KDOQI US Commentary on the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD

Amy K. Mottl,

Radica Alicic,

Christos Argyropoulos,

Frank C. Brosius,

Michael Mauer,

Mark Molitch,

Robert G. Nelson,

Leigh Perreault,

Susanne B. Nicholas

University of North Carolina Kidney Center, University of North Carolina Kidney Center School of Medicine, Chapel Hill, North Carolina (AKM); Providence Medical Research Center, Providence Health Care, Spokane (RA); Department of Medicine, University of Washington School of Medicine, Seattle (RA), Washington; Division of Nephrology, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico (CA); Department of Medicine, University of Arizona, Tucson (FCB); National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix (RGN), Arizona; Departments of Internal Medicine and Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan (FCB); Departments of Pediatrics and Medicine, University of Minnesota, Minneapolis, Minnesota (MMa); Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (MMo); Division of Endocrinology, Metabolism and Diabetes Affiliate, Center for Global Health, University of Colorado Anschutz Medical Campus and Colorado School of Public Health, Aurora, Colorado (LP); and Divisions of Nephrology and Endocrinology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California (SBN)

Abstract

In October 2020, KDIGO (Kidney Disease: Improving Global Outcomes) published its first clinical practice guideline directed specifically to the care of patients with diabetes and chronic kidney disease (CKD). This commentary presents the views of the KDOQI (Kidney Disease Outcomes Quality Initiative) work group for diabetes in CKD, convened by the National Kidney Foundation to provide an independent expert perspective on the new guideline. The KDOQI work group believes that the KDIGO guideline takes a major step forward in clarifying glycemic targets and use of specific antihyperglycemic agents in diabetes and CKD. The purpose of this commentary is to carry forward the conversation regarding optimization of care for patients with diabetes and CKD. Recent developments for prevention of CKD progression and cardiovascular

Address for Correspondence: Amy K. Mottl, MD, University of North Carolina Kidney Center, University of North Carolina Kidney Center School of Medicine, CB 7155, Chapel Hill, NC 27599-7155. amy_mottl@med.unc.edu.

events in people with diabetes and CKD, particularly related to sodium/glucose cotransporter 2 (SGLT2) inhibitors, have filled a longstanding gap in nephrology's approach to the care of persons with diabetes and CKD. The multifaceted benefits of SGLT2 inhibitors have facilitated interactions between nephrology, cardiology, endocrinology, and primary care, underscoring the need for innovative approaches to multidisciplinary care in these patients. We now have more interventions to slow kidney disease progression and prevent or delay kidney failure in patients with diabetes and kidney disease, but methods to streamline their implementation and overcome barriers in access to care, particularly cost, are essential to ensuring all patients may benefit.

Introduction

In October of 2020, KDIGO (Kidney Disease: Improving Global Outcomes) published its first clinical practice guideline dedicated to the management of diabetes in chronic kidney disease (CKD) since the initial KDOQI (Kidney Disease Outcomes Quality Initiative) publication in 2007.[1,2] The nearly decade-long gap between guideline updates reflects the prior scarcity of novel therapies for patients with diabetes and CKD. The emergence of new and highly efficacious drug treatments beneficial to patients with diabetes and CKD were reason enough to update existing guidelines, but this new guideline goes well beyond an expansion of therapeutic options. As conveyed by the title of the guideline, which refers to diabetes management in CKD, KDIGO not only covers glycemia and blood pressure targets, but also provides recommendations on nutrition, exercise, and self-management, underscoring the complexities and unique challenges in caring for the patient with diabetes and CKD. The commentary discusses the importance of multidisciplinary care models to include primary care providers, nephrologists, cardiologists, diabetologists, nurses, dietitians, and social workers in forming a holistic team approach for treating CKD. The emphasis on multidisciplinary care models reflects a shift in the US health care system toward more collaborative multidisciplinary care, represented by the emergence of "accountable care organizations" and "value-based care." Indeed, the KDIGO recommendations are timely for this transformative period in health care.

It is important to highlight that the KDIGO Guideline uses the term "diabetes and CKD," rather than "diabetic kidney disease (DKD)" or "diabetic nephropathy," which historically referred to patients with longstanding diabetes and overt proteinuria (urinary albumin-creatinine ratio [UACR] 300 mg/g). The KDOQI work group agrees that use of "diabetes and CKD" reflects "the current clinical approach of treating most presentations of diabetes and CKD similarly and avoids the connotation that CKD is caused by traditional diabetes physiology."[2] Some are concerned, however, that "diabetes and CKD" may be imprecise and raise confusion at this time when nephrology clinical practice and research enters the world of precision medicine. While DKD is the culmination of multiple and incompletely defined disease processes that differ among individuals, it is not "diabetes and autosomal-dominant polycystic kidney disease," nor is it "diabetes and immunoglobulin A nephropathy," to name 2 examples. The diagnosis of DKD connotes a broad but relatively conserved set of molecular and pathologic changes that have been confirmed by multiple genome-wide transcriptomic and other "omic" analyses,[3–7] which present in clinically recognized patterns and result in a relatively limited set of clinical and renal structural alterations. Given

the prevalence of diabetes, it is not unusual for patients to have clinical and pathologic amalgams of DKD and other (nondiabetic) CKDs, especially in patients with unusual clinical presentations. The preference of our workgroup would be to state that the KDIGO guideline pertains to patients with "DKD," which would include all patients in whom the clinical, pathologic, and molecular analyses support the diabetic milieu as the etiology of CKD. This management guideline may also apply to other patients with nondiabetic CKD occurring in the context of diabetes, but those decisions will require careful consideration of the underlying kidney and systemic disease processes. Nevertheless, to maintain consistency with the KDIGO guideline, this commentary will use the terminology "diabetes and CKD" throughout the document.

This KDIGO guideline has also taken a new approach to guideline format, moving away from guideline "statements" with varying strengths of evidence (including ungraded statements). Guideline statements have been replaced by "recommendations," which continue to be graded based on the current evidence, and "practice points," defined as guidance to be interpreted and applied according to the given clinical scenario. Moreover, the guideline is rendered not only as text, but also as tables, figures, and algorithms, to be succinct in their format. The KDOQI work group supports the adoption of this new format, which represents a 20-year trend[8,9] toward adopting a uniform set of standards intended to facilitate easy comparisons between guidelines from different societies as well as rapid updates.

Review and Approval Process for the KDOQI Commentary

The KDOQI leaders selected cochairs, who then identified individuals with expertise in clinical care and research related to diabetes and CKD and invited them to participate in this KDOQI commentary. The cochairs then divided the commentary workgroup members into groups of 3-4 individuals (2 leads and 1-2 reviewers) to provide a detailed commentary on each section of the KDIGO guideline. The commentaries were then assembled into a single document, with discussion via teleconference to address areas without unanimous agreement, and reviewed and edited by the full KDOQI work group. The final document was reviewed and approved by the KDOQI leadership and the National Kidney Foundation (NKF) Scientific Advisory Board.

For each section of the guideline that is highlighted herein, the text is organized into subsections providing a general commentary (including context for the recommendation, the extent of the KDOQI work group's agreement with the recommendation, and any areas not taken into consideration by KDIGO), followed by discussion of clinical utility, implementation, and challenges. This commentary also discusses topics relevant to patients with diabetes and CKD that were not addressed in the KDIGO guideline—for example, the care of diabetes and CKD in adolescents and young adults. In addition, suggestions are made regarding issues that need more research or were felt to be important to be included in policy decisions. All guideline materials are reproduced with permission of KDIGO.

Guideline Statements and Commentary

Comprehensive Diabetes and CKD Management

The first chapter of the KDIGO guideline begins with an important practice point, the introduction of the concept of comprehensive care for the successful management of CKD in patients with type 1 and type 2 diabetes with emphasis on the multidisciplinary aspects of reducing kidney and cardiovascular risk. The KDIGO work group makes a point to not weigh in on aspects of care that are covered in other guidelines within KDIGO or other professional organizations but addresses the multisystem complications that impact patients with diabetes and CKD. Specifically, they call out the importance of antiplatelet therapies primarily for secondary prevention of cardiovascular events. The benefits of multifactorial intervention are reviewed and care models are more explicitly addressed in the fifth chapter.

Commentary—The KDOQI work group agrees there is great complexity in caring for persons living with diabetes and CKD and agree with the need for multidisciplinary care involving primary care providers and multiple related subspecialties, as well as the important roles of other patient care team members, including educators, dietitians, pharmacists, laboratory technicians, and family members. This strategy has now been endorsed by several professional organizations, including in the 2021 American Diabetes Association (ADA) Standards of Medical Care,[10] the 2019 ADA–European Association for the Study of Diabetes (EASD) Consensus,[11] the 2020 American College of Cardiology (ACC) Expert Consensus Decision Pathway,[12] and the American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE) Consensus Statement.[13] These organizations support the need for multidisciplinary approaches that promote lifestyle changes as the foundation for disease management in patients with diabetes and all severities of CKD, as well as those receiving kidney replacement therapy (KRT), including dialysis and kidney transplantation.[2,14] This concept is illustrated in Fig 1 (adapted from the KDIGO guideline), wherein more specific therapies are targeted to patients at higher risk for CKD progression and cardiovascular events.

