KRT = kidney replacement therapy; SGLT2 = sodium-glucose cotransporter-2; PBO = placebo; T2D = type 2 diabetes; UACR = urine albumin/creatinine ratio.

Information from: Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57; Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2018;6:859-69; Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016a;375:311-22; Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017;377:839-48; Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016b;375:1834-44; Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228-39; Bethel MA, Mentz RJ, Merrill P, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL trial. Diabetes Care 2020;43:446-52; Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019a;394:121-30; Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019b;394:131-8.

therapy in patients with T2D and CKD who are at high risk of CKD progression and CV events. However, until evaluations dedicated to CKD populations are completed, the available evidence affords priority to SGLT2 inhibitors as a primary strategy to reduce CKD progression in patients with and without T2D. Given their respective kidney benefits and distinct mechanisms of action, combination therapy with SGLT2 inhibitors and GLP-1 receptor agonists may confer synergistic effects on kidney outcomes in patients with T2D and CKD. This question will be answered with the EMPASEMA trial, which will study empagliflozin alone or in combination with semaglutide in patients with T2D, eGFR of 30 mL/minute/1.73 m^2 or greater, and UACR greater than 100 mg/g (Steno Diabetes Center Copenhagen 2022).

Guideline recommendations for the role of GLP-1 receptor agonists in the treatment of patients with T2D and CKD underscore their CV risk-reducing properties to address the residual risk of CV events in this patient group. The KDIGO guidelines for managing diabetes and CKD specifically recommend a long-acting GLP-1 receptor agonist, prioritizing those with proven CV benefit (i.e., dulaglutide, liraglutide, and subcutaneous semaglutide), in patients with T2D and CKD who are not achieving glycemic targets despite optimization of metformin and SGLT2 inhibitor therapy, or in patients who are unable to use these therapies (KDIGO 2022). The 2022 ADA and European Association for the Study of Diabetes consensus report recommends a GLP-1 receptor agonist with proven CV benefit after an SGLT2 inhibitor or when an SGLT2 inhibitor is contraindicated or not tolerated in patients with CKD (Davies 2022).

Mineralocorticoid Receptor Antagonists

Evidence showing the role of mineralocorticoid receptors in the inflammatory and fibrotic processes of cardiorenal disease despite adequate RAS inhibition, termed the *aldosterone escape phenomenon*, has prompted research surrounding the usefulness of mineralocorticoid receptor antagonist (MRA) therapy in the management of CKD (Agarwal 2021b; Staessen 1981). Trials of the steroidal MRAs spironolactone and eplerenone in CKD were initially sparse, and few evaluated their effect on clinical kidney outcomes. Early studies of people with less advanced CKD showed improvements in CV surrogate end points with the use of spironolactone independent of its blood pressure–lowering effect, and its addition in patients with severely increased albuminuria taking maximum-dose lisinopril resulted in significant reductions in UACR from baseline (Edwards 2009; Mehdi 2009). However, several systematic reviews have drawn attention to the imprecise effect of MRAs on eGFR and the persistent risk of hyperkalemia, suggesting a questionable benefit-risk ratio in this population (Alexandrou 2019; Bolignano 2014; Edwards 2009; Mehdi 2009). Despite their relative or absolute contraindication in patients with advanced CKD, several evaluations have been performed or are ongoing to assess the CV benefits of steroidal MRAs in patients with ESKD receiving dialysis. Findings to date in this high-risk population have been mixed and eclipsed by the rates of hyperkalemia; however, two ongoing placebo-controlled trials (ACHIEVE and ALCHEMIST) are evaluating the effect of spironolactone on CV outcomes in patients receiving dialysis with or without T2D (Charytan 2019; Population Health Research Institute 2022; University Hospital, Brest 2022).

The development of a more potent and selective nonsteroidal MRA has generated interest in improving the benefit-risk ratio in patients with reduced kidney function at high risk of CV complications. Finerenone is a selective, nonsteroidal MRA and currently the only FDA-approved medication in this

novel class (Agarwal 2021b). Compared with steroidal MRAs, finerenone is more selective for the mineralocorticoid receptor and is at least as potent as spironolactone. Studies of drug tissue distribution have shown that finerenone has a balanced distribution between the heart and the kidney, whereas steroidal MRAs have greater accumulation in the kidney, possibly explaining their greater effect on sodium and potassium balance relative to finerenone. In addition, finerenone is less lipophilic and has a shorter half-life than steroidal MRAs. Finerenone also has no active metabolites, unlike spironolactone, which is a prodrug with several active metabolites that have been detected in the urine samples of patients with an eGFR 25–45 mL/minute/1.73 m^2 up to 3 weeks after cessation of therapy. These distinct differences are proposed to confer a stronger anti-inflammatory and anti-fibrotic effect with finerenone.

Recently published trials showed the beneficial effect of finerenone on kidney and CV outcomes in patients with T2D and CKD. The FIDELIO-DKD and FIGARO-DKD are complementary trials that investigated the efficacy and safety of finerenone on kidney and CV outcomes in patients with mild to severe CKD and T2D (Pitt 2021; Bakris 2020). Both trials included a run-in period in which ACEI or ARB therapy was titrated to maximally tolerated doses, required participants' serum potassium to be 4.8 mEq/L or less at run-in and screening visits, and excluded patients with symptomatic HF with reduced ejection fraction (HFrEF) because MRA therapy would be indicated as part of guideline-directed medical therapy.

The FIDELIO-DKD trial randomized 5674 adults 18 and older with T2D and CKD with (1) an eGFR of 25 to less than 60 mL/minute/1.73 m^2, a UACR of 30 to less than 300 mg/g, and a history of diabetic retinopathy or (2) an eGFR of 25 to less than 75 mL/minute/1.73 m^2 and a UACR of 300–5000 mg/g, and a serum potassium of 4.8 mEq/L or less at screening to finerenone 10–20 mg daily or placebo (Bakris 2020). The primary outcome was a composite of kidney failure (defined as ESKD or an eGFR less than 15 mL/minute/1.73 m^2), a sustained 40% or greater decrease in eGFR from baseline, or death from kidney causes. After a median follow-up of 2.6 years, the primary outcome occurred in significantly fewer patients in the finerenone group than in the placebo group, which was primarily driven by a significant reduction in the sustained 40% or greater eGFR decrease. The key secondary outcome was a composite of time to CV death, nonfatal MI, nonfatal stroke, or HHF and was also significantly lower in the finerenone group than in placebo; however, none of the individual components of the composite outcome were significantly different between groups. With respect to safety, the incidence of investigator-reported hyperkalemia was doubled with finerenone compared with placebo.

The complementary FIGARO-DKD trial aimed to evaluate the effect of finerenone on CV events over a longer kidney failure–free interval and therefore enrolled patients with less severe CKD (Pitt 2021). A total of 7352 adults 18 and older with T2D and CKD with either (1) an eGFR of 25–90 mL/minute/1.73 m^2 and a UACR of 30 to less than 300 mg/g or (2) an eGFR of 60 mL/minute/1.73 m^2 or greater and a UACR of 300–5000 mg/g, and a serum potassium of 4.8 mEq/L or less at screening, were randomized to finerenone 10–20 mg daily or placebo. The primary outcome was a composite of death from CV causes, nonfatal MI, nonfatal stroke, or HHF. After a median follow-up of 3.4 years, the primary outcome occurred in significantly fewer participants in the finerenone group than in the placebo group, which was driven by a statistically significant reduction in HHF. The initial secondary kidney outcome was a composite of time to kidney failure, a sustained 40% or greater decrease in eGFR from baseline, or death from kidney causes and was not significantly different between finerenone and placebo. When adjusted to include a sustained 57% or greater decrease in eGFR, which is equivalent to a doubling of SCr, rather than a 40% or greater decrease in eGFR from baseline, the exploratory kidney composite was significantly reduced with finerenone. Similar to FIDELIO-DKD, the incidence of hyperkalemia in FIGARO-DKD was increased by 2-fold with finerenone compared with placebo.

The Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis (FIDELITY) was a prespecified pooled analysis of the phase III outcomes trials that was intended to provide a more precise estimate of the safety and efficacy of finerenone across a broader spectrum of CKD in patients with T2D (Agarwal 2022). The FIDELITY analysis included a total of 13,026 participants with a mean eGFR of 57.6 mL/minute/1.73 m^2 and a median UACR of 515 mg/g (66.7% with a UACR of 300 mg/g or greater), and 45.6% had a history of CVD at baseline. Over a median of 3 years, the composite outcome of CV death, nonfatal MI, nonfatal stroke, and HHF was significantly lower in the finerenone group (12.7% vs. 14.4%; HR 0.86, 0.78–0.98). Similar to the individual trials, the CV composite was driven by a reduction in HHF (3.9% vs. 5.0%; HR 0.78, 0.66–0.92). The kidney outcome, which was adjusted for purposes of the pooled analysis to a composite of kidney failure, a sustained 57% or greater decrease in eGFR, or death from kidney causes, was also significantly lower in the finerenone group (5.5% vs. 7.1%; HR 0.77, 0.67–0.88), driven by significant reductions in the individual components of kidney failure (HR 0.84, 0.71–0.99) and a sustained 57% or greater decrease in eGFR (HR 0.70, 0.60–0.83). Reflective of the individual trials, rates of investigator-reported hyperkalemia were doubled with finerenone (14.0% vs. 6.9%). Of note, only 6.7% and 7.2% of participants in the FIDELITY pooled population were using an SGLT2 inhibitor and GLP-1 receptor agonists at baseline, respectively. The benefit of finerenone was similar in participants treated with SGLT2 inhibitors and those treated with GLP-1 receptor agonists, with no significant heterogeneity between groups for participants receiving these therapies with respect to the primary outcome. In addition, SGLT2

inhibitors were associated with a reduced risk of hyperkalemia in a post hoc analysis of the FIDELIO-DKD trial, suggesting the potential benefit of this combination in mitigating the primary risk related to finerenone use (Agarwal 2021a). Although these analyses suggest these therapies can be combined, finerenone added to therapy with an SGLT2 inhibitor and/or GLP-1 receptor agonist remains an area of study to be able to confirm that their effects on kidney outcomes are additive.

Because of evidence from its robust phase III cardiorenal outcome program, finerenone was approved by the FDA in July 2021, according to the package insert, to reduce the risk of a sustained eGFR decrease, ESKD, CV death, nonfatal MI, and HHF in adult patients with CKD associated with T2D. Initial dosing is 10–20 mg daily depending on the baseline eGFR, and dose adjustments are based on the current dose and subsequent serum potassium measurements with a target daily dose of 20 mg as outlined in Table 4. Of note, according to the manufacturer, finerenone should not be initiated in people with an eGFR less than 25 mL/minute/1.73 m^2, a serum potassium greater than 5.0 mEq/L, or adrenal insufficiency or in those using strong CYP3A4 inhibitors.

Table 4. Recommendations for Finerenone Initiation and Dose Adjustments

Recommended Initial Dosing	
eGFR (mL/min/1.73 m^2)	**Starting Dose**
≥ 60	20 mg daily
≥ 25 to < 60	10 mg daily
< 25	Not recommended

Recommended Dose Adjustment Given Current Serum Potassium and Current Dose		
Serum potassium (mEq/L)[a]	**Current dose**	
	10 mg daily	**20 mg daily**
≤ 4.8	Increase to 20 mg daily[b]	Continue 20 mg daily
> 4.8–5.5	Continue 10 mg daily	Continue 20 mg daily
> 5.5	Hold Consider reinitiating at 10 mg daily when serum potassium ≤ 5.0 mEq/L	Hold Reinitiate at 10 mg daily when serum potassium ≤ 5.0 mEq/L

[a]Monitor serum potassium 4 wk after initiation and dose adjustment, then periodically throughout treatment; may consider additional serum potassium monitoring within the first 4 wk of initiation if baseline serum potassium > 4.8–5.0 mEq/L; do not initiate if baseline serum potassium > 5.0 mEq/L.

[b]Continue 10 mg daily if > 30% decrease in eGFR.

Information from: manufacturer's package insert.

Historically, guideline recommendations for the use of steroidal MRAs in the management of CKD in patients with T2D were limited to their role as an effective strategy for patients with resistant hypertension, patients with primary hyperaldosteronism, or those with HFrEF, with an accompanying precaution for hyperkalemia in the setting of reduced eGFR. The 2022 ADA Standards of Care was the first clinical practice guideline to recommend finerenone to reduce CKD progression and CV events in patients with diabetes and CKD who were at increased risk of CV events or CKD progression or were unable to use an SGLT2 inhibitor (ADA 2022). Of note, no specification is made on whether this recommendation applies to all patients with diabetes or strictly to those with T2D as studied in the clinical trials and detailed in the approved indication for use.

The 2022 KDIGO guideline for managing diabetes in patients with CKD recommends finerenone in patients with T2D, an eGFR of 25 mL/minute/1.73 m^2 or greater, a normal serum potassium concentration (recommend 4.8 mEq/L or less for initiation vs. less than 5.0 mEq/L as listed in the package insert), and albuminuria despite a maximally tolerated dose of a RAS inhibitor to reduce the progressive decrease in eGFR and risk of CV events (KDIGO 2022). The 2022 KDIGO was the first guideline to explicitly recommend SGLT2 inhibitor initiation before nonsteroidal MRA therapy, stating that finerenone could be considered after foundational therapy with a RAS inhibitor and SGLT2 inhibitor in those still meeting the criteria for initiation (i.e., residual albuminuria and normal serum potassium). Finerenone may also be added to a RAS inhibitor for this indication in patients who cannot tolerate or are not appropriate candidates for SGLT2 inhibitor therapy. The KDIGO work group for diabetes management in CKD also clarified the place in therapy of steroidal MRAs, specifically that they do not have clinical kidney or CV outcome benefits in this population and should not be preferred to nonsteroidal MRAs unless compelling indications (i.e., HF, primary hyperaldosteronism or resistant hypertension) are present. When steroidal MRAs are used for one of these compelling indications, changing to a nonsteroidal MRA to improve outcomes is not recommended because there is no evidence that nonsteroidal MRAs are interchangeable in these clinical scenarios. Finerenone reduced systolic blood pressure (SBP) by a mean of 3 mm Hg in the FIDELITY pooled analysis, currently limiting its usefulness in the management of hypertension. In addition, finerenone has not been studied in an HF clinical outcomes trial and should not be recommended over spironolactone and eplerenone in this population. KDIGO advises against adding a nonsteroidal MRA in patients taking

steroidal MRAs for these compelling indications because of the risk of hyperkalemia.

Optimization of Glycemic Management

Glycemic management to achieve near-normoglycemia delays the onset and progression of CKD and albuminuria in patients with T1D and T2D (ADA 2022). The DCCT/EDIC study of individuals with T1D used insulin alone to lower blood glucose, and a variety of clinical trials of individuals with T2D have shown the benefit of different antihyperglycemic agents in lowering blood glucose to prevent CKD progression, thereby showing that lowering A1C to glycemic target prevents CKD and its progression (ADA 2022; DCCT/EDIC Research Group 2015).

Glycemic Targets

The ADA and KDIGO guidelines continue to recommend using A1C to monitor glycemic management with a target range of from less than 6.5% up to less than 8% in patients with diabetes and CKD not treated with dialysis, depending on patient complexity, goals, and life expectancy (ADA 2022; KDIGO 2022). An individualized approach should be considered when establishing A1C targets, which includes the severity of CKD, macrovascular complications, comorbidities, life expectancy, hypoglycemia awareness, resources for hypoglycemia management, and the propensity of treatment to cause hypoglycemia.

