Annals of Internal Medicine

CLINICAL GUIDELINE

Diabetes Management in Chronic Kidney Disease: Synopsis of the 2020 KDIGO Clinical Practice Guideline

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Description: The Kidney Disease: Improving Global Outcomes (KDIGO) organization developed a clinical practice guideline in 2020 for the management of patients with diabetes and chronic kidney disease (CKD).

Methods: The KDIGO Work Group (WG) was tasked with developing the guideline for diabetes management in CKD. It defined the scope of the guideline, gathered evidence, determined systematic review topics, and graded evidence that had been summarized by an evidence review team. The English-language literature searches, which were initially done through October 2018, were updated in February 2020. The WG used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to appraise evidence and rate the strength of the recommendations. Expert judgment was used to develop consensus practice points supplementary to the evidence-based graded recommendations. The guideline document underwent open public review. Comments from various stakeholders, subject matter experts, and industry and national organizations were considered before the document was finalized.

Recommendations: The guideline includes 12 recommendations and 48 practice points for clinicians caring for patients with diabetes and CKD. This synopsis focuses on the key recommendations pertinent to the following issues: comprehensive care needs, glycemic monitoring and targets, lifestyle interventions, antihyperglycemic therapies, and educational and integrated care approaches.

Ann Intern Med. doi:10.7326/M20-5938 **Annals.org**

For author, article, and disclosure information, see end of text.

This article was published at Annals.org on 10 November 2020.

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The burden of chronic kidney disease (CKD) is increasing around the globe, and diabetes is a leading cause of CKD and kidney failure worldwide (1). In addition to the risk for kidney function decline, patients with diabetes and CKD have high cardiovascular risk (2, 3). Management of diabetes in those with CKD poses several challenges and has been limited by the relatively small number of informative trials. During the past few years, several trials have reported benefits of novel agents in this population, and additional trials are under way.

The overall objective of the Kidney Disease: Improving Global Outcomes (KDIGO) guideline is to inform the management of patients with diabetes and CKD, which often requires a multidisciplinary approach. The target audience includes primary care physicians, nephrologists, endocrinologists, cardiologists, diabetes nurse educators, pharmacists, dietitians or nutritionists, and other clinicians caring for patients with diabetes and CKD worldwide. The guideline includes chapters on the following aspects of diagnosis and treatment in patients with diabetes and CKD: comprehensive care, glycemic monitoring and targets, lifestyle interventions, antihyperglycemic therapies, and approaches to management.

Within the guideline, recommendations for clinical practice, implementation, and future research are highlighted. The guideline considers implementation across international settings because resource availability and allocation may differ by setting. The full guideline, which includes 12 recommendations and 48 practice points, is available at https://kdigo.org/guidelines/diabetes-ckd (4). This synopsis focuses on key recommendations and practice points to guide practitioners in managing patients with diabetes and CKD.

Guideline Development Process, Evidence Grading, and Stakeholder and Public Review

The KDIGO Work Group (WG) consisted of an international group of nephrologists, diabetologists, cardiologists, epidemiologists, primary care practitioners, dietitians, patient representatives, and the Cochrane Kidney and Transplant Evidence Review Team. The WG formulated the scope of the guideline and graded evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, which is KDIGO's usual practice (**Appendix Tables 1** and **2**, available at Annals.org) (5).

The WG identified specific clinical and research questions relevant for clinical practice. The evidence review team then conducted systematic reviews of randomized controlled trials and other study types on the following topics for patients with diabetes and CKD: comprehensive care, glycemic monitoring and targets, lifestyle interventions, antihyperglycemic therapies, and approaches to management. Systematic searches, limited to articles published in English, were done through October 2018 and updated in February 2020. Primary data, reviews, and meta-analyses used to generate the guideline are available on the MAGICapp (MAGIC Evidence Ecosystem Foundation) platform. Evidence from

the systematic reviews was summarized into tables using standard Cochrane and GRADE methods. Primary decision analyses and economic analyses were not done, but resource implications were considered when formulating recommendations.

Guideline development, evidence synthesis, and writing of the guideline were done by the WG, with support from the evidence review team. Recommendations were developed by the WG, with all decisions made by consensus. Full details of the process, topic discussion, and consensus development are presented in the published guideline. In addition to graded recommendations, the guideline includes "practice points," which represent the WG's expert judgment about a specific aspect of care. They were crafted when no formal systematic evidence review was done or when there was insufficient evidence to provide a graded recommendation. For more on practice points, please see the full guideline. A structured public review process was done to elicit feedback from external stakeholders. The final guideline incorporated comments and suggestions from the external review when appropriate.

COMPREHENSIVE CARE

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).