The issue of CKD care in children and adolescents with diabetes was not addressed by the KDIGO work group. The incidences of both type 1 and type 2 diabetes are increasing among children and adolescents,[15] resulting in the growing problem of microvascular complications in youth and young adults.[16–20] It is likely that many general pediatricians and nephrologists may be unaware of the rising prevalence of CKD risk factors among children and adolescents, and lack of screening and aggressive management heightens their lifetime risks of CKD due to the potential longer exposure to the diabetic milieu. To address this, programs and clinical trials directed at multidisciplinary care and transition of care for younger patients with diabetes and CKD could include patients still under the care of pediatric practitioners who often follow their patients into early adulthood.

Weight loss was not specifically addressed by the KDIGO guideline. The obesity pandemic has translated to approximately 44% of patients with CKD having obesity.[21] Moreover, obesity exacerbates major risk factors for CKD progression, including glycemic and blood pressure control, and is likely itself a mediating factor for CKD pathogenesis.[22–24] Obesity also complicates treatment options for kidney failure, such as suitability for transplantation

and feasibility of arteriovenous fistula placement.[25] Weight management is recommended by the ADA, and the KDOQI work group suggests that nephrologists be trained in lifestyle and medical therapies for mitigation of obesity in diabetes and CKD.[2,10]

Clinical Utility—Interdisciplinary care models and shared decision-making structures embracing effective, individualized education have demonstrated improved outcomes including reduction of cardiovascular events, decreased hospitalization rates, and lower risk of all-cause mortality, especially in advanced CKD (stages 4-5).[26–28] There are significant racial and ethnic differences in the burden of diabetes and CKD in children, adolescents, and adults.[15,29–31] The early institution of lifestyle changes in these and other at-risk groups that include moderate to vigorous exercise for 60 minutes per day, limiting computer screen time to no more than 2 hours per day, and dietary referrals are important consideration, and were proved to be effective in younger age groups.[32,33]

Implementation and Challenges—Despite the documented benefits of advancing patient education and multidisciplinary care for patients with diabetes and CKD, the current US health care system and its payment structure may not fully facilitate these practices.[34] Most patients receive fragmented care from clinicians in different locations and health systems, and communication between providers remains poor.[35–37] The growing therapeutic choices for prevention of diabetes complications may aggravate this problem, further underscoring the importance of patient-centered, unified, multidisciplinary approaches. Moreover, communication barriers are greatest for the most marginalized populations, who often suffer the worst health outcomes.[38] While advances in electronic health records and portals for interprovider and patient-provider connections have improved communications, these tools are often not available to patients with low educational attainment and/or income or those residing in remote/rural areas. Consideration of regional infrastructure, involvement of community health workers,[39,40] and improvements in practical, cultural, and financial incentives could help advance widespread and impactful achievements in this forum. Further complicating the delivery of comprehensive care to patients with diabetes is the universally poor implementation of clinical practice guideline recommendations based on scientifically proven clinical interventions to reduce morbidity.[41] In the United States, while only 12%-39% of patients with CKD are receiving angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) therapy,[42,43] up to 25% receive medications that are potentially harmful, such as the use of nonsteroidal anti-inflammatory drugs or proton pump inhibitors.[43] Some of the recognized barriers can be differentiated into education (lack of provider awareness and familiarity with the guidelines and their recommendations), guideline-related (guideline complexity, layout, accessibility, and applicability), and external factors (organizational constraints such as lack of standardization of processes and procedures, time restrictions, heavy workload, and cost).[44] Another significant barrier is low patient awareness.[45] The net result of poor CKD awareness, limited education, as well as personal, financial, and institutional barriers, is the low understanding of the health risks associated with CKD, poor prioritization of CKD management, and reduced adherence to recommended care.[46,47]

The use of "high points" and condensed versions of lengthy practice recommendations tailored for busy clinicians may improve their dissemination, acceptance, and implementation. To reduce potential conflicts between professional societies (such as the American Society of Nephrology, NKF, American Heart Association, ADA, and American College of Physicians), it is important to make a concerted effort to harmonize clinical practice standards. The incorporation of decision support algorithms with a quick reference guide for the treatment of CKD into the electronic medical record system has demonstrated the potential to provide further support for primary care providers.[48]

Ideally, centralized multidisciplinary outpatient clinics offering ready access to nephrologists, cardiologists, endocrinologists, and other relevant specialty providers for patients with diabetes and CKD will provide more focused, efficient, and integrated clinical care than the current siloed care that contributes to poor outcomes. While creation of more ideal models remains aspirational in many countries and regions, a more achievable approach is the use of digital consult platforms, which may be particularly feasible and needed in rural settings where subspecialists may be physically distanced. This approach was demonstrated in a 1-year pilot study that compared digital consult access to nephrology care by primary care physicians versus traditional referral processes. The iKinect Project, comprising a network of 160 virtual community primary care physicians, demonstrated that digital consults resulted in improved care delivery, enhanced patient experiences, reduced nephrology care gaps, and greater health care utilization.[49] In summary, a collaborative effort to change policies governing health care and innovative modifications to the processes of health care delivery may provide a path toward reductions in barriers to implementation of recommended approaches.

Renin-Angiotensin System Blockade

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (*1B*).

Commentary and Clinical Utility—The bulk of this chapter is dedicated to the therapeutic use and implications of renin-angiotensin system (RAS) inhibitors. Current KDIGO recommendations specifically endorse the initiation and subsequent titration of RAS inhibitors (ACEIs or ARBs) to maximally tolerated doses in patients with diabetes, hypertension, and increased albuminuria to achieve at least a 30% reduction in albuminuria, as this may be associated with lower CKD progression and risk of kidney failure.[50] Notably, the quality of evidence from randomized controlled trials (RCTs) on the effect of ACEIs compared to either placebo or standard of care on critical clinical outcomes (all-cause mortality, progression of moderately to severely increased albuminuria, and doubling of serum creatinine) from systematic review was considered as moderate.[51] The KDOQI work group agrees that, based on available evidence, ACEIs and ARBs are well tolerated and are indicated to slow kidney function decline in patients with diabetes, hypertension, and persistent mild/moderate or severe albuminuria. However, the evidence for preservation of kidney function in albuminuric patients with well-preserved baseline kidney function is

quite limited. The use of ACEIs and ARBs in the setting of albuminuria but normal blood pressure was suggested as a "consideration" in a practice point, possibly due to lack of obvious benefit.[52] However, ACEI/ARB use in patients with hypertension and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 but without albuminuria appears to be of little or no benefit over blood pressure control with other agents. Both the KDIGO and ADA guidelines discourage RAS inhibition in normoalbuminuric, normotensive patients with diabetes.[2,53]

KDIGO applies the recommendation of ACEI/ARB use in people with diabetes and CKD to kidney transplant recipients. ACEI/ARB use in kidney transplant recipients at large has not been found to improve life or graft survival, even among people with proteinuria[54]; however, no studies have specifically addressed this question in transplant patients with diabetes and albuminuria. The KDOQI work group agrees that, while there are no data for or against ACEI/ARB use in this population, it is reasonable to use RAS blockade in kidney transplant recipients with diabetes and hypertension and albuminuria. KDIGO also specified that ACEI/ARB use is not indicated in patients on dialysis except as antihypertensives, and we agree with this sentiment.

Several practice points are offered to troubleshoot potential adverse effects with the use of ACEIs/ARBs. Practice point 1.2.6, which suggests that ACEIs or ARBs should only be reduced or discontinued as a last resort in patients with hyperkalemia, is supported by several studies. Discontinuation of ACEIs/ARBs in progressive kidney disease is a clinical dilemma being addressed in the STOP-ACEi RCT.[55] While awaiting outcomes of this trial, a recent retrospective cohort study found a higher risk of death and the composite outcome of cardiovascular death, myocardial infarction, and ischemic stroke after discontinuation of ACEI or ARB therapy in individuals who reached eGFR <30 mL/min/1.73 m^2.[56] Studies addressing another clinical practice dilemma, continuation of RAS blockade after acute kidney injury, demonstrated that patients who continued to receive RAS blockade after an acute kidney injury event had a lower risk of death at 1 and 2 years after hospitalization.[56,57] However, continuation of ACEIs/ARBs was associated with more hospital admissions for kidney causes, pointing to the need for close monitoring.[56] Since RAS inhibitors are associated with an increased risk of hyperkalemia, monitoring for hyperkalemia within 1-2 weeks after initiation remains appropriate. Furthermore, although serum creatinine concentrations often increase acutely with RAS inhibitor initiation, an initial increase of 30% followed by stabilization within 2 months is associated with long-term preservation of kidney function.[58] Therefore, every effort to maintain adequate dosing of RAS inhibitors, even in individuals more likely to develop hyperkalemia, could be useful. An approach to maintain adequate RAS inhibition may be facilitated by dietary restrictions and/or potassium binders as outlined in the KDIGO guideline. The guideline also notes that the concurrent use of ACEIs and ARBs or inclusion of direct renin inhibitors in conjunction with an ACEI or ARB increases adverse outcomes and should be avoided, and the KDOQI work group agrees with this.