The DCCT found that, compared with a less stringent A1C of 9%, achieving a mean A1C of 7% in patients with T1D was associated with 50%–76% reductions in rates of new and worsening retinopathy, neuropathy, and CKD, thereby showing the benefit of optimizing glycemic management on microvascular complications (DCCT Research Group 1993). The UKPDS also showed that intensive glycemic management in those with short-duration T2D decreased rates of microvascular complications throughout long-term follow-up (UKPDS Group 1998a). These trials are the foundation of the recommendation that an A1C target of less than 7% should be instituted early in diabetes management to prevent microvascular complications in patients with T1D and T2D (ADA 2022). In addition, subanalyses of the DCCT and UKPDS suggest that lowering the A1C from 7% to 6% is associated with further reduction in microvascular complication risks, and therapy should not be deintensified for individuals with an A1C of 6%–7% with a low risk of hypoglycemia and longer life expectancy (UKPDS Group 1998b; DCCT Research Group 1993). The ACCORD, ADVANCE, and VADT trials all showed that lower A1C levels were associated with reduced onset or progression of some microvascular complications (Ismail-Beigi 2010; Duckworth 2009; ADVANCE Collaborative Group 2008). In the ADVANCE trial, the rate of ESKD was lower in the intensive group (A1C 6.5% or less) over the posttrial follow-up period (Zoungas 2014). The ADA recommends interpreting the ACCORD trial with caution because this landmark study did not include GLP-1 receptor agonists and SGLT2 inhibitors, which have shown kidney and CV benefit. The latest antihyperglycemic management algorithm recommends adding SGLT2 inhibitors with proven reduction in CKD progression, independent of baseline A1C or individualized A1C target. In addition, the SGLT2 inhibitors and GLP-1 receptor agonists have a low likelihood of causing hypoglycemia, making it possible to maintain more intensive glucose management without the risk of hypoglycemia.

Accuracy and precision of A1C measurement decrease in advanced CKD (eGFR less than 30 mL/minute/1.73 m^2), and A1C measurements may have low reliability in individuals treated with dialysis (KDIGO 2020). The A1C is an advanced glycation end product of hemoglobin. Chronic kidney disease is associated with inflammation, oxidative stress, and metabolic acidosis, which may promote advanced glycation end-product formation and elevate A1C independently of hyperglycemia. Conversely, A1C is lowered by shortened survival age of erythrocytes from anemia, decreased erythropoiesis, transfusions, and use of erythropoiesis-stimulating agents or iron-replacement therapies. These factors are common in those receiving dialysis, making A1C a less reliable marker in advanced CKD. For individuals with CKD requiring dialysis or for older adults with stage 3 CKD or higher, less intensive A1C goals of 8.5% or 8%, respectively, should be implemented. For those with intermediate life expectancy, high treatment burden, several coexisting chronic illnesses such as CKD, and at risk of hypoglycemia, an A1C goal of less than 8.0% is reasonable (ADA 2022). For those with limited life expectancy, the ADA recommends against relying on A1C for glycemic management and instead focusing on avoiding hypoglycemia and symptomatic hyperglycemia as a management strategy.

Noninsulin Antihyperglycemic Medications

When selecting noninsulin antihyperglycemic therapies for patients with T2D, a patient's preferences and chronic comorbidities as well as the safety of these medications in the setting of decreasing kidney function should be considered. Both the ADA and KDIGO give preference to SGLT2 inhibitors that have evidence for reducing CKD progression in kidney outcomes trials as first-line therapy for patients with T2D and CKD and an eGFR of 20 mL/minute/1.73 m^2 or greater (Davies 2022; KDIGO 2022). The ADA and European Association for the Study of Diabetes guidelines recommend a GLP-1 receptor agonist with proven CV benefit after an SGLT2 inhibitor or when an SGLT2 inhibitor is contraindicated or not tolerated in patients with CKD (Davies 2022). Metformin can still be considered for patients with CKD after an SGLT2 inhibitor and GLP-1 receptor agonist if further glycemic lowering is needed as long as the eGFR is sufficient for initiation. KDIGO suggests that most patients with T2D and CKD with an eGFR greater than 30 mL/minute/1.73 m^2

who need additional glucose lowering in addition to SGLT2 inhibitor therapy would benefit from the addition of metformin (KDIGO 2022). KDIGO recommends GLP-1 receptor agonists after metformin and SGLT2 inhibitors on the basis of their proven CV benefit and possible kidney benefits. Glucagon-like peptide-1 receptor agonists are also preferred in the management of obesity and should be considered especially in those with advanced stages of CKD requiring weight loss to qualify for a kidney transplant (KDIGO 2022). Although the evidence for preventing CKD progression is less robust with GLP-1 receptor agonists, these agents can also be considered in patients with CKD after SGLT2 inhibitors and metformin, or in those unable to tolerate SGLT2 inhibitors and/or metformin, to reduce the risk of CV events and/or the progression of albuminuria. Preference should be given to agents with proven CV benefit (i.e., dulaglutide, liraglutide, and subcutaneous semaglutide) and with consideration of eGFR, because immediate- and extended-release exenatide and lixisenatide are eliminated through the kidney and therefore have limitations for use in patients with advanced CKD. The incidence of nausea, vomiting, and subsequent dehydration may be higher with the use of GLP-1 receptor agonists in those with more advanced CKD; consequently, these agents should be initiated at the lowest dose and titrated slowly to minimize GI adverse effects (KDIGO 2022).

Other noninsulin therapies have not shown reductions in CV or kidney outcomes; however, they may still be considered appropriate treatments for T2D in the setting of CKD. Dipeptidyl peptidase-4 (DPP-4) inhibitors are reasonable for this population because of their neutral effect on body weight, limited adverse effect profile, and modest A1C-lowering effects. The DPP-4 inhibitors and GLP-1 receptor agonists are not synergistic and therefore should not be used in combination because of their similar mechanisms of action. Use of DPP-4 inhibitors in patients with CKD should be considered for those unable to tolerate a GLP-1 receptor agonist. Sitagliptin, alogliptin, and saxagliptin are eliminated through the kidney and require dose adjustments on the basis of kidney function, whereas linagliptin is eliminated by the enterohepatic system and does not require dose adjustments on the basis of kidney function. The DPP-4 inhibitors should be initiated at the maximum recommended dose on the basis of kidney function, and titration is not required. Saxagliptin and alogliptin should be used with caution in patients with CKD because an increased risk of HHF has been associated with use of these agents in patients with heart and kidney disease (Zannad 2015; Scirica 2013).

If patients have endogenous insulin production remaining, glipizide or glimepiride can be considered, and these agents are preferred to other agents in the pharmacologic class because of their short duration of action and limited ability to accumulate in kidney impairment (ADA 2022; Neumiller 2017). Glyburide should not be used in patients with an eGFR less than 60 mL/minute/1.73 m^2 and should be avoided in older adults with T2D without CKD at baseline because of the natural decrease in kidney function that is expected with increasing age (ADA 2022). Glipizide is the preferred agent in ESKD because of its hepatic metabolism and shorter duration of action (Gianchandani 2017; Neumiller 2017). Thiazolidinediones are usually not recommended in CKD because of the increased potential for fluid retention in this population. Specifically, rosiglitazone has been associated with an increased risk of acute MI, HHF, and HF-related death, and risks of these adverse outcomes may be accentuated in a CKD population with an elevated baseline risk of CVD (Home 2009; Nissen 2007). Evidence is limited for the treatment of patients with T2D and CKD using amylin analogs, α-glucosidase inhibitors, bile acid sequestrants, and dopamine agonists; therefore, these agents should be reserved for when other noninsulin medications are not tolerated or indicated, and patients are unamenable to the initiation of insulin therapy.

Therapy Considerations in Patients with CKD

Patients with diabetes and stage 3 CKD or higher are at a higher risk of hypoglycemic events than those without CKD because of the presence of increased insulin resistance, reduced gluconeogenesis, and impaired insulin degradation (KDIGO 2020). In addition, altered metabolism and reduced elimination of antihyperglycemic agents may increase the risk of hypoglycemia in these patients.

An SGLT2 inhibitor should be incorporated into the treatment regimen to prevent CKD progression. For those at risk of hypoglycemia, it may be necessary to discontinue or reduce the dose of other antihyperglycemic therapies with higher hypoglycemic risk (i.e., insulin or secretagogues) to facilitate the addition of an SGLT2 inhibitor (KDIGO 2022). In addition, if the person is at risk of hypovolemia or hypotension and receiving diuretic therapy, a dose reduction or discontinuation of the diuretic should be considered to minimize the risk of these adverse events. Once SGLT2 inhibitor therapy is initiated, it is recommended to continue the agent until dialysis as long as the patient is tolerating therapy and no contraindications exist. Although the glucose-lowering effects of SGLT2 inhibitors will be attenuated, the CV and kidney benefits will persist at lower eGFRs (ADA 2022).

