Diabetic Kidney Disease Back in Focus: Management Field Guide for Health Care Professionals in the 21st Century

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Abstract

Chronic kidney disease due to diabetes, or diabetic kidney disease (DKD), is a worldwide leading cause of chronic kidney disease and kidney failure and an increasingly important global public health issue. It is associated with poor quality of life, high burden of chronic diseases, and increased risk of premature death. Until recently, people with DKD had limited therapeutic options. Treatments have focused largely on glycemic and blood pressure control and renin-angiotensin system blockade, leaving patients with significant residual risk for progression of DKD. The availability of newer classes of glucose-lowering agents, namely, sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists, has changed the therapeutic landscape for these patients. These therapies have offered unprecedented opportunities to reduce the risk for progression of kidney disease and the risk of death that have led to recent updates to clinical guidelines. As such, the American Diabetes Association, the Kidney Disease: Improving Global Outcomes, and the European Association for the Study of Diabetes now recommend the use of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists for patients with DKD to provide both kidney and cardiovascular protective benefits. This review highlights the importance of early detection of DKD and summarizes the latest recommendations in the clinical guidelines on management of patients with DKD with hope of facilitating their uptake into everyday clinical practice. An integrated approach to patient care with a multidisciplinary focus can help achieve the necessary shift in clinical care of patients with DKD.

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glomerulosclerosis, and polycystic kidney disease alone or combined with diabetic nephropathy. This review focuses on the management of patients with CKD due to diabetes (without other known causes), which is referred to as DKD.

As a consequence of the worldwide diabetes pandemic, recent decades have seen DKD become a global leading cause of kidney failure and the most frequent indication for kidney replacement therapy. In contrast to the downward trends in other diabetes-related complications, including myocardial infarction, stroke, and limb amputation, the prevalence of DKD has not followed similar downward trends.

Higher albuminuria levels and lower eGFR are independently and additively associated with an increased risk for cardiovascular (CV) and all-cause mortality. For instance, the presence of kidney disease is associated with a sharp increase of 10-year cumulative all-cause mortality from 11.5% among individuals with diabetes and without kidney disease up to 31% among individuals with diabetes and kidney disease, indicating that most of the excess risk of all-cause and CV mortality for individuals with type 2 diabetes relates to the presence of DKD. Overall, individuals with CKD have twice the risk of CV disease (CVD) compared with individuals without CKD, and death from CVD is more likely than progression to kidney failure. From the patient’s perspective, the progression of kidney disease has been associated with reduced quality of life.

Until very recently, treatments to prevent the development and progression of DKD were limited to glycemic and blood pressure control and the use of renin-angiotensin system blockers, resulting in the significant residual risk that helped establish DKD as a growing major global public health problem. The availability of newer classes of glucose-lowering agents, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and the nonsteroidal mineralocorticoid receptor antagonist finerenone, will undoubtedly change this therapeutic landscape.

Surprisingly, contemporary CV outcomes trials demonstrated reductions in not only CV events but also secondary kidney end points associated with the administration of SGLT2 inhibitors and GLP-1 RAs. Subsequently, dedicated kidney outcomes trials have confirmed benefits associated with SGLT2 inhibitors in terms of reductions in the progression of kidney disease and CV death. Similarly, in patients with DKD, finerenone was shown to mitigate the progression of kidney disease, CV risks, and death. As a result, there is increased recognition of the historic opportunity to reshape the care and lives of patients with DKD. The aim of this article is to provide a succinct, user-friendly update on guidelines-recommended care, including the importance of early detection, as well as tailored follow-up with a focus on treatment that reduces the risk of kidney disease.
progression and CV death and improves overall clinical outcomes.