The use of mineralocorticoid receptor antagonists (MRAs) for patients with diabetes and CKD is mentioned briefly in a practice point. It focuses primarily on their use in resistant hypertension, while acknowledging their antiproteinuric qualities. In several studies, an

MRA significantly reduced albuminuria/proteinuria in patients with diabetes and CKD stages 1-4 who were already receiving an ACEI/ARB.[59] However, KDIGO placed little emphasis on this drug class due to the lack of long-term clinical trials demonstrating efficacy in cardiac or renal outcomes. The KDOQI work group agreed that MRAs are certainly advantageous in the setting of resistant hypertension[60] and to reduce proteinuria in some circumstances such as nephrotic-range proteinuria.[61]

Since the publication of the KDIGO guideline, clinical trial data have emerged demonstrating the benefits of the novel nonsteroidal MRA finerenone on primary renal outcomes. The FIDELIO-DKD study demonstrated that, in people with type 2 diabetes and albuminuric CKD treated with finerenone over 2.6 years, there was a slowed progression of CKD (a composite of kidney failure, sustained decrease in eGFR of at least 40%, or death from kidney failure), with a hazard ratio (HR) of 0.86 (95% CI, 0.75-0.99).[62] The availability of another drug class to treat diabetes and CKD provides optimism for the future of this patient population, and we await consideration of this new drug class in future KDIGO updates.

Implementation and Challenges—Although ACEIs and ARBs have remained the mainstay of first-line therapy for patients with diabetes and CKD, observational studies have shown that their use in the United States is suboptimal.[42,43] While not specific to patients with diabetes, data from the National Health and Nutrition Epidemiology Survey (NHANES) showed that only 39% of people with UACR 30 mg/g were receiving an ACEI or ARB.[63] In contrast, data from Europe suggest that 75%-88% of patients with UACR 30 mg/g were receiving this important therapy.[64] The basis for such poor uptake of ACEI/ARB therapy in patients with albuminuric CKD in the United States is unclear and would benefit from further research.

Smoking Cessation

Recommendation 1.3.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (*1D*).

Commentary and Clinical Utility—The endorsement of smoking cessation and avoidance of tobacco products in patients with diabetes and CKD was deemed a strong recommendation based on smoking as a strong risk factor for development and progression of CKD.[65,66] While there is a lack of direct evidence to support the strategy in this specific patient group, the plethora of evidence for the totality of the population makes this a highly useful recommendation. Of note, the recommendation is also supported by the AACE, ACE, ADA, and EASD.[10,11,13]

Glycemic Monitoring

Recommendation 2.1.1: We recommend hemoglobin A1C (HbA1c) to monitor glycemic control in patients with diabetes and CKD (*1C*).

Commentary—Glycemic monitoring in patients with diabetes and CKD has a well-defined role, ie, to balance the benefits of individualizing glycemic control while avoiding

hypoglycemic events, which are associated with increased cardiovascular mortality in patients with diabetes and CKD.[67] How to best monitor glycemia in people with type 2 diabetes and CKD remains controversial. The KDIGO guideline presents observational evidence as to the strength of correlation between tests that measure ambient glycemia (ie, HbA_{1c}, glycated albumin, and fructosamine) with plasma glucose concentration, concluding that, although all correlations weaken as CKD progresses, HbA_{1c} appears to correlate the best across the spectrum of CKD. Importantly, all measures of ambient glycemia are affected by the CKD environment. For example, glycated albumin will be falsely low (implying good glycemic control) when the serum albumin is <3 g/dL or when proteinuria is in the nephrotic range. Similarly, fructosamine levels will be biased in the presence of hypoalbuminemia. On the other hand, HbA_{1c} levels will be affected by factors interfering with red cell turnover: worsening kidney function, anemia, transfusions, erythropoietin-stimulating agents, and iron supplementation, creating the potential for false negatives and, less frequently, false positives (eg, due to hemoglobin carbamylation). Continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG), which directly measure interstitial and blood glucose, provide measures that are not known to be affected by CKD and its treatment. A weakness of SMBG is that it may not detect the wide and often unpredictable glucose excursions common in patients with diabetes and CKD.[68] However, the inconvenience and costs of these approaches are substantially higher than the other glycemic monitoring methods. Currently, there are no RCTs to recommend alternative measures of glycemic control over HbA_{1c} in these patients.

Clinical Utility—Certification and assay standardization activities over the past 20 years have resulted in HbA_{1c} measurements being mostly, but not universally, free of measurement bias when measured in the laboratory.[69] Due to its low cost and availability, it is the preferred method for glycemic monitoring in CKD. It is reasonable to measure HbA_{1c} twice a year in stable patients with diabetes and up to 4 times a year if the individualized glycemic target has not been met and/or therapy is adjusted (practice point 2.1.1). Accuracy and precision of HbA_{1c} will decline with worsening kidney function (practice point 2.1.2),[70,71] and thus one may miss substantial hyperglycemia or excessive hypoglycemia when eGFR declines below 30 mL/min/1.73 m^2 or in patients receiving dialysis. Risk of hypoglycemia is particularly high in patients with diabetes and CKD who are treated with insulin regimens that involve multiple injections per day or with sulfonylureas.[72] There is merit in considering and implementing direct assessment of capillary (SMBG) or interstitial (CGM) glucose in patients with discordant HbA_{1c} and measured plasma glucose levels or those with frequent hypoglycemia (practice points 2.1.3 and 2.1.4).

Implementation and Challenges—Implementing the KDIGO guideline recommendation to use HbA_{1c} to monitor glycemic control is straightforward: the test is widely available and can easily be added to a basic metabolic panel to provide a rough, individualized correlation with the prevailing level of plasma glucose. While the frequency of testing also appears to be straightforward, the declining performance of the HbA_{1c} as kidney function worsens implies that one may need more frequent assessments, particularly in those individuals with rapidly declining kidney function.[68] In such circumstances, as kidney function declines, so will HbA_{1c}, creating a false sense of improving glycemic

control. This appears particularly problematic in patients who have an apparent "acceptable" range of HbA_{1c} between 6.5% and 8%. Neither glycated albumin nor fructosamine has been sufficiently validated to support their use over HbA_{1c} in CKD.[54] SMBG and CGM may offer distinct advantages in this population, especially when these devices are coupled with mobile apps or telemedicine that can identify patients at risk for hypoglycemia. However, SMBG may be inconvenient, CGMs are not currently approved for use in patients receiving dialysis, and insurance coverage or copays limit the wide deployment of these modalities.

Glycemic Targets

Recommendation 2.2.1: We recommend an individualized HbA1C target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis [callout to guideline figure 9 omitted] (*1C*).

Commentary—Landmark trials have clearly demonstrated the benefits of glycemic control in diabetes for preventing microvascular disease.[73–77] Nevertheless, the notion that a universal HbA_{1c} goal was suitable for all patients with diabetes was challenged by a series of trials that showed either lack of benefit or increase in harm for macrovascular outcomes and mortality when strict HbA_{1c} goals (<6.5%) were imposed.[67,78,79] The increased rate of harm was particularly notable for people with diabetes and CKD, with 31% higher all-cause mortality and 41% higher cardiovascular mortality in those randomized to intensive glycemic control.[80] Taken together, it has become evident that weighing risks and benefits for each patient supersede the pursuit of a set HbA_{1c} value; hence, individualized HbA_{1c} goals can be advantageous.

The KDIGO guideline presents evidence that an HbA_{1c} goal <6.5% may be suitable for some patients with diabetes and CKD, whereas an HbA_{1c} goal <8% may be appropriate for others. While they included kidney transplant patients in their recommendations, they clearly state that appropriate goals for HbA_{1c} in dialysis patients are unknown, and the KDOQI work group agreed with this. KDIGO suggests lower HbA_{1c} goals (<6.5%) among lower-risk patients with diabetes, such as early CKD stage 1-2, few other health issues, at low hypoglycemic risk, and with good support systems. A weakness of this strategy is the assumption that HbA_{1c} is equally reflective of blood glucose in all individuals. However, there are factors outside of HbA_{1c} that may vary between individuals beyond glycemia, such as red blood cell turnover and hemoglobin glycation, that are still not well understood.

Safe achievement of optimal HbA_{1c} targets may be facilitated by CGM or SMBG and by selection of antihyperglycemic agents that are not associated with hypoglycemia (practice points 2.1.5 and 2.2.1). Patients with significant comorbidities (diabetes-related or otherwise) and/or limited life expectancy may be candidates for higher HbA_{1c} (eg, <8%), especially if they are taking insulin, sulfonylureas, or glinides, in order to balance avoidance of hyper- and hypoglycemic crises. CGM metrics, such as time in the glycemic range and duration of hypoglycemia, may be considered as alternatives to HbA_{1c} for defining glycemic targets for patients in whom individualized HbA_{1c} has been deemed inadequate to prevent significant hypo- or hyperglycemia and/or their complications (practice points 2.1.6 and 2.2.2).

Clinical Utility—Standardization of the HbA_{1c} assay has facilitated rapid uptake, avoiding the need for overnight fasting or oral glucose tolerance testing to assess glycemic control.[81] Setting lower limits for HbA_{1c} helps prevent hypoglycemic events,[77] whereas use of CGM with low glucose alert settings can prevent hypoglycemia in real time. Setting upper limits for glucose control helps prevent complications, even with and including CKD.[82] It is a central focus of the KDIGO guideline to remind readers that glucose control remains central when caring for patients with diabetes.

