11. Chronic Kidney Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*

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*American Diabetes Association Professional Practice Committee**

31 May 2022. Sections 10 and 11 have been updated to include evidence from trials of medication effects in patients with type 2 diabetes on heart failure, cardiovascular, and chronic kidney disease outcomes, including EMPEROR-Preserved, PRESERVED-HF, FIDELIO-DKD, and FIGARO-DKD, and to remove information associated with the discontinued trial PROMINENT.

The changes are described in detail in: Addendum. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45(Suppl. 1):S144–S174 (https://doi.org/10.2337/dc22-ad08).
And in: Addendum. 11. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes—2022: Diabetes Care 2022;45(Suppl. 1):S175–S184 (https://doi.org/10.2337/dc22-ad08a).

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc22-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc22-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents" (https://doi.org/10.2337/dc22-S014).

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1a At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be assessed in patients with type 1 diabetes with duration of ≥5 years and in all patients with type 2 diabetes regardless of treatment. **B**

11.1b Patients with diabetes and urinary albumin ≥300 mg/g creatinine and/or an estimated glomerular filtration rate 30–60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy. **B**

Treatment

Recommendations

11.2 Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**

11.3a For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce chronic kidney disease progression and cardiovascular events. **A**

11.3b For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc22-SPPC.*

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with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urine albumin ranging from normal to 200 mg/g creatinine. **B**

11.3c In patients with chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression or are unable to use a sodium–glucose cotransporter 2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended to reduce chronic kidney disease progression and cardiovascular events (**Table 9.2**). **A**

11.3d In patients with chronic kidney disease who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression. **B**

11.4 Optimization of blood pressure control and reduction in blood pressure variability to reduce the risk or slow the progression of chronic kidney disease is recommended. **A**

11.5 Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. **A**

11.6 For people with nondialysis-dependent stage 3 or higher chronic kidney disease, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). **A** For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients. **B**

11.7 In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) **B** and is strongly recommended for those with urinary albumin-to-creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. **A**

11.8 Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. **B**

11.9 An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. **A**

11.10 Patients should be referred for evaluation by a nephrologist if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. **A**

11.11 Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **A**

EPIDEMIOLOGY OF DIABETES AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). In this section, the focus is on CKD attributed to diabetes (diabetic kidney disease), which occurs in 20–40% of patients with diabetes (1,3–5). Diabetic kidney disease typically develops after diabetes duration of 10 years in type 1 diabetes but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in the U.S. (6). In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (7).

ASSESSMENT OF ALBUMINURIA AND ESTIMATED GLOMERULAR FILTRATION RATE

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine (Cr) is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (8). Thus, to be useful for patient screening, semiquantitative or qualitative (dipstick) screening tests should be >85% positive in those with moderately increased albuminuria (≥30 mg/g) and be confirmed by albumin-to-creatinine values in an accredited laboratory (9,10). Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal UACR is defined as <30 mg/g Cr, and high urinary albumin excretion is defined as ≥30 mg/g Cr. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (7,11,12). Furthermore, because of high biological variability of >20% between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have high or very high albuminuria (1,2,13,14). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (15).

Traditionally, eGFR is calculated from serum creatinine using a validated formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is preferred (2). eGFR is routinely reported by laboratories with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently <60 mL/min/1.73 m^2 in concert with a urine albumin value of >30 mg/g creatinine is considered abnormal, though optimal

thresholds for clinical diagnosis are debated in older adults over age 70 years (2,16). Historically, a correction factor for muscle mass was included in a modified equation for African Americans; however, due to various issues with inequities, it was decided to revamp the equation such that it applies to all (116). Hence, a committee was convened, resulting in the recommendation for immediate implementation of the CKD-EPI creatinine equation refit without the race variable in all laboratories in the U.S. Additionally, increased use of cystatin C, especially to confirm estimated GFR in adults who are at risk for or have chronic kidney disease, because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.

DIAGNOSIS OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of diabetic kidney diease may be present at diagnosis or without retinopathy in type 2 diabetes, and reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (3,4,17,18).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for patients with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (19).

STAGING OF CHRONIC KIDNEY DISEASE

Stages 1–2 CKD have been defined by evidence of high albuminuria with eGFR ≥60 mL/min/1.73 m^2, while stages 3–5

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 11.1—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria are depicted. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state as well as the likelihood of impacting a change in management for any individual patient must be taken into account. "Refer" indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti et al. (115).