**METHODS**

Recent guidelines for type 2 diabetes management are included for review, specifically, guidelines from the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) in addition to joint guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology and joint guidelines from the European Society of Cardiology and the European Association for the Study of Diabetes. Additional literature included CV outcomes trials with kidney outcomes data and prescribing information for guideline-recommended therapies. Also, the MEDLINE database was searched through...
PubMed to retrieve relevant articles on type 2 diabetes and GLP-1 RAs, SGLT2 inhibitors, and finerenone between 2010 and 2021 (limits: humans, English language). A total of 32 trials in patients with type 2 diabetes and GLP-1 RAs, 53 trials with SGLT2 inhibitors, and 9 trials with finerenone were identified. Of these identified trials, 20 trials were reviewed in detail. Other relevant literature was obtained on the basis of personal knowledge and experience. Manual assessment of retrieved references was used as the basis for a narrative overview of the literature.

**DIAGNOSIS OF DKD**

Diabetic kidney disease is generally diagnosed and classified as the presence of albuminuria or a reduction in eGFR in the absence of clinical indicators of other causes of kidney disease (Figure 1). Typically, DKD is manifested in a patient with long-standing (>10 years) type 2 diabetes in the presence of retinopathy, albuminuria without macroscopic hematuria, and progressive eGFR decline. Alternatively, in a subset of patients, evidence of DKD with reduced eGFR can be present at diagnosis of type 2 diabetes in the absence of retinopathy and without albuminuria. Albuminuria is best assessed with spot urine samples (ideally, early morning samples) to calculate the UACR. Because DKD is usually asymptomatic until advanced stages, guidelines from the ADA and KDIGO recommend that all individuals with type 2 diabetes have eGFR and UACR measured within 5 years of diagnosis. Evaluation of DKD, especially at the time of initial diagnosis, should include careful medical and family history to look for other possible causes of kidney disease, such as family history of polycystic kidney disease, presence of chronic infections (such as HIV infection, hepatitis C), autoimmune disorders (systemic lupus erythematosus, vasculitis), malignant neoplasms (lymphoma, myeloma, solid tumors), episodes of acute kidney injury, frequent infections, and exposure to toxins. Kidney function is assessed by a serum creatinine or cystatin C—based eGFR calculation, preferably with the CKD Epidemiology Collaboration (CKD-EPI) equation, which is more accurate than the Modification of Diet in Renal Disease study equation. The serum creatinine—based CKD-EPI eGFR equation includes approximately 16% higher eGFR values for individuals self-identified as Black because of the use of a correction factor for self-reported Black race. Incorporation of the correction factor in the serum creatinine—based eGFR calculation was derived from findings of a small study that showed higher serum creatinine levels in Black vs White patients. Although the findings were not validated by direct measurements of glomerular filtration or lean body mass, the correction factor for race has subsequently been used inappropriately as a proxy for serum creatinine, which is derived primarily from skeletal muscle, in other eGFR equations. However, serum creatinine values may reflect other conditions, such as dietary protein levels, vigorous exercise, or long-term glucocorticoid therapy, as well as changes in creatinine filtration. On the other hand, the cystatin C—based CKD-EPI eGFR equation does not include a modifier for race and appears to have a more linear association with CV events compared with the creatinine-based CKD-EPI equation. Given the approximately 4-fold higher prevalence of CKD in Blacks/African Americans, the National Kidney Foundation and the American Society of Nephrology created a Task Force to address the use of Black race in eGFR reporting in these vulnerable patients. As such, the Task Force has provided the following recommendations: use of the CKD-EPI creatinine-based equation without the race variable; use of cystatin C for eGFR confirmation in clinical decision-making; and research on new endogenous filtration markers that interventions may eliminate racial and ethnic disparities. These approaches would advance unbiased assessments on informed decisions toward achieving health care equity for all individuals with CKD.
When used together, eGFR and UACR improve risk stratification and diagnostic accuracy.34,45 More frequent testing is recommended for elevated UACR above 300 mg/g or eGFR of 30-60 mL/min per 1.73 m².6,34,35 For instance, the ADA recommends twice-yearly monitoring for individuals with UACR of 300 mg/g or higher and CKD stage 3b and stage 4 (eGFR <45 mL/min per 1.73 m²) irrespective of therapy.34 In addition, repeated testing should be performed if there is a change in clinical status (indicating rapid progression or advanced stages of DKD) or when new medications are started (such as an SGLT2 inhibitor, angiotensin-converting enzyme inhibitor [ACEI], or angiotensin receptor blocker [ARB]).6,34 Initiation of SGLT2 inhibitors or ACEI/ARBs may result in a transient reduction of up to 25% in eGFR, attributed to a change in glomerular hemodynamics rather than intrinsic renal disease, such as renal artery stenosis.5,34 Timely referral to a nephrologist may be considered for individuals with eGFR below 45 mL/min per 1.73 m² for coordinated care to slow the