Implementation and Challenges—Implementing individualized HbA_{1c} goals should be straightforward, based on recommendations from the KDIGO guideline. A critical first step is shared decision-making between the patient and his/her provider(s) as to what the HbA_{1c} goal should be. A clear second step is in monitoring to determine whether or not the goal has been met, with subsequent discussion about ways to achieve the goal or change the goal. Education, activation, and involvement of patients in shared decision-making remains vital to diabetes care and achieving HbA_{1c} goals.[83] Primary care providers are most likely to be responsible for implementing individualized HbA_{1c} goals early in the diabetes and CKD course. Referral to endocrinology or nephrology may be recommended, particularly for patients with type 1 diabetes, when the primary care provider deems the diabetes or diabetes-related CKD, respectively, to be poorly controlled or outside the scope of their expertise. Once care with an endocrinologist has been established, setting and seeking of the HbA_{1c} goal is then the combined responsibility of the endocrinologist and primary care provider in partnership with the patient, and close communication among all providers is important. It may be valuable for nephrology to communicate the status of the patient's kidney function, recent laboratory tests, and capillary glucose measures during dialysis when applicable. At that time, endocrinology may alter the HbA_{1c} goal and/or recommend SMBG and/or CGM surveillance of glycemic control in conjunction with HbA_{1c} if not already initiated.

Protein Intake

Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis *(2C)*.

Commentary—The 2012 KDIGO CKD guideline suggested maintaining a protein intake of 0.8 g/kg/d in adults with and without diabetes and eGFR <30 mL/min/ 1.73 m^2.[84] The 2020 KDIGO diabetes and CKD guideline expands this recommendation to all patients (regardless of eGFR) with CKD not receiving KRT and diabetes. Despite this expansion, the 2020 KDIGO guideline does not differ significantly from recommended protein intake for all adults by other organizations.[85,86] In contrast, in 2020, KDOQI updated its clinical practice guideline for nutrition in CKD, which now recommends a slightly lower goal of 0.6-0.8 g/kg/d, specifically in patients with CKD stage 3-5 and diabetes (not on dialysis).[87] The KDOQI work group felt the difference between a range of 0.6-0.8 versus 0.8 g/kg/d is unlikely to be statistically, clinically, or practically different (given the day-to-day variation in diet), and it is unlikely that trials to undertake this question will ever be done. The 0.8-g/kg/d definition of "moderate protein intake" derives from data in the general and CKD populations, which have found potential for malnutrition with lower protein intake

and associations of higher protein intake with worsening CKD, overweight/obesity, and cardiovascular disease. Specific to diabetes and CKD is the observation that high-protein diets in a rodent model can exacerbate hyperfiltration and subsequent interstitial fibrosis, processes that are intrinsic to the natural history of diabetic glomerulosclerosis.[88]

Additional studies may be warranted to support the KDIGO recommendation for moderate protein intake in people with diabetes and CKD. Results of observational studies and clinical trials of protein restriction are highly variable, and it is difficult to draw definitive conclusions due to significant heterogeneity in study design, participant characteristics, definition of "low" protein diet, and study duration. Some of the variability in results may be related to whether the studies were conducted before or after ACEI/ARB use became standard of care in diabetes and CKD. There are data to suggest that protein restriction has similar mechanisms to RAS inhibition, and it has been hypothesized that protein restriction in combination with ACEIs/ARBs could have an additive beneficial effect, although this remains to be proven.[89] Moreover, safety data for protein restriction is equivocal, as studies of protein restriction to <0.8 g/kg are sparse, with evaluation of nutritional status focusing on serum albumin or prealbumin, which are of questionable validity.[2]

Practice point 3.1.2 states that protein intake in patients with diabetes on dialysis may need to be somewhat higher (1.0-1.2 g/kg) than for nondialysis patients, which is consistent with the 2020 KDOQI nutrition guideline in CKD.[87] While there is little hard evidence for this, the guideline arises from the knowledge of a higher risk for malnutrition in dialysis patients who frequently suffer low serum albumin levels, particularly those on peritoneal dialysis.[2]

In addition to the total intake of protein, there is increasing awareness of considering the origin and quality of protein, which influence its digestibility, advanced glycation end-product intake, and dietary acid load. The KDIGO guideline does not make a specific recommendation for increasing vegetable sources of protein due to the lack of clinical trials in this space. However, the guideline did reference its legitimacy in a practice point that is supported with observational data.[2] The guideline suggests that patients with diabetes and CKD consume a diet high in vegetables, fruits, fiber, legumes, plant-based proteins, unsaturated fats, and nuts, with lower intake of processed meats, but a detailed review of evidence for this practice point is not provided. In animal studies, intake of acid-inducing foods (rich in animal proteins) versus base-inducing foods (fruits and vegetables) is associated with kidney disease progression.[90–92] In humans, vegetable and fruit supplementation in patients with advanced CKD may preserve eGFR.[90,91] Notably, dietary patterns can be modified to prevent the onset of CKD.[93,94] In a large community-based prospective cohort study, high intake of nonfermented vegetables significantly decreased the risk for incident proteinuria by 32% and the risk for incident eGFR <60 mL/min/1.73 m^2 by 14% compared to the lowest intake during an average follow-up of 8 years.[94] In another large population-based cohort study of health-related behaviors in the northern Netherlands, dietary patterns characterized by a high intake of eggs, dairy products, fruits, vegetables, and legumes and low intake of meat and sweets was associated independently with a lower risk of eGFR decline.[93] Moreover, these studies suggest that health behaviors and health education should not remain confined to those who already developed CKD but should be part of the therapeutic approach in patients at risk for CKD.

Clinical Utility—As stated in the KDIGO guideline, there is little evidence for clinical utility of protein restriction in patients with diabetes and CKD. The most rigorous appraisal of the evidence was a 2009 Cochrane systematic review that concluded that restricting protein intake in patients with diabetes and CKD may slow progression to kidney failure, but to a nonsignificant degree.[95] A more recent meta-analysis included a few additional trials and found heterogeneity by diabetes type, with the type 1 diabetes subgroup (as well as nondiabetic patients) seeing a greater benefit than the type 2 diabetes subgroup.[96] The impact on mortality and kidney failure has only been evaluated by a single, small (N = 82) study in people with long-duration type 1 diabetes, but it did find a statistically significant benefit.[97] While there is little evidence for significant benefit from moderating protein intake and switching to vegetable protein sources, there is also no harm imposed.[2]

Implementation and Challenges—Implementation of restricting protein in addition to carbohydrate, salt, and lipids while maintaining an adequate nutritional intake requires significant lifestyle changes that must be maintained indefinitely for optimal results. The complexity of such changes may overwhelm both clinicians, who need to be aware of various sources of macronutrients, and patients, who will navigate the availability, cost, and preparation when adopting these changes. The cost of following the KDIGO dietary recommendations is not insignificant,[2] particularly when taken in the context of high prescription drug costs for patients with diabetes and CKD. Food insecurity is common, occurring in 12% of adults with diabetes, and is associated with worse HbA_{1c} control and adherence to medications, indices important to kidney and cardiovascular health.[98,99] There are very few data regarding food insecurity specific to the population with diabetes and CKD, an area that could benefit from greater attention. Moreover, the rapid pace inherent to US culture has led to the pervasive multi-billion-dollar fast food industry and "ready-made meals" that offer limited quantities of the recommended nutritional values[100,101] that may be important to people living with diabetes and CKD. This obstacle will be difficult to overcome. However, a major, well-organized, well-financed, and unified approach from the medical community, similar to that taken in antismoking campaigns, may be helpful.

It is unknown what proportion of individuals with diabetes and CKD adhere to a moderate protein restriction and whether this has changed over time. Appropriately, the current KDIGO practice points recommend individualized nutrition education at diagnosis of diabetes and yearly nutrition education to help build self-management skills in patients with longstanding diabetes and CKD.[102] While the KDOQI work group agrees with these suggestions, dietary counseling by registered dietitians, accredited nutrition providers, behavioral therapists, or diabetes education programs will incur additional health care costs that, in some countries, is covered by health care systems, while, in other countries, is shouldered by the patient. In the United States, for the approximately 34 million people with diabetes, there are 102,000-106,000 registered dietitian and dietitian nutritionists, a group whose composition lacks diversity in both sex and race/ethnicity.[103] Notably, broadening the diversity of dietitians may be effective in reaching and impacting the population with diabetes and CKD, who are notably quite diverse.[47] Moreover, less than 25% of this workforce is found in outpatient care centers, schools, residential care facilities, or physician offices,[103] suggesting an insufficient and inefficient referral system. Much patient education

is shifting online, where patients with diabetes can find tools and programs for lifestyle changes; however, these are rarely tailored for CKD and are inaccessible to people without access to the internet.

Sodium Intake

Recommendation 3.1.2: We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD (*2C*).

Commentary—This recommendation is unchanged from that of the 2012 KDIGO guideline for CKD of all causes[84]; the 2020 KDIGO diabetes and CKD guideline elaborates on the lack of studies specific to this patient group. Accordingly, the basis for this guideline is extrapolated from the general population or people with CKD in general. The updated 2020 KDOQI clinical practice guideline for nutrition in CKD recommends a slightly higher sodium allowance, up to 2.3 g (100 mmol) per day, only in patients with CKD stage 3 or higher, and indicated specific utility for not only blood pressure and volume control, but also to reduce proteinuria.[87] The KDOQI work group felt that there is unlikely to be a clinically meaningful difference with a salt intake upper limit of 2 g versus 2.3 g per day. Furthermore, while salt reduction has clear short-term clinical benefits, studies on risks associated with long-term salt restriction particularly in diabetes and hypertension have not reported consistent findings,[104,105] and the impact of salt restriction in patients taking a sodium/glucose cotransporter 2 (SGLT2) inhibitor has not been assessed. Thus, the relative risks and benefits have not been completely determined for this population.