Dose Adjustments in CKD

Many noninsulin antihyperglycemic medications require dosing adjustments in CKD, and the frequency of monitoring should be increased to at least every 3–6 months in those with an eGFR less than 60 mL/minute/1.73 m^2. Table 5 lists recommended dose adjustments for these medications on the basis of kidney function.

Insulin

Insulin is the most effective therapy to lower A1C, though it is not without risks in the setting of kidney disease. Degradation

Table 5. Dose Recommendations for Noninsulin Antihyperglycemic Therapy in Patients with CKD

Medication Class and Agents	Recommended Dose
Biguanides	
Metformin	eGFR ≥ 45 to < 60 mL/min/1.73 m^2: No dose adjustment necessary; monitor eGFR every 3–6 mo eGFR 30 to < 45 mL/min/1.73 m^2: Initiation not recommended; however, if already receiving therapy, may continue at reduced maximum dose of 500 mg twice daily; monitor eGFR every 3 mo eGFR < 30 mL/min/1.73 m^2: Contraindicated
SGLT2 Inhibitors	
Canagliflozin	eGFR ≥ 60 mL/min/1.73 m^2: Initiate 100 mg/day; may increase to 300 mg/day, as needed, to improve glycemic management eGFR 30 to < 60 mL/min/1.73 m^2: Initiate 100 mg/day; do not increase eGFR < 30 mL/min/1.73 m^2: Initiation not recommended; however, if already receiving therapy, patients with albuminuria > 300 mg/day may continue 100 mg/day Dialysis: Contraindicated
Dapagliflozin	eGFR ≥ 45 mL/min/1.73 m^2 (antihyperglycemic therapy): Initiate 5 mg/day; may increase to 10 mg/day, as needed, to improve glycemic management eGFR ≥ 25 mL/min/1.73 m^2 (CKD or HF, regardless of diabetes status): Initiate 10 mg/day eGFR < 25 mL/min/1.73 m^2: Initiation not recommended; however, if already receiving therapy, may continue 10 mg/day Dialysis: Contraindicated
Empagliflozin	eGFR ≥ 30 mL/min/1.73 m^2 (antihyperglycemic therapy): Initiate 10 mg/day; may increase to 25 mg/day, as needed, to improve glycemic management eGFR ≥ 20 mL/min/1.73 m^2 (CKD or HF, regardless of diabetes status): Initiate 10 mg/day eGFR < 20 mL/min/1.73 m^2: Initiation not recommended; however, if already receiving therapy, may continue 10 mg/day Dialysis: Contraindicated
Ertugliflozin	eGFR ≥ 45 mL/min/1.73 m^2: Initiate at 5 mg/day; may increase to 15 mg/day, as needed, to improve glycemic management eGFR < 45 mL/min/1.73 m^2: Not recommended Dialysis: Contraindicated
GLP-1 Receptor Agonists	
Dulaglutide	No dose adjustment necessary in patients with kidney impairment; use caution in ESKD because of limited clinical evidence
Exenatide	CrCl < 30 mL/min: Not recommended
Exenatide, extended release	eGFR < 45 mL/min/1.73 m^2: Not recommended
Liraglutide	No dose adjustment necessary in patients with kidney impairment; use caution in ESKD because of limited clinical evidence
Lixisenatide	eGFR 15 to < 30 mL/min/1.73 m^2: No dose adjustment provided by manufacturer labeling; however, exposure increased in these patients eGFR < 15 mL/min/1.73 m^2: Not recommended
Semaglutide, oral	No dose adjustment necessary in patients with kidney impairment; use caution in ESKD because of limited clinical evidence
Semaglutide, subcutaneous	No dose adjustment necessary in patients with kidney impairment; use caution in ESKD because of limited clinical evidence

(*continued*)

Table 5. Dose Recommendations for Noninsulin Antihyperglycemic Therapy in Patients with CKD (*continued*)

Medication Class and Agents	Recommended Dose
DPP-4 Inhibitors	
Alogliptin	eGFR ≥ 60 mL/min: 25 mg/day eGFR 30 to < 60 mL/min: 12.5 mg/day eGFR < 30 mL/min: 6.25 mg/day ESKD, HD: 6.25 mg/day, administered without regard to timing of dialysis ESKD, PD: Not studied
Linagliptin	No dose adjustment necessary
Saxagliptin	eGFR ≥ 45 mL/min/1.73 m^2: 5 mg/day eGFR < 45 mL/min/1.73 m^2: 2.5 mg/day ESKD, HD: 2.5 mg/day, administered after dialysis ESKD, PD: Not studied
Sitagliptin	eGFR ≥ 45 mL/min/1.73 m^2: 100 mg/day eGFR 30 to < 45 mL/min/1.73 m^2: 50 mg/day eGFR < 30 mL/min/1.73 m^2: 25 mg/day ESKD, HD, or PD: 25 mg/day, administered without regard to timing of dialysis
Sulfonylureas	
Glimepiride	Initiate conservatively at 1 mg/day in kidney impairment ESKD: Not recommended
Glipizide, immediate and extended release	eGFR < 50 mL/min/1.73 m^2 (including ESKD): Initiate conservatively at 2.5 mg/day; may cautiously titrate depending on glycemic control up to a maximum of 20 mg/day
Glyburide	Not recommended in CKD
Meglitinides	
Nateglinide	eGFR < 30 mL/min/1.73 m^2: Initiate conservatively at 60 mg with meals
Repaglinide	CrCl ≥ 40 mL/min: No dose adjustment necessary CrCl 20 to < 40 mL/min: Initiate conservatively at 0.5 mg with meals CrCl < 20 mL/min: Not studied
Thiazolidinediones	
Pioglitazone	No dose adjustment necessary; usually not recommended in CKD because of potential for fluid retention
Rosiglitazone	No dose adjustment necessary; usually not recommended in CKD because of potential for fluid retention

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; ESKD = end-stage kidney disease; GLP-1 = glucagon-like peptide-1; HD = hemodialysis; HF = heart failure; HHF = hospitalization for HF; PD = peritoneal dialysis; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes; UACR = urine albumin/creatinine ratio.

Information from: American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2022. Diabetes Care 2022;45:S1-S264; Lipska K, Bailey C, Inzucchi S. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431-7; Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care 2013;36:1067-73; Gianchandani RY, Neupane S, Iyengar JJ, et al. Pathophysiology and management of hypoglycemia in end-stage renal disease patients: a review. Endocr Pract 2017;23:353-62; Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. Diabetes Care 2014;37:2864-83.

of insulin in the kidney accounts for about one-third of the body's ability to catabolize insulin (KDIGO 2013). As kidney function declines, exogenous insulin acts longer and in an unpredictable manner, characterized by recurrent or severe hypoglycemia in some individuals. In addition, anorexia that may present in advanced stages of CKD before starting dialysis will result in dietary changes that may reduce carbohydrate consumption and further affect the patient's

insulin requirements. Thus, the challenge in predicting insulin requirements in various stages of CKD results in the need for frequent evaluation to properly individualize therapy, especially as disease progresses.

Optimization of Blood Pressure Management

Hypertension is the leading cause of CKD, and blood pressure management is essential to slow CKD progression. Although both CKD and hypertension are independent risk factors for CVD, their coexistence further increases the risk of coronary and cerebrovascular events, especially in the presence of albuminuria (USRDS 2021). Thus, optimizing the management of hypertension is paramount to delaying the progression of kidney disease as well as reducing overall CV risk (Retnakaran 2006). Individuals with T1D with concomitant CKD are at highest risk of developing hypertension (Nørgaard 1990).