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<th>TABLE 1. Summary of International Guideline Recommendations for Monitoring of Kidney Function and Risk Factor Management in Patients with Diabetes and DKD</th>
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AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESC/EASD, European Society of Cardiology/European Association for the Study of Diabetes; HbA₁c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; SBP, systolic blood pressure; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin to creatinine ratio.
progression of DKD, to improve the management of complications as the disease worsens, and to prepare patients adequately for kidney replacement therapy, as indicated. Referral to a nephrologist may also increase appropriate use of renin-angiotensin-aldosterone system blockers and optimal management of comorbidities, such as anemia, hypertension, and CKD mineral and bone disorders. Furthermore, referral to a nephrologist is strongly recommended once the eGFR drops below 30 mL/min per 1.73 m², if there is consistent finding of significant albuminuria (UACR ≥300 mg/g), if DKD progresses to a new CKD category, or if there is an abrupt, sustained decline in eGFR of more than 5 mL/min per 1.73 m² per year (Figure 1).

**Review of Key Points From Current Clinical Guidelines**

To slow the progression of kidney disease and to reduce CV events, individuals with DKD should receive comprehensive care. The foundation of this care includes a diabetes structured self-management education program, diet, exercise, and smoking cessation counseling, as well as treatment of hyperglycemia, optimization of blood pressure control using ACEIs or ARBs, and lipid management. The significant positive results of recent trials involving SGLT2 inhibitors, GLP-1 RAs, and finerenone on top of standard of care therapy with an ACEI or an ARB laid the foundation for new clinical guidelines recommending these agents in the treatment of DKD for their proven kidney and CV protective benefits (Table 1).

Current clinical guidelines advocate a patient-centered approach to management, with a focus on shared decision-making. Table 1 summarizes the main recommendations from the clinical management guidelines for patients with type 2 diabetes from the ADA, joint guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology, KDIGO guidelines on diabetes with CKD and blood pressure management, and joint guidelines from the European Society of Cardiology and the European Association for the Study of Diabetes, as detailed here.

**Lifestyle Interventions.** Special emphasis in the approach to treatment of all DKD patients should be placed on adherence to a healthy diet high in vegetables, vegetable-based proteins, whole grains, unsaturated fat, fiber, and nuts. Sodium chloride intake should be limited to less than 5 g/d (equivalent to <2 g, or 90 mmol of sodium per day). The recommended protein intake for all DKD patients, not on dialysis, is approximately 0.8 g/kg per day. Lower levels of physical activity have been associated with higher risk of atherosclerotic CVD (ASCVD) and risk of dying. Therefore, it is recommended that patients with DKD undertake 150 minutes per week of moderate-intensity activity. Similarly, to achieve the glycemic target, the level and intensity of activity should be adjusted to individual CV and physical tolerance.

**Glycemic Targets.** Achieving glycemic targets in individuals with DKD and especially advanced DKD is challenging primarily because of reduced kidney capacity for gluconeogenesis and altered metabolism and clearance of glucose-lowering therapies. Consequently, patients with DKD may be at high risk for hypoglycemia and other adverse drug events. Within the guidelines, there is agreement on the need for individualized glycemic targets for people with type 2 diabetes. The choice of tighter or less rigorous targets should be based on individual factors, including CKD stage, presence and severity of comorbidities, and age of the patient. Overall, the guidelines recommend a target glycated hemoglobin (HbA1c) level of less than 6.5% for patients at low risk of hypoglycemia and no comorbidities, less than 7.0% for most patients, and less than 8.0% for elderly patients and those with multiple comorbidities or advanced DKD.