Clinical Utility—RCTs have indicated that moderate salt restriction significantly reduces blood pressure, fluid overload, albuminuria, and cardiac hypertrophy in patients with CKD.[106] The effects of sodium reduction are assumed to have greater importance in persons with than without CKD,[106] as the former experience higher prevalence of hypertension, a major risk factor for worsening kidney and cardiovascular outcomes. Further, CKD is associated with increased sodium sensitivity and inadequate blood pressure regulation by the renin-angiotensin-aldosterone system, and, in advanced CKD and/or comorbid heart failure, volume overload from high salt is common, often necessitating hospitalization.[107] Still, long-term effects on kidney outcomes and mortality remain unclear. Two meta-analyses published after February 2020,[107,108] and therefore not included by the KDIGO work group, confirm the beneficial effects of lowering sodium intake starting from early stages of CKD, and suggest that moderate dietary salt restriction, defined as <2.5 g sodium per day, significantly reduces blood pressure and proteinuria with few adverse effects. Still, results are conflicting, and there is significant heterogeneity of study designs and follow-up time, and important shortcomings to measurement of salt intake. Controlled clinical trials with long follow-up time, pre-specified clinical end points, and sound statistical analyses for multifactorial causality may be valuable to define the optimal level of salt intake at which progression of CKD may be ameliorated in patients with diabetes.

Implementation and Challenges—The average sodium intake in the United States is 3,400 mg/d, well above the updated KDIGO recommendations. Of those encouraged

to limit their sodium intake, virtually all exceed the recommended limit on a daily basis.[109,110] A review of studies evaluating the effect of urinary sodium excretion on kidney failure and cardiovascular outcomes found that less than one third of those with CKD consumed <2 g per day.[108] These studies indicate that implementation of low-sodium diets is challenging, particularly given the numerous other nutritional restrictions in patients with diabetes and CKD, including carbohydrates, protein, and, in more advanced CKD, potassium, magnesium, and phosphorus. Innovative approaches could be advantageous to ease patients' control of their diets. Suggested methods for self-monitoring salt intake include urine chloride strips and web-based self-management programs, though the utility of these interventions is limited, depending on educational attainment, income, and access to technology. An online aid is available to clinicians for developing and implementing sodium reduction programs, policies, and initiatives aimed at lowering sodium intake.[111]

Physical Activity

Recommendation 3.2.1: We recommend that patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (*1D*).

Commentary and Clinical Utility—Physical activity is a cornerstone of diabetes management, as it improves insulin sensitivity and management of hyperglycemia, blood pressure, hepatic steatosis, depression, and strength and mobility, adding disability-free years. This guideline recommendation is similar to the previous guidance on this issue in the 2012 KDIGO blood pressure and CKD guidelines,[84,112] as well as the 2019 guideline from the American College of Cardiology and the American Heart Association on the primary prevention of cardiovascular diseases[113] and the 2021 guideline from the ADA.[114] Because of a paucity of reliable studies on the role of physical activity in patients with diabetes and CKD, this recommendation was largely derived from studies in the general population or those at high risk for cardiovascular disease that sometimes included relatively small numbers of participants with diabetes and CKD. The KDOQI work group agrees that the guideline is reasonably derived from evidence in other populations; however, additional studies may be warranted to support the KDIGO conclusion. Indeed, a recent meta-analysis of RCTs indicated that, while exercise training among nondialysis CKD patients improved physical and walking capacity, it had no significant effect on all-cause mortality and kidney function relative to usual care.[115] The specific target of 150 minutes of moderate-intensity physical activity per week is poorly supported for patients with diabetes and CKD.[115] The prevalence of disability is higher in people with CKD than without CKD, with 26%-31% reporting difficulties in lower-extremity mobility and general physical activity and limitations in their ability to work (22%) and in the type of work they perform (34%).[116] Since light-intensity physical activity has been shown to improve outcomes in CKD patients and has not been shown to be inferior to moderate-intensity physical activity,[117] the KDIGO guideline suggests light or moderate-intensity physical activity for patients with diabetes and CKD to a level compatible with their cardiovascular and physical tolerance.

Implementation and Challenges—Even though the long-term benefits of encouraging regular physical activity remain uncertain among patients with diabetes and CKD, a sedentary lifestyle increases cardiovascular risk,[116] and therefore recommending any degree of regular physical activity can have important physical, psychological, and social benefits.[118,119] Implementation of the recommendation for physical activity, with or without intentional weight loss, will rely on a multidisciplinary network of physicians and health care providers to assess baseline activity level, identify suitable physical activities, personalize lifestyle programs, and monitor the clinical effectiveness of interventions. It is therefore valuable to increase awareness of CKD and CKD-related lifestyle interventions among physicians, podiatrists, and advanced practice providers from multiple specialties.

The practice points developed by KDIGO are derived from the overall guideline and focus on its implementation. The focus on individualizing care in each of the practice points is based on limited data and is reasonable but leaves the practicing clinician without clear direction.[2] Practice point 3.2.1 mentions patient ethnicity as a consideration in physical activity recommendations; in fact, there is no evidence to vary the amount of physical activity because of ethnic differences,[2] and, as such, ethnicity should not be a factor in its determination. Further, patients with diabetes and CKD are at increased risk for physical activity–related adverse events, including falls, dehydration, hypoglycemia, and hypotension, that may offset the benefits of maintaining an active lifestyle. These events could be mitigated through self-management of and directed education about fluid consumption, glycemic control before and after physical activity, and foot care, among other issues.[120]

Metformin

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR 30 mL/min per 1.73 m^2 with metformin (*1B*).

Commentary—Metformin is an appropriate first-line agent for the treatment of type 2 diabetes because of its proven efficacy in improving glycemia, its cardiovascular benefits as shown in the UKPDS,[121] long-term safety data,[122] and its low cost.[123] The KDIGO recommendation is in line with guidelines from the ADA[124] and the AACE,[125] which recommend metformin plus lifestyle modification as initial therapy. However, the European Society of Cardiology (ESC) recently recommended that a glucagon-like peptide 1 receptor agonist (GLP-1 RA) or an SGLT2 inhibitor be given instead of metformin as an initial agent in drug-naïve patients with high or very high cardiovascular risk, and that metformin be limited to those without evidence of cardiovascular disease.[126] This ESC recommendation was based on several cardiovascular outcome trials (CVOTs) showing significant benefits of GLP-1 RAs and SLGT2 inhibitors, but, in fact, in all of these studies, the investigational drug was added to a base therapy with metformin.

Data supporting the choice of metformin as a first-line agent come from several studies spanning over 2 decades. In addition to the cardiovascular benefit of metformin demonstrated by the UKPDS,[121] a retrospective cohort study of Korean patients with type 2 diabetes and stage 3 CKD showed metformin to decrease all-cause mortality as well

as progression to kidney failure.[127] Likewise, 2 systematic reviews and meta-analyses also showed decreased progression to kidney failure and reduced all-cause mortality with metformin use in patients with diabetes and CKD stage 3.[128,129]

The KDIGO guideline discusses the change in the Federal Drug Administration (FDA) warning regarding the risk for lactic acidosis and mentions the recommendation that metformin can be used safely without an increased risk of lactic acidosis down to an eGFR of 30 mL/min/1.73 m^2.[130,131] Additional more recent large studies showing a lack of risk for lactic acidosis above this eGFR cutoff now support this recommendation.[45,127,130] While the FDA does not explicitly state that dose adjustments are required above an eGFR of 30 mL/min/1.73 m^2, we agree with the KDIGO guideline, which offers a practice point to halve the dose for an eGFR <45 mL/min/1.73 m^2. Not mentioned by KDIGO is the FDA recommendation that metformin not be initiated in people with an eGFR <45 mL/min/1.73 m^2, based upon the notion that these patients are likely to progress to an eGFR <30 mL/min/1.73 m^2, wherein metformin would be contraindicated. KDIGO does, however, provide a suggestion to reduce the dose of metformin, even when the eGFR is 45-59 mL/min/1.73 m^2, in the presence of conditions that predispose patients to hypoperfusion and hypoxemia. These transient conditions generally are seen in the inpatient setting.[2] Other inpatient factors that could cause problems include radiology dye-induced acute kidney injury and sepsis. We agree with the recommendation of the ADA and the AACE that metformin should be discontinued when most patients are admitted to the hospital because of their increased risks for these conditions that also increase the risk for lactic acidosis.[132]

Clinical Utility—The KDIGO guideline includes several practice points that are particularly useful and worth reiterating. These include (1) the use of metformin in kidney transplant patients with the same eGFR cut point of 30 mL/min/1.73 m^2,[133–135] (2) the suggestion for more than annual monitoring of kidney function when patients reach CKD stage 3 because of the possibility of a more rapid fall in eGFR possibly necessitating modification of metformin dosing,[2] (3) a reduction in dosing of metformin to 1,000 mg/d when the eGFR falls to <45 mL/min/1.73 m^2,[2] and (4) the need to monitor for vitamin B$_{12}$ deficiency with use of metformin for more than 4 years.[136,137]

While the KDOQI work group agrees with these statements, it should be noted that the KDIGO practice point regarding the need to reduce the dose of metformin to a maximum of 1,000 mg/d when the eGFR is <45 mL/min/1.73 m^2 is based upon expert opinion rather than being data-driven. It may be important to determine from existing databases and prospective studies whether such a recommendation is actually needed.