CKD have been defined by progressively lower ranges of eGFR (20) (**Fig. 11.1**). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (7). Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex and does not translate directly to treatment decisions (2). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. This is also important since eGFR levels are essential to modify drug dosage or restrictions of use (**Fig 11.1**) (21,22). The degree of albuminuria should influence choice of antihypertensive (see Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010) or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (23).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is diagnosed by a 50% or greater sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (24,25). People with diabetes are at higher risk of AKI than those without diabetes (26). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease (27) or high cardiovascular disease risk with normal kidney function (28–30). It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) fail to increase the risk of AKI when used to slow kidney disease progression (31). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (32).

Small elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (33). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrates that those randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (34–37). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (36). Accordingly, ACE inhibitors and ARBs should not be discontinued for minor increases in serum creatinine ($<$30%), in the absence of volume depletion.

Lastly, it should be noted that ACE inhibitors and ARBs are commonly not dosed at maximally tolerated doses because of fear that serum creatinine will rise. As noted above, this is an error. Note that in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximally tolerated doses were used—not very low doses that do not provide benefit. Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR $<$30 mL/min/1.73 m^2 (37). Additionally, when increases in serum creatinine are up to 30% and do not have associated hyperkalemia, RAS blockade should be continued (35,38).

SURVEILLANCE

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored in patients treated with diuretics because these medications can cause hypokalemia, which is associated with cardiovascular risk and mortality (39–41). For patients with eGFR $<$60 mL/min/1.73 m^2, those receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically. Additionally, people with this lower range of eGFR should have appropriate medication dosing verified, exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and potential CKD complications should be evaluated (**Table 11.1**).

There is a clear need for annual quantitative assessment of albumin excretion. This is especially true after diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure control. Early changes in kidney function may be detected by increases in albuminuria before changes in eGFR (42) and this also significantly affects cardiovascular risk. Moreover, an initial reduction of $>$30% below where it was initially measured, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the U.S. Food and Drug Administration (FDA) (10). Continued surveillance can assess both response to therapy and disease progression and may aid in assessing adherence to ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria to levels $<$300 mg/g Cr or by $>$30% from their baseline has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to maximize reduction in UACR. Data from post hoc analyses demonstrate less benefit on cardiorenal outcomes at half doses of RAS blockade

Table 11.1—Selected complications of chronic kidney disease

Complication	Medical and laboratory evaluation
Elevated blood pressure >140/90 mmHg	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolyte
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated 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 indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

(43). In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (44,45).

The prevalence of CKD complications correlates with eGFR (41). When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 11.1**). Early vaccination against hepatitis B virus is indicated in patients likely to progress to ESRD (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," https://doi.org/10.2337/dc22-S004, for further information on immunization).

INTERVENTIONS

Nutrition

For people with nondialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline (46).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk (47,48), and restriction of dietary potassium may be necessary to control serum potassium concentration (26,39–41). These interventions may be most important for patients with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients (49). Recommendations for dietary sodium and potassium intake should be individualized on the basis of comorbid conditions, medication use, blood pressure, and laboratory data.

Glycemic Targets

Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 diabetes (50,51) and type 2 diabetes (1,52–57). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that glycemic control itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C targets (see **Table 6.2**).

The presence of CKD affects the risks and benefits of intensive glycemic control and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline (58,59). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (55,60,61). Therefore, in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,62).

Direct Renal Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (29,63–66). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by >50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity (67–69). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (70–73). Renal effects should be considered when selecting antihyperglycemia agents (see Section 9, "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc22-S009).

Selection of Glucose-Lowering Medications for Patients With Chronic Kidney Disease

For patients with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate high risks of CKD progression, CVD, and hypoglycemia (74,75). Drug dosing may require modification with eGFR <60 mL/min/1.73 m^2 (1).

The FDA revised its guidance for the use of metformin in CKD in 2016 (76), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of patients with

kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2; eGFR should be monitored while taking metformin; the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m^2 (77,78); metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m^2; and metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m^2. Within these constraints, metformin may be considered as initial treatment of glycemic control for all patients with type 2 diabetes, including those with early CKD.

SGLT2 inhibitors should be given to all patients with stage 3 CKD or higher and type 2 diabetes regardless of glycemic control, as they slow CKD progression and reduce heart failure risk independent of glycemic control (79). GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression (80–82).

A number of large cardiovascular outcomes trials in patients with type 2 diabetes at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (65,70,73,83). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g Cr, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESRD, or death from ESRD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g Cr, doubling of serum creatinine, or ESRD) by 36% (each $P < 0.01$).