**Glycemic Monitoring.** The recommended biomarker for long-term monitoring of
glycemia is HbA1c, with several important caveats to keep in mind. The HbA1c value may be decreased by factors that reduce the erythrocyte life span and are frequently present in patients with more advanced CKD, such as in the presence of anemia, after blood transfusion, and during the use of erythrocyte-stimulating agents or iron replacement therapy.53 These factors can decrease the precision and accuracy of HbA1c measurements in advanced CKD, particularly in patients undergoing dialysis.54 Conversely, in later stages of DKD, levels of HbA1c may be falsely increased by metabolic acidosis, carbamylation, and advanced glycation end-product formation.53,54 In these patients and in individuals undergoing hemodialysis, for whom the reliability of the HbA1c measurements is uncertain, self-monitoring of blood glucose concentration or continuous monitoring of glucose level is recommended to inform daily treatment decisions.6

### Antihyperglycemic Therapeutic Options

The 2022 ADA standards of care specify that in individuals with or at high risk for ASCVD, heart failure, or kidney disease, SGLT2 inhibitors or GLP-1 RAs can be used as first line-therapy with and without metformin.34,46 Although SGLT2 inhibitors were initially developed as antihyperglycemic agents, at this point they are recommended for most patients with type 2 diabetes and eGFR below 60 mL/min per 1.73 m² without albuminuria and for those with albuminuria of 200 mg/g or higher independent of the need for HbA1c lowering or individualized HbA1c target.34 The GLP-1 RAs with proven CV benefits (long-acting GLP-1 RAs) can be used interchangeably with SGLT2 inhibitors in patients with eGFR below 60 mL/min per 1.73 m² or in those with albuminuria who are intolerant of SGLT2 inhibitors.34 The 2022 KDIGO guideline recommendations differ from the 2022 ADA guidance as the 2022 KDIGO guideline recommends the use of SGLT2 inhibitors in all patients with eGFR above 20 mL/min per 1.73 m² independent of the presence of albuminuria. The GLP-1 RAs with proven CVD benefits can be used if SGLT2 inhibitors are not tolerated or are contraindicated.6 The decision may be further informed by consideration of the individual preferences of the patient and balancing the risk of possible adverse effects with the risk of DKD progression.6 If additional therapy is required for glycemic management, a GLP-1 RA is generally preferred.6