Blood Pressure Targets

The 2021 KDIGO clinical practice guideline for managing blood pressure in CKD suggests that adults with high blood pressure and CKD be treated to an SBP of less than 120 mm Hg, if tolerated (KDIGO 2021). KDIGO notes that this recommendation does not apply to kidney transplant recipients or those receiving dialysis. This recommendation is derived from findings of the SPRINT, which showed that, in most patients with CKD and high blood pressure, including frail populations and older adults, the CV benefit of targeting an SBP less than 120 mm Hg outweighed the risk of AKI or electrolyte abnormalities (KDIGO 2021; SPRINT Research Group 2015). The SPRINT study excluded individuals with diabetes, making this recommendation less conclusive in patients with diabetes and CKD. The ACCORD trial examined people with diabetes and randomized them to the same SBP targets as in SPRINT (less than 120 mm Hg vs. less than 140 mm Hg); however, this trial excluded those with an SCr greater than 1.5 mg/dL. The ACCORD trial showed no overall CV benefit in the intensive treatment arm, though there was a significant reduction in stroke events (Beddhu 2018; ACCORD Study Group 2010). The KDIGO 2021 guideline committee factored the ACCORD trial data into their decision to target an SBP less than 120 mm Hg; however, they stated that the CV benefits of intensive blood pressure lowering could not be excluded in people with concomitant diabetes and CKD and recommended future randomized control trials in this particular population (KDIGO 2021). The KDIGO guidelines also draw attention to the common perception that blood pressure lowering is kidney protective, which is likely true if the SBP is lowered from greater than 160 mm Hg to less than 140 mm Hg and less conclusive when lowering from less than 140 mm Hg to less than 120 mm Hg. The recommendation to target an SBP of less than 120 mm Hg is based on data showing CVD benefit and survival but not kidney-protective effects (KDIGO 2021).

The American College of Cardiology (ACC)/American Heart Association (AHA) multisociety clinical practice guideline for managing high blood pressure recommends a blood pressure goal of less than 130/80 mm Hg to slow CKD progression (Whelton 2018). The ADA recommends a blood pressure goal of less than 140/80 mm Hg for those with diabetes and hypertension and endorses an individualized approach through shared decision-making to address CV risk, potential adverse effects of antihypertensive therapy, and patient preferences. If an individual has established ASCVD or a 10-year ASCVD risk of 15% or greater, a lower blood pressure goal of less than 130/80 mm Hg may be appropriate (ADA 2022).

Antihypertensive Therapy

Treatment of hypertension with RAS inhibitors has been the standard of care for patients with CKD and diabetes. In individuals with T1D or T2D who have hypertension and established CKD, ACEI or ARB therapy delays the decline in kidney function and progression to ESKD (ADA 2022; Brenner 2001; Lewis 1993). Initiation of an ACEI or ARB is recommended first line for the treatment of high blood pressure in individuals with an eGFR less than 60 mL/minute/1.73 m^2 or those with an eGFR of 60 mL/minute/1.73 m^2 or greater with severely increased albuminuria (greater than 300 mg/g) (ADA 2022).

Many guidelines recommend against combination therapy with an ACEI and ARB because concomitant use has shown no additional CV or kidney benefit, and there is an increased risk of adverse events such as hyperkalemia and AKI (ADA 2022; KDIGO 2022; Whelton 2018). The combination of a direct renin inhibitor and an ACEI or ARB is also contraindicated in the treatment of patients with CKD and high blood pressure because of the worsening risk of CVD and kidney disease (Whelton 2018). If further blood pressure lowering is required after the initiation and titration of an ACEI or ARB to its maximally tolerated dose, an alternative first-line agent for managing hypertension, such as a dihydropyridine calcium channel blocker (CCB) or a thiazide or thiazide-like diuretic, can be considered (ADA 2022; Whelton 2018).

The addition of a dihydropyridine CCB to an ACEI or ARB in patients with hypertension and CKD may be the preferred combination regimen, given the results of the ACCOMPLISH trial (Jamerson 2008). This trial evaluated treatment with the ACEI, benazepril, and either the dihydropyridine CCB, amlodipine, or the thiazide diuretic, hydrochlorothiazide, in patients with hypertension at high CV risk, including those with T2D and CKD. Combination treatment with benazepril/amlodipine significantly reduced the primary composite end point of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization compared with benazepril/hydrochlorothiazide.

The selection of add-on antihypertensive therapy in patients with CKD and high blood pressure considers a variety of patient-specific factors, including current kidney

function, serum electrolyte levels, and an assessment of CV risk. Historically, thiazide diuretics have been avoided or used with caution in individuals with an eGFR below 30 mL/minute/1.73 m^2 because of concerns of decreased efficacy and safety (Agarwal 2021c). Edema associated with CKD has also historically facilitated the transition to loop diuretics in patients with lower eGFRs. A recent 12-week study evaluated the safety and efficacy of chlorthalidone in individuals with hypertension and stage 4 CKD, 76% of whom had diabetes (Agarwal 2021c). In a population with a mean eGFR of 23.2 mL/minute/1.73 m^2, chlorthalidone lowered SBP by 10.5 mm Hg and reduced UACR by 54% from baseline after 12 weeks compared with 4% with placebo. Hypokalemia, increases in SCr, dizziness, hyperuricemia, and hyperglycemia were more common in the chlorthalidone arm.

CVD Risk Reduction

The primary cause of death in patients with CKD is CVD, and the presence of diabetes as a comorbid condition further increases the risk of CV death (USRDS 2021). An eGFR below 60 mL/minute/1.73 m^2 and a UACR greater than 30 mg/g are recognized as independent risk factors for CVD, and the risk is multiplied when both factors are present (Grundy 2019). Current recommendations are to initiate moderate-intensity statin therapy for primary prevention of CVD in adults 40–75 years of age with diabetes and an LDL of at least 70 mg/dL, regardless of the patient's estimated 10-year ASCVD risk (ADA 2022; Grundy 2019). The ADA recommends high-intensity statin therapy be considered in adults with diabetes and several risk factors for CVD, such as CKD, or in patients 50–75 years of age, and in those with established ASCVD (ADA 2022). The ADA recommendations align with those from the combined ACC/AHA guidelines for blood cholesterol, which encourage high-intensity statin therapy in patients with an estimated 10-year ASCVD risk of at least 20% or those with several CVD risk factors, and patients with established CVD (Grundy 2019). Increasing rates of earlier-onset T2D and the subsequent prolonged lifetime exposure to hyperglycemia and atherogenic risk factors (i.e., insulin resistance, hypertension, dyslipidemia) have substantially increased the risk of CV morbidity and mortality in young adults. As a result, the ACC/AHA guidelines for managing blood cholesterol now recommend at least moderate-intensity statin therapy for patients with a prolonged duration of diabetes, defined as at least 10 years for T2D and at least 20 years for T1D, or in the presence of albuminuria (UACR of at least 30 mg/g), eGFR below 60 mL/minute/1.73 m^2, retinopathy, neuropathy, or ankle-brachial index less than 0.9 (Grundy 2019).

Both diabetes and CKD serve as individual risk factors for CVD and are therefore compelling indications for statin therapy in adults with an LDL of at least 70 mg/dL; however, initiation of statin therapy in patients with advanced CKD requiring dialysis is not recommended, given the proposed lower rate of deaths as a result of atherosclerotic causes and the lack of benefit of statin initiation in this patient population (Grundy 2019). Patients with advanced CKD requiring dialysis who were initiated on a statin before starting dialysis may continue to have CV benefit once they are receiving dialysis; therefore, it may be reasonable to continue statin therapy in these patients.

Monitoring

Early changes in kidney function may be detected by an increase in the UACR before the eGFR decreases (ADA 2022). For individuals with a UACR of at least 300 mg/g, a reduction of 30% or greater in UACR is recommended to slow the progression of CKD and CVD. Medications with proven kidney benefit should be titrated to the maximally tolerated dose to optimize the reduction in UACR. Blood pressure should be assessed and managed, if indicated, at each clinic visit to reduce or slow CKD progression. Patients receiving ACEIs, ARBs, or MRAs should have serum potassium and SCr measured within 2–4 weeks after initiation or titration of these medications, or within 1–2 weeks if at risk of hyperkalemia, and periodically thereafter, especially if the eGFR is below 60 mL/minute/1.73 m^2. The ADA and KDIGO guidelines recommend against discontinuing RAS inhibitors for minor increases in SCr (less than 30%) in the absence of volume depletion and recommend managing hyperkalemia with measures to reduce serum potassium concentrations (e.g., dietary potassium restriction, removing other medications associated with hyperkalemia, initiating loop diuretic therapy or newer oral potassium binders [e.g., sodium zirconium cyclosilicate, patiromer]) rather than discontinuing the RAS inhibitor.