The KDIGO practice point about the use of metformin in transplant patients is based primarily upon registry and pharmacy claims data and 1 small prospective study. Additional data from large, prospective studies may be valuable to confirm the efficacy and safety of metformin in such patients.

Implementation and Challenges—Primary care and diabetes clinicians often prescribe metformin as the initial pharmacological therapy in patients with type 2 diabetes.[138] The change in the FDA guideline from using serum creatinine levels to eGFR calculations with

a cutoff of 30 mL/min/1.73 m^2 may reduce the challenges for clinicians in determining when to stop metformin, as most laboratories now report the actual eGFR when it is <60 mL/min/1.73 m^2.[139] The KDIGO practice point about measuring the eGFR more frequently than annually when the eGFR is <60 mL/min/1.73 m^2 is reasonable.[2] However, it may require education on the part of nonnephrology clinicians, highlighting the importance of concerted efforts to improve uptake of this guideline. Moreover, other antihyperglycemic agents also have caveats with respect to their use in CKD and transplant, issues often overlooked by all clinicians. Table 1 summarizes the salient features of antihyperglycemic agents not otherwise discussed by the KDIGO guideline and issues important to their use in patients with CKD.

SGLT2 Inhibitors

Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and an eGFR 30 mL/min per 1.73 m^2 with an SGLT2i (*1A*).

Commentary—The discovery of the cardiorenal protective effects of SGLT2 inhibitors has been a turning point for the treatment and prognosis of patients with type 2 diabetes and CKD. The magnitude of their mitigating effect on cardiorenal end points and general consistency of findings across SGLT2 inhibitor trials is a rarity in clinical research, and thus the scientific and academic communities have embraced this long-awaited innovation.[11,14,126] It is important to mention that the CVOT with ertugliflozin was published soon after the KDIGO guideline became available and did not meet statistical significance for its primary cardiovascular or kidney outcomes.[140] The effect of ertugliflozin on heart failure, however, was statistically significant and in line with other SGLT2 inhibitor CVOTs. Moreover, study design and outcome definitions differed between the trials, and post hoc analysis showed that ertugliflozin did lower the risk of the kidney outcome defined as a composite of sustained 40% decline from baseline eGFR, KRT, or kidney disease–related death (HR, 0 66; 95% CI, 0.50-0.88).[141] Given this new information, the panel felt that, when initiating patients on therapy, providers should consider the beneficial class effect of SGLT2 inhibitors,[142] the specific drug choices that are evidence-based, using where possible the most effective drug for the individual patient, according to trial eligibility criteria, trial design, and subgroup analyses outcomes.

The KDIGO guideline reviews the data demonstrating the cardiorenal benefits of SGLT2 inhibitors for type 2 diabetes, including (1) reduction in composite kidney end points of doubling of creatinine, kidney failure, and death from kidney failure and (2) reduction in composite major adverse cardiovascular outcomes of cardiovascular death, nonfatal myocardial infarction and stroke, and hospitalization for congestive heart failure. The impact of this drug class on cardiovascular as well as kidney outcomes is of particular importance to patients with type 2 diabetes and CKD given that the majority of people with type 2 diabetes and CKD are more likely to die of cardiovascular causes than to progress to advanced CKD or kidney failure.[143] Furthermore, the notion that diabetes increases the risk of cardiovascular death has recently been found to be predominantly mediated by the presence of CKD.[143,144]

An important practice point underscores the lack of data for efficacy or safety in kidney transplant recipients, particularly given their immunosuppressed status and the potential increased risk for infection. There are, in fact, a few small studies suggesting that their safety is similar to that in the native CKD population. Kidney transplant patients suffer high rates of congestive heart failure,[145] cardiovascular events,[146] death with a functioning graft,[147] and graft loss due to nonimmunologic causes (ie, graft CKD progression[148]). A clinical trial with sufficient power to address efficacy in this growing population could be highly impactful.

Notably, KDIGO does not mention albuminuria as a criterion in their recommendation for use of SGLT2 inhibitors in type 2 diabetes and CKD. The rationale for this omission is not specifically addressed, but may be based on a benefit in kidney outcomes even in the SGLT2 inhibitor CVOTs, in which roughly half of participants had normoalbuminuria and another 30% had moderate albuminuria.[149] Additionally, a post hoc analysis of the CANVAS-R trial analyzed eGFR slope, stratifying by severity of albuminuria (mild, moderate, or severe), and found that, while the greatest numeric reduction was in the severe albuminuria group (3.0 [95% CI, 2.0-4.0] mL/min/1.73 m^2 per year), reductions in the moderate and mild albuminuria groups were also statistically significant (1.0 [95% CI, 0.6-1.4] and 1.0 [95% CI, 0.9-1.3] mL/min/1.73 m^2 per year, respectively).[150] The difference in eGFR slope in the mild albuminuria group, however, was driven by a positive direction in the canagliflozin group, which has not been replicated by other studies.

The most convincing evidence that the presence or magnitude of albuminuria is unnecessary for the benefit of SGLT2 inhibitors comes from recent post hoc analyses of the EMPA-REG and CANVAS studies,[151,152] which analyzed cardiorenal outcomes, stratifying participants according to KDIGO CKD risk categories. While the absolute risk reductions were greater for higher risk categories, the relative risk reductions for both cardiac and kidney outcomes were similar across KDIGO CKD risk categories. Particularly noteworthy is that even participants in the low-risk category (eGFR 90 mL/min/1.73 m^2 and UACR <30 mg/g) experienced a decreased risk for incident or worsening nephropathy and the composite end point. This finding has great implications given the much greater numbers of individuals with earlier CKD stages who stand to benefit.

The KDIGO guideline specifies a lower limit eGFR of 30 mL/min/1.73 m^2 for initiation of SGLT2 inhibitor but maintains that it is safe to continue until reaching the need for KRT. Available evidence supports this statement, as the majority of trials have used this minimum eGFR as an inclusion criterion.[153] Notably, however, 2 trials published shortly after the release of the KDIGO guideline, DAPA-CKD and EMPEROR, enrolled patients down to an eGFR of 25 and 20 mL/min/1.73 m^2, respectively. EMPA-KIDNEY (ClinicalTrials.gov identifier NCT03594110)[154] is enrolling patients down to an eGFR of 20 mL/min/1.73 m^2, and thus may provide additional evidence of safety and efficacy in patients with CKD stage 4. It may be appropriate in patients with UACR >1,000 mg/g who are at high risk for rapid decline in eGFR or have a history of rapid eGFR decline to initiate an SGLT2 inhibitor at an eGFR of 25 mL/min/1.73 m^2, as the DAPA-CKD trial is directly applicable to patients with CKD.

Clinical Utility—Evidence supports the additional practice points provided by the KDIGO guideline, which encompass the addition of an SGLT2 inhibitor to existing antihyperglycemic agents unless there is concern for hypoglycemia, in which case it is recommended to reduce the dose or discontinue antihyperglycemic medications other than metformin.[2] The rationale for maintaining metformin is that the vast majority of evidence for SGLT2 inhibitor cardiorenal efficacy in type 2 diabetes is based on trials adding SGLT2 inhibitor to metformin unless the patient is intolerant. The KDOQI work group agrees with this sentiment; however, there may be room for exceptions. While an infrequent situation, the patient with type 2 diabetes and CKD on metformin monotherapy with HbA_{1c} in the low or normal range (eg, <7.0%) might not be initiated on an SGLT2 inhibitor based on the KDIGO guideline, thus not reaping the benefits of this therapeutic class. Approximately 18%-25% of participants in 3 large SGLT2 inhibitor CVOTs[155–157] and 50% in the CREDENCE trial[158] were not on metformin at baseline. There are no post hoc analyses comparing outcomes according to baseline metformin therapy; however, such information may be helpful to inform clinical decisions. Moreover, SGLT2 inhibitor cardiorenal outcomes have been similar in diabetic and nondiabetic strata, strongly suggesting there is potential benefit regardless of the use of metformin.[159] Therefore, in some cases, it may be reasonable to reduce or discontinue metformin in order to safely utilize an SGLT2 inhibitor from a glycemic perspective.

The KDOQI work group agreed with other practice points, including withholding of SGLT2 inhibitors during hospitalization or periods of fasting when risk for diabetic ketoacidosis is higher, and to consider decreasing or holding diuretics in euvolemic individuals with initiation of SGLT2 inhibitor to reduce the risk for hypovolemia.[2] It is particularly important to underscore the practice point regarding the expected and benign initial decline in eGFR with SGLT2 inhibitor initiation.[160]

Implementation and Challenges—KDIGO offers a clinical practice point to prioritize agents with proven cardiorenal benefit, while also acknowledging that choice of therapy will mostly depend upon insurance formulary and availability of public and private patient assistance programs. While not all agents have met statistical significance for individual and even composite cardiorenal outcomes, meta-analyses have demonstrated consistency in end point results and show that benefits are most likely a class effect.[142,161,162]

The primary implementation challenge for the recommended usage of SGLT2 inhibitor in patients with type 2 diabetes and CKD will likely be the wide adoption of this recommendation.[163] As an example, despite the evidence of cardiorenal benefit of ACEI/ARB therapy for patients with type 2 diabetes, in the United States, only 21%-50% of people with a clear indication are currently receiving these important medications.[42,43] This is in contrast to Europe, wherein 75%-80% of eligible patients are receiving ACEI/ARB therapy.[64] To avoid similar experience with SGLT2 inhibitors, it may be advantageous to place a greater emphasis on the effective delivery of clinical practice guidelines across specialties. This effort may include concise discussion on the tolerability, adverse effects, as well as the risk-benefit ratio, with clear guidance on how to mitigate undesired harmful effects.