The GLP-1 RAs with proven CVD benefit are the preferred choice for patients with type 2 diabetes and eGFR of 2 mL/min per 1.73 m² or lower or UACR of 30 mg/g or higher (no dosage adjustments required), with existing or high risk of ASCVD, or in the presence of metabolic risk factors such as poorly controlled type 2 diabetes and obesity (Table 3 55-64; Figure 2 50,65).6,45,47,48,50,66 Furthermore, semaglutide is recommended...
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<tr>
<th>Agent</th>
<th>Route and frequency of administration</th>
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<tr>
<td>GLP-1 RAs</td>
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<tr>
<td>Exenatide (^5)</td>
<td>Subcutaneous injection; twice daily</td>
<td>Glucose lowering</td>
<td>Initially, 5 μg twice daily within the 60-minute period before the morning and evening meals; Can increase to 10 μg twice daily after 1 month of therapy, based on clinical response</td>
<td>Not recommended for patients with CrCl &lt;30; caution recommended when initiating or escalating the dose in patients with CrCl 30-50</td>
</tr>
<tr>
<td>Exenatide XR (^6)</td>
<td>Subcutaneous injection; once weekly</td>
<td>Glucose lowering</td>
<td>2 mg once weekly at any time of day</td>
<td>Not recommended for patients with eGFR &lt;45 or with kidney failure</td>
</tr>
<tr>
<td>Lixisenatide (^7)</td>
<td>Subcutaneous injection; once daily</td>
<td>Glucose lowering</td>
<td>Initially, 10 μg once daily within the 60-minute period before the first meal of the day; on day 15, increase to 20 μg once daily</td>
<td>Not recommended for patients with CrCl &lt;15</td>
</tr>
<tr>
<td>Liraglutide (^8)</td>
<td>Subcutaneous injection; once daily</td>
<td>Glucose lowering</td>
<td>To reduce risk for MI, stroke, and CV death in adults with T2D who have established CVD; Weight management among obese patients (BMI &gt;30 kg/m(^2)) aged &gt;12 years</td>
<td>Initially, 0.6 mg once daily at any time of day; after 1 week of 0.6-mg dose, increase to 1.2-1.8 mg once daily; Obesity dose 3 mg once daily</td>
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<td></td>
<td>No dosage adjustments required</td>
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<tr>
<td>Dulaglutide (^9)</td>
<td>Subcutaneous injection; once weekly</td>
<td>Glucose lowering</td>
<td>To reduce risk of CV death, nonfatal MI, or nonfatal stroke in adults with T2D with CVD or with multiple CV risk factors</td>
<td>No dosage adjustments required</td>
</tr>
<tr>
<td>Semaglutide (^10)</td>
<td>Subcutaneous injection; once weekly</td>
<td>Glucose lowering</td>
<td>Weight management among adult patients with BMI &gt;30 kg/m(^2) or BMI &gt;27 kg/m(^2) with at least one weight-related comorbidity (hypertension, high cholesterol level)</td>
<td>No dosage adjustments required</td>
</tr>
<tr>
<td></td>
<td>Oral; once daily</td>
<td>Glucose lowering</td>
<td>Initially, 0.25 mg once weekly at any time of day; after 4 weeks on 0.25-mg dose, increase to 0.5 mg once weekly; if additional glycemic control is required, can increase to 1 mg once weekly after ≥4 weeks of treatment with the 0.5-mg dose; Weight management dose 2.4 mg weekly</td>
<td>No dosage adjustments required</td>
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<tr>
<th>Agent</th>
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<th>General recommended dosing for glycemic control</th>
<th>Recommended kidney dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliiflozin</td>
<td>Oral; once daily</td>
<td>Glucose lowering</td>
<td>10 mg, may titrate up to 25 mg if needed</td>
<td>Not recommended for glucose lowering in T2D patients with eGFR &lt; 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce risk of CV death in patients with T2D and CVD</td>
<td></td>
<td>Data are insufficient to provide a dosing recommendation in patients with T2D and established CVD and eGFR &lt; 30 or who have HFrEF and eGFR &lt; 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce risk of CV death plus hospitalization for HF in adults with HFrEF</td>
<td></td>
<td>Contraindicated in dialysis</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Oral; once daily</td>
<td>Glucose lowering</td>
<td>5 mg, may titrate up to 10 mg if needed</td>
<td>Not recommended for glucose lowering in T2D patients with eGFR &lt; 45</td>
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<tr>
<td></td>
<td></td>
<td>Risk reduction of sustained eGFR decline, kidney failure, CV death, and hospitalization for HF in adults with CKD</td>
<td></td>
<td>Use for HF or CKD indications eGFR 25 to &lt; 45: 10 mg</td>
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<tr>
<td></td>
<td></td>
<td>Risk reduction of CV death and hospitalization for HF in adults with HFrEF (NYHA class II-IV)</td>
<td></td>
<td>If eGFR &lt; 25, initiation not recommended; may continue 10 mg in patients with HF and CKD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk reduction of hospitalization for HF in adults with T2D and established CVD or multiple CV risk factors</td>
<td></td>
<td>Contraindicated in dialysis</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Oral; once daily</td>
<td>Glucose lowering</td>
<td>100 mg before first meal, may titrate to 300 mg if needed</td>
<td>Not recommended for glucose lowering in T2D patients with eGFR &lt; 30 eGFR ≥ 60: no dosage adjustment necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce risk of kidney failure, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2D and DKD with albuminuria &gt; 300 mg/d</td>
<td></td>
<td>eGFR 30 to &lt; 60: 100 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce risk of CV death, nonfatal MI, and stroke in adults with T2D and established CVD</td>
<td></td>
<td>eGFR &lt; 30 with albuminuria &gt; 300 mg/d: 100 mg/d</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eGFR &lt; 30 with no albuminuria: initiation not recommended</td>
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BMI, body mass index; CKD, chronic kidney disease; CrCl, creatinine clearance (mL/min per 1.73 m²); CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m²); GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Glucose-lowering effect blunted with reduced kidney function.
as an effective therapy for weight management in people with type 2 diabetes.\textsuperscript{34} Patients should be monitored for rare but serious possible adverse effects mentioned later. In addition, patients should receive advice on symptom recognition and mitigating strategies.