The risk of complications of CKD, such as elevated blood pressure, volume overload, electrolyte abnormalities, anemia, and metabolic bone disease, increases in those with stage 3 CKD or greater. Laboratory evaluation of serum electrolytes, hemoglobin, and iron stores, if indicated, is recommended every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as clinically necessary to evaluate symptoms or changes in medication therapy (ADA 2022).

MANAGEMENT OF ESKD

Diabetes is the primary cause of ESKD, accounting for 38.6% of cases (CDC 2020). Once an individual with diabetes reaches stage 5 CKD, options are KRT as either maintenance dialysis or transplantation. Two types of maintenance dialysis are available for individuals with ESKD: hemodialysis (HD) and peritoneal dialysis (PD), which includes continuous ambulatory PD and continuous cyclic PD. Peritoneal dialysis is less commonly used because of the increased risk of infection and less efficient clearance per unit of time (Liu 2021). Both HD and PD have differing effects on blood glucose, and individuals with diabetes will require more frequent follow-ups to determine diabetes medication requirements (Boyle 2015). In

Patient Care Scenario

A 67-year-old woman presents to the clinic for a follow-up for chronic disease management. Her medical history is significant for resistant hypertension, obesity, T2D, coronary artery disease (history of MI 2 years ago with no additional episodes of acute coronary syndrome or revascularization), and CKD. Her current medications include metformin extended release 2000 mg daily, rosuvastatin 40 mg daily, losartan 100 mg daily, carvedilol 25 mg twice daily, spironolactone 25 mg daily, amlodipine 10 mg daily, chlorthalidone 25 mg daily, and aspirin 81 mg daily. Her blood pressure in the clinic today is 134/80 mm Hg (132/80 mm Hg on repeat) and heart rate is 78 beats/minute. Her most recent A1C was 8.5%, her BMI is 41 kg/m^2, and her laboratory values include eGFR 38 mL/minute/1.73 m^2, SCr 1.5 mg/dL, and UACR 550 mg/g.

ANSWER

The first step is to assess the appropriateness and safety of the patient's medication therapy. Her eGFR is between 30 and 44 mL/minute/1.73 m^2, and all of her medications are dose adjusted appropriately for her kidney function except for metformin. Metformin may be continued because she is on an established regimen; however, it should be reduced to a maximum daily dose of 1000 mg. Because the patient has CKD with severely increased albuminuria and a history of CVD, it would be appropriate to initiate an SGLT2 inhibitor with proven CV and kidney benefit, such as empagliflozin 10 mg daily or canagliflozin 100 mg daily. Her A1C is 8.5%, and because SGLT2 inhibitors are less efficacious in their blood glucose–lowering effect in declining kidney function, she might also benefit from the addition of a GLP-1 receptor agonist with proven CV and kidney benefit, such as liraglutide, dulaglutide, or subcutaneous semaglutide, with preference given to the once-weekly formulations to reduce the number of total weekly injections. Dulaglutide 0.75 mg subcutaneously or semaglutide 0.25 mg subcutaneously weekly should be initiated and titrated slowly, depending on response, to prevent unwanted GI adverse effects. Addition of the GLP-1 receptor agonist will also facilitate weight loss, which may help slow the progression of her CKD. Once the SGLT2 inhibitor and GLP-1 receptor agonist are titrated to maximally tolerated doses, the addition of finerenone may be considered if she continues to have residual albuminuria. She currently takes spironolactone for her resistant hypertension. If her blood pressure improves secondary to weight loss from the GLP-1 receptor agonist and with the addition of the SGLT2 inhibitor, she may not require additional blood pressure lowering with spironolactone, and finerenone may be considered instead. In clinical trials, finerenone only lowered blood pressure by about 3 mm Hg and may not be as effective as spironolactone in resistant hypertension.

1. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2022. Diabetes Care 2022;45:S1-S264.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2020;98:S1-S115.
3. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474-84.

addition, A1C values may be inaccurate in patients with ESKD, complicating the assessment of blood glucose management over time.

Treatment Considerations in HD

Individuals with T2D and ESKD have increased insulin resistance, reduced gluconeogenesis, and decreased rates of insulin catabolism (Williams 2014). Dialysis may improve insulin sensitivity, clearance, and secretion because of improvements in uremia, acidosis, and phosphate metabolism (Boyle 2015). Hemodialysis may also clear glucoregulatory hormones such as insulin, C-peptide, and glucagon; thus, insulin requirements may fluctuate depending on the net balance between tissue sensitivity and insulin clearance, and glucose metabolism (Gregory 2019). Although insulin is the preferred antihyperglycemic therapy for patients receiving HD, it is difficult to predict insulin requirements. Patient-specific responses to HD require more frequent follow-ups for antihyperglycemic dose adjustments, especially during HD initiation. Changes in appetite, decreased activity, and emotional stress on dialysis days also alter glucose concentrations and medication requirements compared with nondialysis days. In addition, glucose is a smaller molecule that easily passes into the dialysate, whereas insulin formulations are large proteins and not filtered. Insulin requirements may decrease with the initiation of HD, and more frequent glucose monitoring may be required during this time (KDIGO 2020). Inquiring about individual glycemic patterns, dietary habits, and activity levels on dialysis days compared with nondialysis days will help elucidate the fluctuations in blood glucose concentrations.

There are no specific evidence-based recommendations for managing insulin in patients with diabetes receiving HD; however, studies have shown that blood glucose concentrations are significantly lower on dialysis days than on nondialysis days because of improved insulin sensitivity (Blaine 2022; Gregory 2019). This variation results in differing insulin requirements on dialysis versus nondialysis days. Insulin detemir and degludec bind to serum albumin, which may lead to unpredictable absorption in those with low serum albumin concentrations (Blaine 2022). Despite this concern, a head-to-head study comparing insulin detemir with insulin glargine

in individuals with T2D undergoing HD showed that insulin detemir had lower glycemic variability and proinflammatory profiles than insulin glargine (Savu 2016). In a recent systematic literature review of insulin dose adjustments, the most common recommendation regarding HD was to reduce the basal insulin dose by up to 25% on HD days to prevent hypoglycemia; however, the literature has shown reductions of 25%–50% (Blaine 2022; Gianchandani 2017).

There is no preferred recommendation regarding mealtime insulin therapy; however, similar to non-HD patients, rapid-acting insulins may be preferred because of timing of administration and pharmacokinetic profile compared with short-acting insulins (Gianchandani 2017; Boyle 2015). Reduced GFR results in increased half-life and serum concentrations of regular human insulin, which may increase the likelihood of a hypoglycemic event compared with rapid-acting insulin (Blaine 2022; Gregory 2019; Boyle 2015). For patients with variable mealtime schedules and a reduction in insulin requirements, rapid-acting insulin may be preferred to basal insulin to prevent hypoglycemia (Blaine 2022). If an individual is having frequent hypoglycemic episodes during dialysis, it may be prudent to hold the mealtime insulin dose on the morning of dialysis.

Treatment Considerations in PD

Peritoneal dialysis allows for the removal of uremic toxins daily and usually does not require as stringent dietary or fluid restrictions as HD. Typically, dextrose or a nonabsorbable carbohydrate, such as icodextrin, is included to increase the hypertonicity of the dialysate because PD relies on hypertonicity to drive solute removal, rather than concentration gradients as in HD (Liu 2021). Despite increased absorption of glucose from dextrose-containing solutions, intraperitoneal administration of insulin by adding it to the dialysate has been proposed to assist with glycemic management (Quellhorst 2002). Such administration allows for continuous delivery of insulin into the portal circulation. When insulin is instilled into the abdominal cavity with the dialysate, there may be some loss of insulin activity because of delayed absorption secondary to dilution, or through its adsorption to the dialysate bag; therefore, supplemental subcutaneous insulin may still be required. Intraperitoneal insulin can also be an additional source of bacterial contamination in the dialysate during continuous ambulatory PD, resulting in peritonitis and increased total insulin requirements. These limitations coupled with the increasing costs of insulin therapy may limit the usefulness of intraperitoneal administration of insulin.