We agree with the KDIGO guideline that reasons for the limited implementation of proven therapies in the United States are complex and multifactorial, and include physician and patient awareness and appreciation of the impact of CKD on cardiovascular morbidity and mortality, physician awareness and harmonization of clinical practice guidelines, physician inertia, competing health issues, polypharmacy, and differences in cost by country location.[44] The majority of clinical practice guidelines, KDIGO included, have taken steps to harmonize recommendations for SGLT2 inhibitor initiation.[11,14] The complex and multifactorial issues may only be addressed with intentional, multidisciplinary efforts at local, regional, and national levels.[164]

Glucagon-Like Peptide 1 Receptor Agonists

Recommendation 4.3.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (*1B*).

Commentary—This KDIGO recommendation is reasonable given the very high cardiovascular risk in patients with type 2 diabetes who have CKD.[143] However, the KDIGO recommendation does not specify that all GLP-1 RAs are equal with respect to cardiovascular or kidney benefits. In their discussion, they do note that cardiovascular benefit has been shown for liraglutide, dulaglutide, injectable semaglutide, and albiglutide (not available in the United States) and the lack of cardiovascular benefit with lixisenatide and exenatide and oral semaglutide. It can be noted that, in the oral semaglutide PIONEER 6 study, which was not powered to show cardiovascular benefit, there were significant reductions in cardiovascular and all-cause mortality.[165] A full postmarketing cardiovascular outcome study for oral semaglutide is ongoing. Thus, the cardiovascular benefit is not truly a class effect, and a suggested modification of the guideline recommendation would be "…we recommend a long-acting GLP-1 RA with proven cardiovascular benefits."

In their discussion of kidney benefits, KDIGO notes that the composite kidney outcome benefit for liraglutide was driven primarily by the reduction in new severely increased albuminuria. However, they omitted this proviso when discussing the composite kidney outcome benefits for semaglutide and dulaglutide. They do mention that the exploratory analyses show possible preservation of eGFR with dulaglutide in the REWIND study when using eGFR reductions of 40% and 50% from baseline and acknowledge that these will need confirmation, as the primary analysis of a sustained reduction of 30% from baseline did not show this.[166] In the discussion of harms of GLP-1 RAs, they recognize that "Treatment with GLP-1 RA may be used to prevent end-organ damage (heart and kidney) as well as manage hyperglycemia." Since there is no proven benefit of this class on eGFR preservation outside the possible effect of dulaglutide,[167] we feel that this statement that includes "kidney" may be too strong.

Clinical Utility—The following guideline practice points are especially worthy of mention: (1) the prioritization of GLP-1 RAs to those agents with documented cardiovascular benefits, (2) starting with a low dose and titrating upward slowly to minimize gastrointestinal side effects, (3) not using GLP-1 RAs with dipeptidyl peptidase 4

(DPP-4) inhibitors, and (4) pointing out the lack of hypoglycemia risk with this class unless they are being used with insulin or sulfonylureas. These practice points are of particular importance to CKD patients who are more susceptible to hypoglycemia.[68] In the AWARD-7 trial, participants treated with dulaglutide experienced significantly lower rates of hypoglycemia (blood glucose 70 mg/dL) compared to insulin glargine.[168] Specifically, liraglutide, semaglutide, and dulaglutide do not require dose adjustment for low eGFR.[169–172] Recommendations are the same for kidney transplant recipients as for other CKD patients; however, experience in patients requiring dialysis is lacking, but pharmacokinetic studies showed no excess of side effects or changes in efficacy in patients on peritoneal dialysis.[173,174]

KDIGO also briefly mentions the weight-loss benefits of GLP1 agonists; however, given the rising prevalence of obesity and its independent effect on CKD and CVD pathogenesis, we feel this effect should be highlighted. Studies have shown a 5%-10% body weight loss with GLP-1 RAs in obese individuals, which is often maintained over the long term. This benefit is far-reaching, impacting not only cardiovascular and kidney health, but also the potential for improvements in other chronic illnesses and quality of life.[175]

Implementation and Challenges—The lack of uniformity of cardiovascular benefits among the approved drugs in this class precludes concluding that the cardiovascular benefits are a class effect. While insurance and pharmacy benefit manager policies may dictate which drug can be used for a given patient, it may be important for clinicians to recognize this lack of class effect, and it may take additional effort with prior approvals to specify use of a GLP-1 RA with proven cardiovascular benefit.

Although the AWARD-7 trial of patients with stage 3 CKD treated with dulaglutide suggested that there was some preservation of eGFR,[168] the subgroup with stage 3 CKD in the larger REWIND trial did not show a significant benefit on the sustained decline of eGFR of >30%.[166] The FLOW trial may help clarify the role of the injectable semaglutide on reduction of kidney disease progression as a primary outcome.[176]

Self-Management Education Programs

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD [callout to guideline figure 28 omitted] (*1C*).

Commentary and Clinical Utility—In its final chapter, the KDIGO guideline addresses the issue of self-management in patients with diabetes and CKD as well as the related topic of implementing team-based integrated care.[2] The content is similar to recommendations issued in a recent consensus report issued by the ADA and other professional groups entitled "Diabetes Self-Management Education and Support in Adults With Type 2 Diabetes"[177] and rely, to a large extent, on similar analyses of supporting literature.

The general recommendations and practice point guidance presented in the guideline are supported by available evidence.[2] The KDOQI work group agrees that the goal of self-management would be embraced by patients, at least in most situations.[178] This was

the major reason KDIGO raised the guideline to the level of 1C (ie, a recommendation, instead of 2C [suggestion]). A systematic review supports the efficacy of well-structured self-management educational programs in improving surrogate outcomes, such as blood pressure and glycemic control,[179] in a generally cost-effective manner.[180] However, we agree with the KDIGO guideline that the evidence supporting this recommendation is relatively weak, largely due to the lack of reporting of critical outcomes and relatively low quality of evidence for surrogate end points. Finally, it may be beneficial to use multiple educational modalities for effective self-management education.

Implementation—The KDIGO guideline authors noted some concern regarding cost-effectiveness of telehealth approaches; however, this conclusion was based on mostly low-quality studies performed 10-15 years ago in which costs of implementing telemedicine education were significantly higher than other approaches.[180] It is unlikely that such a cost differential still exists. Results from a more recent pragmatic RCT on the cost-effectiveness of home telemonitoring in patients with CKD have not yet been reported.[181] It is expected that the COVID-19 pandemic has facilitated much of the infrastructure and cultural acceptance of telehealth, particularly regarding individual and group-based educational sessions and peer support groups. Moreover, strategies to best develop, implement, and evaluate effective programs tailored to the complex and diverse population of patients with diabetes and CKD may not be universally applicable. Embedded in a practice point, KDIGO suggests that health care systems take on this role; however, it seems the main challenge to this will be the cost of such programs and difficulty in assessing their cost-effectiveness.

Team-Based Integrated Care

Recommendation 5.2.1: We suggest that policymakers and institutional decision-makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD (*2B*).

Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (eg, trained nurses and dietitians, pharmacists, health care assistants, community workers, and peer supporters) preferably with knowledge of CKD [callout to guideline figure 33 omitted].

Commentary—KDIGO recommendation 5.2.1 reflects the well-established practice of team-based approaches to the management of diabetes, adding in the management of CKD.[2] Importantly, the other impetus for this recommendation is the recognition of the worldwide pandemic of diabetes and that improved management of the millions of patients with diabetes and CKD will likely require a systematic, team-based integrated care system.[182] Studies of patients with both CKD and diabetes are limited, but implementing a team-based approach in this group will likely not be inherently different than in other chronic disease populations. The KDOQI work group feels that the guideline as written is vague in delineating which policy makers and institutional decision-makers they are calling on and what, specifically, their role would be. While these details could be considered beyond the scope of international clinical guidelines, the lack of such specifics could potentially impede progress in designing impactful care models for patients with diabetes and CKD. State

governments, academic medical centers, public health departments, and pharmaceutical organizations may collaborate to (1) identify regions with unacceptably high rates of diabetes and CKD, (2) set benchmarks for reductions in disease prevalence, and (3) design, implement, and test results of team-based programs, propagating those with greatest efficacy to each and every targeted locale.