**Blood Pressure Control.** The 2022 ADA standard of medical care in diabetes recommends a target blood pressure below 140/90 mm Hg for patients with 10-year ASCVD risk of less than 15%. For patients at higher risk including existing ASCVD, 10-year ASCVD risk of 15% or higher, and mild to moderate albuminuria (UACR >30 to 300 mg/d), a target blood pressure below 130/80 mm Hg is appropriate if it can be achieved safely.\textsuperscript{34} The 2021 KDIGO guideline recommended a blood pressure target that is lower. Specifically, for patients with hypertension and CKD, KDIGO recommends systolic blood pressure below 120 mm Hg, when tolerated.\textsuperscript{37} To achieve reductions in albuminuria development, DKD progression, and risk of kidney failure in patients with hypertension and mild to moderate (UACR of 30 to 300 mg/d) or severe albuminuria (UACR >300 mg/d), both KDIGO and ADA endorsed the initiation and subsequent up-titration to maximally tolerated doses of ACEIs and ARBs.\textsuperscript{6,34} In nonalbuminuric DKD patients, ACEIs and ARBs are not superior to other antihypertensive agents in slowing the progression of kidney disease. Importantly, they can be used as first-line therapy in patients with eGFR below 60 mL/min per 1.73 m\textsuperscript{2} and CV heart disease and may be considered in patients with proteinuria and mild to moderate blood pressure to ameliorate proteinuria (Table 1\textsuperscript{6}). The combination ACEI plus ARB therapy, however, is not recommended because of the lack of additive benefit and increased risks for hyperkalemia and acute kidney injury.\textsuperscript{47} The recently approved nonsteroidal mineralocorticoid receptor antagonist finerenone has lower rates of hyperkalemia compared with the steroidal mineralocorticoid receptor antagonists (eg, spironolactone, eplerenone).\textsuperscript{67} Finerenone is recommended to reduce progression of CKD and risk of CV events.\textsuperscript{34}

**Lipid Management.** In 1998, the National Kidney Foundation Task Force on Cardiovascular Disease recommended that CKD patients be considered in the “highest risk group” for subsequent CV events.\textsuperscript{68} The landmark Study of Heart and Renal Protection showed a significant decrease in atherosclerotic events with simvastatin and ezetimibe compared with placebo in dialysis-dependent and non—dialysis-dependent patients and helped shape the KDIGO clinical practice guidelines for lipid management in CKD patients.\textsuperscript{69,70} Therefore, KDIGO recommends that at the time of CKD diagnosis, all adults with diabetes should have a lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides).\textsuperscript{70} All adults aged 18 to 49 years not treated with long-term dialysis or kidney transplant should be treated with statin, and those 50 years of age and older should be treated with statin or statin/ezetimibe combination. Follow-up measurement of lipid levels after starting of a pharmacologic agent is not required for most patients. It could be considered to assess compliance with pharmacologic therapy. Because of concerns of increased toxicity, CKD-specific lipid management guidelines suggest using dose reduction of statins for individuals with an eGFR below 60 mL/min per 1.73 m\textsuperscript{2}.\textsuperscript{70} Unadjusted dosing used in the general population, including a high-intensity statin dosing, could be considered for individuals with eGFR of 45 to 59 mL/min per 1.73 m\textsuperscript{2} with acute coronary syndrome. In this scenario, unadjusted dosing could be considered with even lower eGFRs unless there are significant drug interactions with concomitant medications.\textsuperscript{71}