These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of renal effects as secondary outcomes. However, all of these trials included large numbers of people with stage 3a (eGFR 45–59 mL/min/1.73 m^2) kidney disease. In addition, subgroup analyses of CANVAS and LEADER suggested that the renal benefits of canagliflozin and liraglutide were as great or greater for participants with CKD at baseline (30,72) and in CANVAS were similar for participants with or without atherosclerotic cardiovascular disease (ASCVD) at baseline (84).

Some large clinical trials of SGLT2 inhibitors focused on patients with advanced CKD, and assessment of primary renal outcomes are completed or ongoing. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300 mg/g Cr, and mean eGFR 56 mL/min/1.73 m^2 with a mean albuminuria level of over 900 mg/day, had a primary composite end point of ESRD, doubling of serum creatinine, or renal or cardiovascular death (27,85). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESRD over control (27). Additionally, the development of the primary end point, which included chronic dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the patients (27). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (27,86,87).

A second trial in advanced diabetic kidney disease was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study (88). This trial examined a cohort similar to that in CREDENCE; however, the end points were a little different. The primary outcome was time to the first occurrence of any of the components of the composite including ≥50% sustained decline in eGFR or reaching ESRD or cardiovascular death or renal death. Secondary outcome measures included time to the first occurrence of any of the components of the composite kidney outcome (≥50% sustained decline in eGFR or reaching ESRD or renal death), time to the first occurrence of either of the components of the cardiovascular composite (cardiovascular death or hospitalization for heart failure), and, lastly, time to death from any cause. The trial had 4,304 participants with a mean eGFR at baseline of 43.1 ± 12.4 mL/min/1.73 m^2, the median UACR was 949 mg/g, and 67.5% of participants had type 2 diabetes. There was a significant benefit by dapagliflozin for the primary end point (hazard ratio 0.61 [95% CI 0.51–0.72]; $P < 0.001$) (88).

The hazard ratio for the kidney composite of a sustained decline in eGFR of ≥50%, ESRD, or death from renal causes was 0.56 (95% CI 0.45–0.68; $P < 0.001$). The hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI 0.55–0.92; $P = 0.009$). Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P < 0.004$).

In addition to renal effects, while SGLT2 inhibitors demonstrated reduced risk of heart failure hospitalizations, some also demonstrated cardiovascular risk reduction. GLP-1 RAs clearly demonstrated cardiovascular benefits. Namely, in EMPA-REG OUTCOME, CANVAS, DECLARE, LEADER, and SUSTAIN-6, empagliflozin, canagliflozin, dapagliflozin, liraglutide, and semaglutide, respectively, each reduced cardiovascular events, evaluated as primary outcomes, compared with placebo (see Section 10, "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc22-S010, for further discussion). While the glucose-lowering effects

of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen down to eGFR levels of 25 mL/min/1.73 m^2 with no significant change in glucose (27,29,50,58,62,73,83,88,89). Most participants with CKD in these trials also had diagnosed ASCVD at baseline, although ~28% of CANVAS participants with CKD did not have diagnosed ASCVD (30).

Based on evidence from the CREDENCE trial and secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardiovascular and renal events are reduced with SGLT2 inhibitor use in patients down to an eGFR of 30 mL/min/1.73 m^2, independent of glucose-lowering effects (86,87).

While there is clear cardiovascular risk reduction associated with GLP-1 RA use in patients with type 2 diabetes and CKD, the proof of benefit on renal outcome will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (90). As noted above, published data address a limited group of CKD patients, mostly with coexisting ASCVD. Renal events have been examined, however, as both primary and secondary outcomes in published large trials. Also, adverse event profiles of these agents must be considered. Please refer to **Table 9.2** for drug-specific factors, including adverse event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in CKD patients are ongoing and will be reported in the next few years.