Clinical Utility—Much of the literature supporting the clinical efficacy of such approaches comes from the team-based management of general diabetes populations.[182] Widespread data specific to the population with diabetes and CKD is lacking; nevertheless, the potential clinical and economic impact of such programs is best represented by the Special Diabetes Program for American Indians, which resulted in a decreased incidence in diabetes-related kidney failure by 54% between 2000 and 2013.[183]

Implementation and Challenges—The institution of a team-based integrative care strategy for patients with diabetes and CKD worldwide faces challenges, including changes to payment systems, processes of care, cultures within the health care system and access to care, and structural racism and classism, which is not better illustrated than in the space of diabetes and CKD. Most importantly, there is no commitment worldwide to devote the resources needed for this approach. Until such a commitment is made, this recommendation will likely remain aspirational for most countries. Nations with the economic and political resources and, perhaps most importantly, the necessary advocacy can at least start to pave the road. In the United States, one approach to addressing these challenges is the Advancing American Kidney Health Initiative, which set a benchmark to reduce the incidence of all kidney failure by 25% by the year 2030.[184]

Conclusions

We are at a pivotal moment in the care of people with diabetes and CKD. Never before has there been so much attention paid and resources provided to this important disease state. While many challenges remain in this field (Box 1), KDIGO has made a significant step forward in providing a comprehensive clinical practice guideline dedicated to diabetes and CKD. Importantly, this guideline is in sync with those of most other major national and international professional organizations, providing clarity for providers of varying subspecialties. While some recommendations are quite clear, such as early incorporation of RAS and SGLT2 inhibition in the care of patients with diabetes and CKD, others raise questions, such as how to integrate multidisciplinary and comprehensive care models into the current structure of health care in the United States. There is much work to be done to improve the health and quality of life for patients with diabetes and CKD, but KDIGO has now provided a platform from which the research, policy, and clinical communities can unite to make further impactful changes.

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Because they are designed to reflect the views and recommendations of the responsible KDOQI Commentary work group and they are reviewed and approved by KDOQI and NKF leadership, KDOQI Commentaries are not peer reviewed by AJKD. *This article was prepared by a KDOQI Commentary work group comprising the authors and cochaired by Drs Amy Mottl and Susanne Nicholas. It was reviewed and approved by the NKF Scientific Advisory Board and the KDOQI Chair and Vice Chair.*

Box 1.

Areas Identified That Are Complementary and Supplemental to Those Described in KDOQI Guideline for Further Research and Policy Changes to Improve Care of People With Diabetes and CKD

Research

- Uptake of CKD screening and treatment for diabetes complications in adolescents and young adults

- Optimal approaches to transition from pediatric to adult diabetes care and risk for complications

- Medical therapies for weight loss in children with obesity and diabetes

- Medical therapies for weight loss in people with diabetes and CKD

- Improvements in and testing of electronic health record/patient portals with best practice advisory to both patients and providers

- Efficacy of community health workers in improving risk factors slowing progression of diabetes complications

- Identifying practical, cultural, political, and financial incentives to improve multidisciplinary care models

- Benefits of ACEI/ARBs in nonalbuminuric CKD and diabetes

- Quantitative and qualitative studies regarding lack of prescribing ACEI/ARBs in diabetes and CKD

- Precision medicine approaches to targeting specific drugs based on individual pathogenetic etiology, eg, ACEIs, ARBs, SGLT2 inhibitors, GLP-1 RAs, MRAs

- Identifying optimal, individualized glycemic control parameters in diabetes and CKD

Policy Changes

- Expanding access to continuous glucose monitors for patients with type 2 diabetes and CKD

- Expanding access to SGLT2 inhibitors and GLP-1 RAs for inadequately insured patients with diabetes at high risk of CKD and cardiovascular events

- Incentivizing and forming individual and group educational forums for diabetes care and complications

- Incentivizing subspecialty care in rural areas with high rates of diabetes and/or providing transportation for high-risk patients with poor access to subspecialty care

- Incentivizing multidisciplinary/shared clinics between subspecialties and e-consults for primary care providers

- Improved access to healthy foods for people with diabetes and food insecurity

- Broadening the diversity of dietitians and training specific to diabetes, CKD, and weight loss

- Expanding access to exercise trainers for people with diabetes, CKD, and obesity

- Broadening the use of social workers to provide guidance to providers and patients regarding social support networks and access to medications

Abbreviations: CKD, chronic kidney disease; ACEI, angiotensin II converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SGLT2, sodium/glucose transporter 2; GLP-1 RA, glucagon-like peptide 1 receptor agonist; RAS, renin-angiotensin system; MRA, mineralocorticoid receptor antagonist.
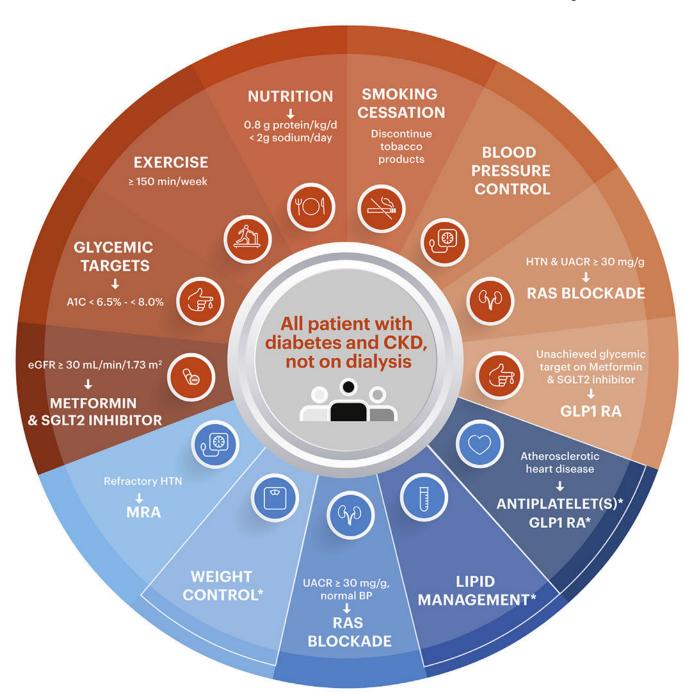
Figure 1.
Schematic for comprehensive care of the patient with type 2 diabetes and CKD. Recommendations from KDIGO (Kidney Disease: Improving Global Outcomes) are represented in orange. Practice points from KDIGO are represented in blue. Asterisk refers to recommendations not specifically addressed by the original schematic in the KDIGO guidelines but deemed important worthy of inclusion by the KDOQI work group. Abbreviations: CKD, chronic kidney disease; HTN, hypertension; GLP-1 RA, glucagon-like peptide 1 receptor agonist; RAS, renin-angiotensin system; MRA,

mineralocorticoid receptor antagonist; SGLT2, sodium/glucose transporter 2; UACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; BP, blood pressure.

Table 1.

Commonly Used Antihyperglycemic Agents Used for Type 2 Diabetes With HbA$_{1c}$ Above Target in the Setting of Current Use, Contraindication, or Intolerance With Combination Metformin, SGLT2 Inhibitors, and GLP-1 RA

Antihyperglycemic Class	Mechanism (Range of HbA$_{1c}$ Change)	Risks/Drawbacks	Benefits	Factors to Consider in CKD/Transplant/Dialysis
Sulfonylureas (glipizide, glyburide, glimepiride, gliclazide)	Increased insulin secretion (0.8%-1.5%)	Hypoglycemia, weight gain	Inexpensive	- Glipizide and gliclazide are safer in CKD; not renally cleared, no active metabolites[185,186] - Glyburide and glimepiride pose increased hypoglycemia risk - Glyburide and glimepiride should not be used with eGFR <60 and <30 mL/min/1.73 m², respectively[187,188] - Glyburide and glimepiride effectively increase cyclosporine levels; glipizide does not[189,190] - Cotrimoxazole combined with glipizide increases risk for hypoglycemia[191]
DPP-4 inhibitors (linagliptin, sitagliptin, saxagliptin, alogliptin)	Decreased breakdown of GLP-1 (0.5%-0.8%)	Do not use with GLP-1 RA	None	- Only linagliptin does not need dose adjustment in CKD[192] - Cyclosporine and itraconazole increase saxagliptin levels, so dose should be reduced[193]
Thiazolidinediones (pioglitazone)	Increased insulin sensitivity (0.5%-1.4%)	Fluid retention[194], fracture risk[194,195]	Inexpensive, decreased insulin needs	- No dose adjustments required[188,196] - Safe in kidney transplantation[197]
Glinides (nateglinide, repaglinide)	Rapid, short-lived insulin secretion with meals (0.5%-0.8%)	Hypoglycemia, weight gain	Reduces postprandial hyperglycemia	- Repaglinide safer in CKD; not renally cleared, but if eGFR <30 mL/min/1.73 m², use with caution[198,199] - Nateglinide has active metabolites that are renally cleared, so if eGFR <60 mL/min/1.73 m², increased hypoglycemia risk[198,199] - Nateglinide cleared by hemodialysis[198] - Cyclosporine and itraconazole increase repaglinide levels[200]
α-Glucosidase inhibitors (acarbose, miglitose)	Delays carbohydrate absorption in small intestine (0.5%-0.8%)	Flatulence, diarrhea	Reduces postprandial hyperglycemia	- Miglitol renally excreted, so if eGFR <60 mL/min/1.73 m², not recommended[186,201] - Acarbose minimally absorbed, but metabolites renally cleared, so if eGFR <30 mL/min/1.73 m², not recommended[186,201]
Insulin	Exogenous insulin	Hypoglycemia, injectable, weight gain	None, no dose limitations or ceiling on HbA$_{1c}$ reduction	- Renally metabolized and doses should be adjusted with decreasing eGFR, particularly rapid-acting insulin[202,203] - Rapid-acting insulins given after meal may be helpful in patients with gastroparesis

Abbreviations: CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; RA, receptor agonist; HbA$_{1c}$, hemoglobin A$_{1c}$.