The most important factor when determining how to optimize diabetes medication use in individuals with diabetes receiving PD is the type of dialysate solution used. For those using dextrose-based dialysates, it has been recommended to empirically increase the basal insulin dose by 4 units per day for each 2.5% dextrose exchange (Blaine 2022). In patients with diabetes, an icodextrin solution (7.5%) may be substituted for traditional dextrose-containing dialysate. Icodextrin has been shown to have minimal impact on blood glucose, decreased insulin resistance, and less potential for weight gain (Liu 2021). If icodextrin or another non–dextrose-based

Practice Points

- **CKD is diagnosed on the basis of the presence of persistent albuminuria (defined as two of three spot UACRs of at least 30 mg/g within a 3- to 6-month period) and/or an eGFR less than 60 mL/minute/1.73 m^2.**
- **Patients with diabetes should be screened for CKD by assessing eGFR and UACR at least annually, starting 5 years after diagnosis for patients with T1D and at diagnosis for patients with T2D.**
- **Once diagnosed, CKD should be staged using GFR and degree of albuminuria, and disease surveillance should be continued by measuring eGFR and UACR at least twice yearly.**
- **Nonpharmacologic therapies for CKD are aimed at mitigating modifiable risk factors, such as engaging in physical activity; maintaining a healthy weight; following a healthy diet; smoking cessation, if applicable; and avoiding nephrotoxic agents.**
- **An ACEI or ARB is recommended as first-line antihypertensive therapy for patients with diabetes, high blood pressure, and CKD.**
- **SGLT2 inhibitors should be considered for all patients with T2D, CKD, and an eGFR of at least 20 mL/minute/1.73 m^2 to reduce CKD progression and CV events, unless contraindicated or not tolerated. Selection of an agent with documented kidney or CV benefits should be prioritized.**
- **Initiation of metformin should be considered in most patients with T2D and CKD with an eGFR of 45 mL/minute/1.73 m^2 or greater who need additional glucose lowering after SGLT2 inhibitor therapy and should be dose reduced to a maximum of 1000 mg/day in people with an eGFR of 30–44 mL/minute/1.73 m^2.**
- **Long-acting GLP-1 receptor agonists with proven CV benefit should be considered in patients with T2D and CKD who are not achieving glycemic targets despite optimization of SGLT2 inhibitor and metformin therapy, or in patients unable to use or tolerate these therapies.**
- **Finerenone should be considered in patients with T2D, eGFR of at least 25 mL/minute/1.73 m^2, normal serum potassium concentration, and albuminuria despite maximally tolerated ACEI or ARB and SGLT2 inhibitor therapy.**
- **Blood pressure and glycemic targets should be individualized in patients with diabetes and CKD, considering the most recent evidence and patient-specific goals.**
- **Statins should be initiated for CV risk reduction in patients with diabetes and CKD not treated with dialysis. Patients with diabetes and dialysis-treated CKD should not be initiated on a statin; however, statin therapy may be continued if it was initiated before dialysis.**
- **More frequent follow-ups will be required for patients with diabetes and dialysis-treated CKD to safely and effectively manage glucose concentrations because of the variable effects of HD and PD on blood glucose concentrations and the inaccuracies of A1C in ESKD.**

dialysate is used, many studies recommend decreasing the total daily dose of insulin by 50% at initiation of dialysis to prevent hypoglycemia (Blaine 2022).

Because icodextrin is a glucose polymer and produces maltose upon metabolism, there is a potentially harmful effect when glucometers requiring glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) cofactor-based test strips are used (Williams 2014). The GDH-PQQ cofactor-based test strips use a method that cannot distinguish between glucose and non-glucose sugars, including maltose, xylose, and galactose. As a result, these non-glucose sugars may be read by such test strips as a falsely elevated serum glucose concentration, thereby masking a hypoglycemic episode or causing inappropriate insulin management resulting in hypoglycemia. For patients receiving icodextrin dialysate solution, clinicians should avoid recommending a home glucose monitoring system that uses GDH-PQQ cofactor-based test strips.

CONCLUSION

The societal burden of CKD will continue to grow in parallel with the increased prevalence of diabetes. Recent advances in therapies for patients with diabetes and CKD together with pivotal CV and kidney outcomes trials have resulted in major updates to the recommendations for managing these comorbid conditions. Clinical pharmacists play a key role in optimizing medication therapy in this population. Patients with diabetes and CKD should be counseled on risk factor mitigation and appropriate lifestyle modifications, and medications should be selected and dosed appropriately according to kidney function, comorbidities, and patient preferences. Pharmacists are well positioned to improve both safe medication use and care in patients with diabetes and CKD.

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Self-Assessment Questions

1. A 15-year-old female adolescent presents with a chief concern of new-onset polyuria, polydipsia, and polyphagia over the past few weeks. Her A1C today is 8.6%. The patient is diagnosed with type 1 diabetes (T1D). Which one of the following is best to recommend to screen for chronic kidney disease (CKD) in this patient?

   A. Timed 24-hour urine collection today
   B. Spot urine albumin/creatinine ratio (UACR) today
   C. Timed 24-hour urine collection in 5 years
   D. Spot UACR in 5 years

Questions 2–4 pertain to the following case.

W.A., a 41-year-old non-Hispanic white man, has a medical history of type 2 diabetes (T2D) (diagnosed 6 months ago), hypertension, and hyperlipidemia. W.A.'s average blood pressure in the clinic today is 122/68 mm Hg and BMI is 24 kg/m^2. His laboratory values 1 week ago were A1C 6.5%, eGFR 89 mL/minute/1.73 m^2, and UACR 7 mg/g. His home medications include metformin 500 mg twice daily, subcutaneous semaglutide 1 mg weekly, amlodipine 10 mg daily, and rosuvastatin 10 mg daily. He currently smokes 2 pack/day. W.A. reports that his father was recently initiated on chronic hemodialysis (HD) and expresses that his primary concern today is his risk of developing CKD.

2. Which one of the following puts W.A. at greatest risk for developing CKD?

   A. Age
   B. Sex
   C. Family history
   D. Race and ethnicity

3. Which one of the following is best to recommend to reduce W.A.'s risk of developing CKD?

   A. Optimize blood pressure management with the addition of lisinopril 5 mg daily, titrated to the maximally tolerated dose.
   B. Optimize glucose management with the addition of a sodium-glucose cotransporter-2 (SGLT2) inhibitor at a dose adjusted for kidney function.
   C. Facilitate weight management through calorie restriction and increased physical activity.
   D. Implement smoking cessation with the use of combination nicotine replacement therapy.

4. One year later, W.A. returns to the clinic with polyuria, polydipsia, and dry mouth. He reports changing his insurance coverage to a high-deductible commercial plan and has been unable to afford his semaglutide prescription. His laboratory values today are A1C 10.6%, eGFR 69 mL/minute/1.73 m^2, and UACR 367 mg/g. Which one of the following best evaluates W.A.'s kidney laboratory values?

   A. CKD stage G2, A2
   B. CKD stage G2, A3
   C. CKD stage G3a, A3
   D. Unable to make a diagnosis

Questions 5 and 6 pertain to the following case.

T.S., a 77-year-old man, has a medical history of hypertension, T2D, and transient ischemic attack (2 years ago). T.S.'s most recent A1C from 2 weeks ago was 6.7%. His average blood pressure in the clinic today is 132/78 mm Hg. All of his laboratory values are within normal limits except for SCr 2.5 mg/dL (eGFR 27 mL/minute/1.73 m^2) and UACR 435 mg/g. His home drugs include metformin 1000 mg twice daily, sitagliptin 50 mg daily, losartan 100 mg daily, chlorthalidone 25 mg daily, atorvastatin 80 mg daily, and aspirin 81 mg daily.

5. Which one of the following is best to recommend for T.S.?

   A. Decrease both metformin and sitagliptin.
   B. Decrease metformin and discontinue sitagliptin.
   C. Discontinue metformin and decrease sitagliptin.
   D. Discontinue both metformin and sitagliptin.