For patients with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors may be more useful for patients at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.3**) because they appear to have large beneficial effects on CKD incidence. The 2022 guideline recommended use of SGLT2 inhibitors empagliflozin and dapagliflozin with eGFR 25–45 mL/min/1.73 m^2 for kidney/heart failure outcomes (as approved by the FDA). Empagliflozin can be started with eGFR >30 mL/min/1.73 m^2 (though pivotal trials for each included participants with eGFR ≥30 mL/min/1.73 m^2 and demonstrated benefit in subgroups with low eGFR) (29,30,91). Canagliflozin is approved to be started down to eGFR levels of 30 mL/min/1.73 m^2. However, for patients with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor in patients with eGFR ≥20 mL/min/1.73 m^2 and UACR ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. This an A-level recommendation. This is a change in eGFR from previous recommendations that suggested an eGFR level >25 mL/min/1.73 m^2. The reason for the lower limit of eGFR is as follows. The major clinical trials for SGLT2 inhibitors that showed benefit for patients with diabetic kidney disease are CREDENCE and DAPA-CKD (27,117). CREDENCE enrollment criteria included eGFR >30 mL/min/1.73 m^2 and UACR >300 mg/g. DAPA-CKD enrolled patients with eGFR >25 mL/min/1.73 m^2 and UACR >200 mg/g. Analyses from the EMPEROR heart failure trials (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [EMPEROR-Preserved] enrolled 5,998 participants [118], and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction [EMPEROR-Reduced] enrolled 3,730 participants [119]; enrollment criteria included eGFR >60 mL/min/1.73 m^2, but efficacy was seen at eGFR >20 mL/min/1.73 m^2 in people with heart failure) as well as subgroup analyses from DAPA-CKD (120) suggest that SGLT2 inhibitors are safe and effective at eGFR levels of >20 mL/min/1.73 m^2. Hence, the new recommendation is to use SGLT2 inhibitors in patients with eGFR as low as 20 mL/min/1.73 m^2. In addition, SGLT2 inhibitors appear to be safe and effective in nonalbuminuric patients. The EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) trial (NCT03594110) was stopped early due to effectiveness of the study medication. The data have not been published, but the study enrolled 6,609 participants and enrolled normoalbuminuric participants. The preliminary reports are that the drug was safe and effective even in the absence of albuminuria. In addition, Dapagliflozin Effect on Cardiovascular Events–Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) suggested effectiveness in participants with normal urine albumin levels (121). Hence, the American Diabetes Association is recommending the following at a B level for now: for patients with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in patients with an eGFR ≥20 mL/min/1.73 m^2 and urine albumin ranging from normal to 200 mg/g creatinine. Some GLP-1 RAs require dose adjustment for reduced eGFR (the majority—liraglutide, dulaglutide, semaglutide—do not require it).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

MRAs historically have not been well studied in diabetic kidney disease because of the risk of hyperkalemia (92,93). However, data that do exist suggest benefit on albuminuria reduction that is sustained. There are two different classes of MRAs, steroidal and nonsteroidal, with one group not extrapolatable to the other (94). Late in 2020, the results of the first of two trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, which examined the renal effects of finerenone, demonstrated a significant reduction in diabetic kidney disease progression and cardiovascular events in patients with advanced diabetic kidney disease (31,95). This trial had a primary end point of time to first occurrence of the composite end point of onset of kidney failure, a sustained decrease of eGFR >40% from baseline over at least 4 weeks, or renal death. A prespecified secondary outcome was time to first occurrence of the composite end point cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, hospitalization for heart failure). Other secondary outcomes included all-cause mortality, time to all-cause hospitalizations, and time to first occurrence of the following composite end point: onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks or renal death and change in UACR from baseline to month 4.

The double-blind, placebo-controlled trial randomized 5,734 patients with CKD and type 2 diabetes to receive finerenone, a novel nonsteroidal MRA, or placebo. Eligible patients had a UACR of 30 to <300 mg/g, an eGFR of 25 to

<60 mL/min/1.73 m^2, and diabetic retinopathy, or a UACR of 300–5,000 mg/g and an eGFR of 25 to <75 mL/min/1.73 m^2. Mean age of the patients was 65.6 years, and 30% were female. The mean eGFR was 44.3 mL/min/1.73 m^2. Mean albuminuria (interquartile range) was 852 (446–1,634) mg/g. The primary end point was reduced with finerenone compared with placebo (hazard ratio 0.82, 95% CI 0.73–0.93; P = 0.001), as was the key secondary composite of cardiovascular outcome (hazard ratio 0.86, 95% CI 0.75–0.99; P = 0.03). Hyperkalemia resulted in 2.3% discontinuation in the study group compared with 0.9% in the placebo group. However, the study was completed and there were no deaths related to hyperkalemia. Of note, 4.5% of the total group were being treated with SGLT2 inhibitors.