**Strategies to Overcome Key Clinical Concerns**

In view of the benefits of treatment with SGLT2 inhibitors and GLP-1 RAs, their incorporation into the clinical care of
patients with type 2 diabetes and DKD is strongly encouraged. The existence of multiple clinical with similar yet not identical recommendations, compounded by the high cost and inconsistent insurance coverage may be contributing to the slow adoption of the new recommendations. Furthermore, concerns about the use of SGLT2 inhibitors, in particular with respect to possible adverse effects, such as euglycemic diabetic ketoacidosis and the risk of gangrene and genital fungal infections, may account for the restrained uptake of SGLT2 inhibitors in clinical practice. Similarly, limited experience of primary care providers with GLP-1 RAs and concerns about tolerability, in particular gastrointestinal adverse effects, have contributed to slow uptake of these agents.

Discussion of the occurrence of adverse effects and strategies to mitigate them can assist clinicians and patients in balancing the risks and benefits of different treatment options, which are summarized here.

**SGLT2 Inhibitors.** Clinical studies with SGLT2 inhibitors have indicated that these agents are associated with an initial decrease in eGFR of 3 to 5 mL/min per 1.73 m² in patients with type 2 diabetes and baseline eGFR above 30 mL/min per 1.73 m². However, clinicians should be aware that after the initial “eGFR dip,” kidney function will generally return toward baseline in the following weeks and remain stable during SGLT2 inhibitor therapy or until drug discontinuation. Among more than 4000 participants of the

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**FIGURE 2.** Algorithm of glucose-lowering therapy for cardiorenal benefit. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; PAD, peripheral artery disease; SGLT2, sodium-glucose cotransporter 2.
In the CREDENCE trial, the initial decline in eGFR (>10% or <10%, and even >30%) had no influence on the subsequent course of eGFR, except in those with eGFR of 45 to 59 mL/min per 1.73 m², in whom the initial dip was associated with a slower decline of eGFR. In an analysis of 6700 participants enrolled in the EMPA-REG OUTCOME trial, a decrease of more than 10% from baseline eGFR was found to be associated with more advanced DKD and diuretic use and did not raise safety concerns or have an impact on CV or kidney outcomes. Thus, the decline in eGFR is not a reason to discontinue treatment.

One of the more common adverse effects of SGLT2 inhibitor therapy is the development of genital fungal infections, occurring more frequently in women than in men (3% to 7% vs 2% to 4%, respectively, vs <2% in nonusers). The risk of this event can be reduced by counseling patients on the practice of hygiene measures, including daily rinsing of the genital area after micturition and at bedtime. Another common concern with the use of SGLT2 inhibitors is the development of volume depletion and hypovolemia due to their diuretic action, particularly among patients receiving concurrent diuretic therapy. However, it is not usually necessary to stop or to alter diuretic therapy with initiation of SGLT2 inhibitors, although monitoring of electrolyte levels is advised in adjusting the dose of diuretic or antihypertensive agents.

Diabetic ketoacidosis is a rare but potentially serious adverse effect associated with SGLT2 inhibitor therapy that occurs with a minimal or absent increase in blood glucose concentration. It is thought to be due to increased oxidation of fatty acids combined with reduced insulin secretion and generally occurs in patients with long-standing type 2 diabetes who are receiving insulin therapy. Factors that can trigger diabetic ketoacidosis include intercurrent illness, reduced food and fluid intake, reduced insulin doses, and alcohol consumption. Clinicians and patients should also be aware that diabetic ketoacidosis may be manifested with normal or mildly elevated plasma glucose concentration (<200 mg/dL; “euglycemic diabetic ketoacidosis”) and nonspecific symptoms. Therefore, the risk of this adverse outcome can be reduced by raising awareness and counseling patients on the potential triggers, advising them to seek immediate medical attention if symptoms develop (eg, malaise, nausea, vomiting, abdominal pain). An important consideration is discontinuation of the SGLT2 inhibitor 3 days before (for canagliflozin, dapagliflozin, and empagliflozin; or 4 days for ertugliflozin) any elective or anticipated invasive procedures.