6. Which one of the following antihyperglycemic agents is best to recommend initiating for T.S.?

   A. Exenatide ER 2 mg once weekly
   B. Dapagliflozin 10 mg once daily
   C. Dulaglutide 0.75 mg once weekly
   D. Canagliflozin 100 mg once daily

7. A 79-year-old woman has a medical history of T2D, CKD, hypertension, and dyslipidemia. Her home medications include canagliflozin 100 mg daily, irbesartan 300 mg daily, amlodipine 10 mg daily, and atorvastatin 40 mg daily. Her average blood pressure in the clinic today is 122/78 mm Hg and heart rate is 79 beats/minute; her most recent laboratory values are A1C 8.2%, eGFR 28 mL/minute/1.73 m^2, UACR 223 mg/g, and serum potassium 5.0 mEq/L. She has been unable to tolerate glucagon-like peptide-1 (GLP-1) receptor agonists in the past because of GI adverse effects, and she is very concerned about hypoglycemia because she lives alone. Which one of the following is best to recommend for this patient?

   A. Sitagliptin 25 mg daily
   B. Glipizide 5 mg daily
   C. Metformin 500 mg daily
   D. Finerenone 10 mg daily

8. A 59-year-old man has a medical history of T2D, hypertension, CKD, and myocardial infarction (MI) 6 months ago. His home medications include saxagliptin 2.5 mg daily, carvedilol 25 mg twice daily, lisinopril 20 mg daily, atorvastatin 80 mg daily, and aspirin 81 mg daily. His most recent A1C from 2 weeks ago was 7.5%. His laboratory values are within normal limits, except for SCr 2.3 mg/dL and eGFR 32 mL/minute/1.73 m^2. His physician would like to change his antihyperglycemic regimen to reduce his risk of kidney disease progression and future cardiovascular (CV) events. Which one of the following is best to recommend for this patient?

   A. Discontinue saxagliptin and initiate liraglutide.
   B. Discontinue saxagliptin and initiate canagliflozin.
   C. Continue saxagliptin and initiate exenatide extended release.
   D. Continue saxagliptin and initiate ertugliflozin.

9. A 78-year-old woman has a medical history of hypertension, T2D, and acute MI (after percutaneous coronary intervention 2 years ago). She currently takes metformin 500 mg twice daily, empagliflozin 25 mg daily, rosuvastatin 40 mg daily, aspirin 81 mg daily, hydrochlorothiazide 25 mg daily, lisinopril 40 mg daily, amlodipine 10 mg daily, and metoprolol succinate 50 mg daily. She reports that she misses a dose of each of her medications no more than once per month. Her average blood pressure is 148/78 mm Hg and heart rate is 61 beats/minute in the clinic today. Her laboratory values show A1C 7.2%; eGFR 44 mL/minute/1.73 m^2, decreased from 52 mL/minute/1.73 m^2 4 months ago; UACR 12 mg/g; and serum potassium 3.5 mEq/L. Which one of the following is best to recommend to reduce this patient's risk of CKD progression?

   A. Increase metformin to 1000 mg twice daily.
   B. Increase metoprolol succinate to 100 mg daily.
   C. Initiate spironolactone 12.5 mg daily.
   D. Initiate finerenone 10 mg daily.

10. A 54-year-old man has a medical history of T2D, hypertension, and CKD. His home drugs include metformin 500 mg twice daily, canagliflozin 100 mg daily, dulaglutide 4.5 mg subcutaneously weekly, valsartan 320 mg daily, amlodipine 5 mg daily, and rosuvastatin 20 mg daily. His blood pressure is 110/66 mm Hg, relatively unchanged from previous visits (114/68 mm Hg and 116/74 mm Hg), and his most recent laboratory values include A1C 6.8%, eGFR 53 mL/minute/1.73 m^2, UACR 562 mg/g, and serum potassium 3.9 mEq/L. Finerenone is initiated at 10 mg daily to address his residual risk of CKD progression and CV events. His basic metabolic panel at the 4-week follow-up includes an eGFR of 35 mL/minute/1.73 m^2 and a serum potassium of 4.6 mEq/L. Which one of the following is best to recommend regarding the use of finerenone at follow-up for this patient?

    A. Increase to 20 mg daily
    B. Continue at 10 mg daily
    C. Decrease to 5 mg daily
    D. Discontinue finerenone

11. The DAPA-CKD trial in patients with albuminuric CKD with and without diabetes found that the primary composite outcome of a sustained 50% or greater decrease in eGFR from baseline, end-stage kidney disease (ESKD), or death from kidney or CV causes occurred in 9.2% of participants in the dapagliflozin group and 14.5% in the placebo group (HR 0.61, 0.51–0.72). Results for the primary outcome were driven by a reduction in individual composite components, a sustained 50% or greater decrease in eGFR from baseline (5.2% vs. 9.3%; HR 0.53, 0.42–0.67), and ESKD (5.1% vs. 7.5%; HR 0.64, 0.50–0.82). Key secondary outcomes included a composite of CV death and hospitalization for HF (HHF) (4.6% vs. 6.4%; HR 0.71, 0.55–0.92), a kidney-specific composite end point (6.6% vs. 11.3%; HR 0.56, 0.45–0.68), and all-cause mortality (4.7% vs. 6.8%; HR 0.69, 0.53–0.88). Which one of the following best evaluates the DAPA-CKD trial results?

    A. Dapagliflozin decreased new-onset ESKD with a number needed to treat (NNT) of 19.
    B. Dapagliflozin reduced the kidney-specific composite end point by 58% relative to placebo.
    C. Dapagliflozin decreased all-cause mortality with a NNT of 48.
    D. Dapagliflozin reduced the primary composite end point by 63% relative to placebo.

12. A 33-year-old man has a medical history of T2D, hypertension, hyperlipidemia, HFrEF (stage C, NYHA class III, left ventricular ejection fraction 30%–35% 5 months ago), and ST-segment elevation MI (after percutaneous coronary intervention 2 years ago). He currently takes metformin 1000 mg twice daily, empagliflozin 25 mg daily, oral semaglutide 14 mg daily, atorvastatin 80 mg daily, carvedilol 25 mg twice daily, lisinopril 20 mg daily, spironolactone 25 mg daily, and aspirin 81 mg daily. The patient confirms he administers semaglutide with no more than 120 mL of water 30 minutes before his first meal, other beverages, or medications. He adamantly declines the use of injectable therapies because of a fear of needles. Today's laboratory values are A1C 8.2%, eGFR 48 mL/minute/1.73 m^2, and UACR 124 mg/g. Which one of the following is best to recommend for this patient?

    A. Insulin glargine 10 units daily
    B. Pioglitazone 15 mg daily
    C. Glipizide 2.5 mg daily
    D. Linagliptin 5 mg daily

13. A 56-year-old Black woman has a medical history of T2D, CKD, and hypertension. Her home drugs include metformin 500 mg twice daily, chlorthalidone 25 mg daily, and rosuvastatin 20 mg daily. Her most recent A1C was 6.5%, and her laboratory values are eGFR 35 mL/minute/1.73 m^2, SCr 1.7 mg/dL, K 4.2 mEq/L, and UACR 550 mg/g. Today, her average blood pressure in the clinic is 146/82 mm Hg and heart rate is 68 beats/minute. Her fasting blood glucose concentrations range from 90 to 108 mg/dL before breakfast and from 121 to 149 mg/dL 2 hours after dinner. Which one of the following is best to recommend for this patient?

    A. Lisinopril 5 mg daily
    B. Finerenone 10 mg daily
    C. Dapagliflozin 10 mg daily
    D. Amlodipine 5 mg daily

14. An 85-year-old woman was diagnosed with T2D 2 months ago, for which her primary care physician recommended lifestyle modifications and initiated metformin 500 mg twice daily. She has a medical history of stage 4 CKD (eGFR 20 mL/minute/1.73 m^2) and stage III breast cancer. Her most recent A1C 2 months ago was 8.2%. Which one of the following is best to recommend for this patient?

    A. Continue current therapy.
    B. Continue metformin and add dapagliflozin 5 mg daily.
    C. Discontinue metformin and add linagliptin 5 mg daily.
    D. Discontinue metformin and add exenatide extended release 2 mg subcutaneously weekly.

15. A 50-year-old man takes insulin glargine 45 units subcutaneously once daily and insulin lispro 16 units subcutaneously three times daily with meals for T1D management. He will start HD next week, and his physician asks for your recommendation regarding insulin adjustments. Which one of the following is best to recommend for this patient's insulin dosing on dialysis days?

    A. Hold insulin lispro.
    B. Hold insulin glargine.
    C. Decrease insulin glargine to 35 units.
    D. Decrease insulin lispro to 14 units.