Finerenone In Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) assessed the safety and efficacy of finerenone in reducing cardiovascular events among patients with type 2 diabetes and CKD with elevated UACR (30 to <300 mg albumin/g creatinine), and eGFR 25–90 mL/min/1.73 m^2 (122). The study randomized eligible subjects to either finerenone (n = 3,686) or placebo (n = 3,666). Patients with an eGFR of 25–60 mL/min/1.73 m^2at the screening visit received an initial dose at baseline of 10 mg once daily, and if eGFR at screening was ≥60 mL/min/1.73 m^2, the initial dose was 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was ≤4.8 mmol/L and the eGFR was stable. The mean patient age was 64.1 years (31% of patients were female), and the median follow-up duration was 3.4 years. The median A1C was 7.7%, mean systolic blood pressure was 136 mmHg, and mean GFR was 67.8 mL/min/1.73 m^2. Patients with heart failure with a reduced ejection fraction and uncontrolled hypertension were excluded.

The primary composite outcome was cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The finerenone group showed a 13% reduction in the primary endpoint: 12.4% vs. 14.2% (hazard ratio [HR] 0.87 [95% CI 0.76–0.98]; P = 0.03). This benefit was primarily driven by a reduction in heart failure hospitalizations: 3.2% vs. 4.4% (HR 0.71 [95% CI 0.56–0.90]).

Of the secondary outcomes, the most noteworthy was a 36% reduction in end-stage kidney disease: 0.9% vs. 1.3% (HR 0.64 [95% CI 0.41–0.995]). There was a higher incidence of hyperkalemia, 10.8% vs. 5.3%, although only 1.2% of the 3,686 patients on finerenone stopped the study due to hyperkalemia of 0.6% vs. 0.4% of the placebo group.

The FIDELITY prespecified pooled efficacy and safety analysis incorporated patients from both FIGARO and FIDELIO (N = 13,171) to allow for evaluation across the spectrum of severity of chronic kidney disease, since the populations were different (with a slight overlap) and the study designs were similar (123). The analysis showed a 14% reduction in composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure, for finerenone vs. placebo: 12.7% vs. 14.4% (HR 0.86 [95% CI 0.78–0.95]; P = 0.0018).

It also demonstrated a 23% reduction in the composite kidney outcome, consisting of sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death, for finerenone vs. placebo (5.5% vs. 7.1%; HR 0.77 [95% CI 0.67–0.88]; P = 0.0002).

The pooled FIDELITY analysis confirms and strengthens the positive cardiovascular and renal outcomes with finerenone across the spectrum of chronic kidney disease, irrespective of baseline ASCVD history (excluding those with reduced ejection fraction heart failure, as they were excluded from these trials).

Cardiovascular Disease and Blood Pressure

Hypertension is a strong risk factor for the development and progression of CKD (96). Antihypertensive therapy reduces the risk of albuminuria (97–100), and among patients with type 1 or 2 diabetes with established CKD (eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g Cr), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD (101–103). Moreover, antihypertensive therapy reduces risks of cardiovascular events (97).

Blood pressure levels <140/90 mmHg are generally recommended to reduce CVD mortality and slow CKD progression among all people with diabetes (100). Lower blood pressure targets (e.g., <130/80 mmHg) should be considered for patients based on individual anticipated benefits and risks. Patients with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD and therefore lower blood pressure targets may be suitable in some cases, especially in those with ≥300 mg/g Cr albuminuria.

ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes, hypertension, eGFR <60 mL/min/1.73 m^2, and UACR ≥300 mg/g Cr because of their proven benefits for prevention of CKD progression (101–104). In general, ACE inhibitors and ARBs are considered to have similar benefits (105,106) and risks. In the setting of lower levels of albuminuria (30–299 mg/g Cr), ACE inhibitor or ARB therapy at maximally tolerated doses in trials has reduced progression to more advanced albuminuria (≥300 mg/g Cr), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESRD (104,107). While ACE inhibitors or ARBs are often prescribed for high albuminuria without hypertension, outcome trials have not been performed in this setting to determine whether they improve renal outcomes. Moreover, two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs in type 1 and type 2 diabetes among those who were normotensive with or without high albuminuria (formerly microalbuminuria) (108,109).

Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (110). In a trial of people with type 2 diabetes and normal urine albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (111). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (108). This was further supported by a similar trial in patients with type 2 diabetes (109). *Therefore, ACE inhibitors or ARBs are not recommended for patients without hypertension to prevent the development of CKD.*

Two clinical trials studied the combinations of ACE inhibitors and ARBs and

found no benefits on CVD or CKD, and the drug combination had higher adverse event rates (hyperkalemia and/or AKI) (112,113). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Referral to a Nephrologist

Consider referral to a nephrologist when there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good blood pressure control, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal replacement therapy for ESRD (2). The threshold for referral may vary depending on the frequency with which a provider encounters patients with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (114). However, other specialists and providers should also educate their patients about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

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