Another rare but serious adverse effect is Fournier gangrene, a type of necrotizing fasciitis that affects the external genitalia and perineum. This occurs more commonly in men than in women and has been reported in postmarket safety reports with a frequency of around 1 in 10,000 patients. Clinicians should retain a high index of suspicion for this rare adverse event and advise patients to seek urgent medical advice in the presence of a severe or worsening genital infection.

Identification of another possible rare adverse event with SGLT2 inhibitor therapy has followed the observation of an increased risk of lower extremity amputation (6.3 vs 3.4 per 1000 person-years) and fractures (15.4 vs 11.9 per 1000 person-years) in a clinical trial with canagliflozin. It is unclear whether this is a chance finding because higher risks of amputation and fractures have not been observed with other SGLT2 inhibitors or with canagliflozin in the CREDENCE trial.

In addition to potential adverse events, an added barrier to the use of SGLT2 inhibitors can be their relatively high cost. However, the cost of treatment should be balanced against the significant savings...
achieved by reduction in CKD progression. A United Kingdom–based modeling study, based on the heart failure subpopulation of the EMPA-REG OUTCOME study, showed that adding empagliflozin to standard of care for patients with type 2 diabetes and heart failure would result in longer average life and overall health care savings and an overall increase in average life expectancy (by 1.2 years). 87

GLP-1 RAs. Delayed gastric emptying, due to the same mechanism that results in the robust postprandial antihyperglycemic effect of this class of medications, underlies the most common adverse effects of GLP-1 RAs of nausea, vomiting, and diarrhea. 88 The risk of these effects may be reduced by starting treatment at the lowest possible dose and increasing the dose during several weeks. 66

Furthermore, patients’ adherence can be improved by advising that these effects are generally self-limited after 2 to 4 weeks of therapy. The GLP-1 RAs can also cause stimulation of the sympathetic nervous system, leading to an increase in heart rate, although no harmful effect of this increase has been reported to date. 69

An increased risk of biliary tract–related events has been reported with liraglutide. 90 As a consequence, GLP-1 RAs should be used with caution in patients with a history of cholelithiasis. 66 In addition, concerns have been raised about a risk of pancreatitis with GLP-1 RA therapy, although the risk of this event appears to be low (≤1%). 89 Nonetheless, GLP-1 RAs should be used cautiously or avoided in patients with a history of pancreatitis. 98 In animal studies, GLP-1 RAs have been linked with the development of medullary thyroid cancer. 89 It is unclear whether GLP-1 RAs cause medullary thyroid cancer in humans, but they are contraindicated in patients with a medical history or family history of this cancer. 55–57,61,89,90

After the occurrence of a single adverse event, the decision of whether to discontinue therapy should be individualized according to the clinical situation, the patient’s concerns, and the potential benefits of continued treatment.

CONCLUSION
The health consequences of DKD are severe. Early identification and initiation of interventions that can prevent progression of kidney disease combined with reduction in rates of CVD and the risk of dying are crucial. Until the introduction of SGLT2 inhibitors and GLP-1 RAs into clinical practice, even state-of-the-art standard of care resulted in a significant residual risk for DKD progression. For the very first time we have at our disposal therapeutic agents that offer promise to abate and ultimately to reverse the trend of DKD-associated morbidity and mortality and associated human suffering. Simultaneously we are increasingly becoming aware of the importance of the active role of patients in their own care, with treatment approaches tailored for their individual needs. Involving patients in shared clinical decision-making, including counseling about possible adverse effects, is key to optimizing treatment compliance with the new antihyperglycemic agents. To achieve this paradigm shift in care, we aspire to an integrated approach with a multidisciplinary focus that incorporates opportunities for primary care physicians and subspecialists, including nephrologists, cardiologists, and endocrinologists, to comanage treatments in the harmonized effort to reduce burden of disease and to improve quality of lives for patients with DKD. In parallel to medical care, there is a need for the reenergized legislative effort that will allow access to lifesaving therapies for all eligible individuals.

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Drs Alicic and Nicholas contributed equally to the manuscript.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2, sodium-glucose cotransporter 2; UACR, urinary albumin to creatinine ratio.

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