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

Multimorbidity Care

Given that multimorbidity is common among persons with diabetes and CKD, management often requires multidisciplinary efforts involving primary care physicians, nephrologists, endocrinologists, cardiologists, and dietitians. Apart from CKD progression, higher cardiovascular burden requires comprehensive management, ranging from lifestyle intervention to addressing underlying comorbidities with appropriate pharmacotherapy that depends on the severity of kidney disease and that may need modification as kidney function declines (6).

Renin–Angiotensin System Inhibitor Use

Renin–angiotensin system (RAS) inhibitors slow the progression of kidney disease in persons with albuminuria and hypertension independent of their effects on blood pressure (7). Patients with diabetes, hypertension, and albuminuria (albumin–creatinine ratio >30 mg/g) should receive RAS inhibitors. They should be titrated to the maximal tolerated dose, with close monitoring of serum potassium and serum creatinine levels within 2 to 4 weeks of initiation of or change in dose. Combination therapy with ACEis and ARBs is harmful and should be avoided in patients with diabetes and CKD (8). Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, are effective for resistant hypertension. Studies examining the long-term risks and benefits of adding a mineralocorticoid receptor antagonist to concomitant use of ACEis or ARBs are due to be reported soon. Recently the FIDELIO trial reported that treatment with finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, in patients with CKD and type 2 diabetes already on RAS blockade resulted in lower risks for CKD progression and cardiovascular events.

Although clinical trial evidence is limited, given the strong association between albuminuria and kidney disease progression and cardiovascular disease (CVD), RAS blockade may be considered in patients with diabetes, albuminuria, and normal blood pressure. On the other hand, for patients with diabetes, high blood pressure, and normal albumin excretion, RAS inhibitors have not been proved to offer kidney protective effects, and other antihypertensive agents may be equally effective for cardiovascular risk reduction (9).

In general, RAS inhibitors are well tolerated in patients with diabetes and CKD. For those who develop a cough while using ACEis, ARBs are an acceptable alternative. For patients who develop hyperkalemia during drug initiation or dose titration, various measures to control potassium levels, such as moderating potassium intake, diuretic initiation, use of sodium bicarbonate in those with metabolic acidosis, and concomitant use of gastrointestinal cation exchangers, should be considered. Although serum creatinine level may increase during drug initiation or dose titration, RAS inhibitors may be continued unless the creatinine level increases by more than 30% (10). The dose should be reduced or withdrawn in those who develop symptomatic hypotension, uncontrolled hyperkalemia (despite measures discussed earlier), and acute kidney injury. Figure 1 guides clinicians on how to monitor serum creatinine and potassium levels during RAS inhibitor treatment or dose escalation.

Smoking Cessation

Tobacco use, a leading cause of death worldwide, is associated with kidney disease progression and CVD. Few studies have examined the potential benefits of smoking cessation in patients with diabetes and CKD. However, given the known health and economic benefits of avoiding tobacco products in the general population, the guideline suggests that health care providers recommend tobacco cessation.

GLYCEMIC MONITORING AND TARGETS

We recommend using hemoglobin A_{1c} (HbA_{1c}) to monitor glycemic control in patients with diabetes and CKD (1C).

We recommend an individualized HbA_{1c} target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (1C).

Hemoglobin A_{1c} is the primary tool for monitoring glycemic control in patients with diabetes and CKD. Studies that compare HbA_{1c} with direct measurements of blood glucose suggest that the accuracy and precision of HbA_{1c} does not vary by estimated glomerular filtration rate (eGFR) down to an eGFR of 30 mL/min/

1.73 m^2 (**Appendix Figure**, available at Annals.org). Below this level, shortened erythrocyte lifespan biases measurement toward low HbA_{1c}, particularly in patients receiving dialysis and erythropoietin-stimulating agents (11). Hemoglobin A_{1c} values should be interpreted with these limitations in mind for patients at lower levels of eGFR, particularly in those with an eGFR less than 15 mL/min/1.73 m^2.

Continuous glucose monitoring (CGM) is an alternative approach to glucose monitoring that is not affected by CKD. Continuous glucose monitoring or self-monitoring of blood glucose may be particularly useful among patients in whom HbA_{1c} is not concordant with directly measured blood glucose levels or clinical symptoms (12).

Glycemic targets should be individualized for patients with diabetes and CKD (13). Appropriate individualized targets may vary from as low as less than 6.5% to as high as less than 8%, depending on patient factors that place them at risk for hypoglycemia. With the growing availability of medication classes (such as sodium–glucose cotransporter-2 [SGLT2] inhibitors, glucagon-like peptide-1 receptor agonists [GLP-1 RAs], and dipeptidyl peptidase-4 inhibitors) not associated with greater risk for hypoglycemia, more intensive glycemic targets may be pursued in appropriate circumstances. In addition, CGM or self-monitoring of blood glucose may facilitate achieving lower targets while mitigating risk for hypoglycemia. For some patients, metrics derived from CGM (such as time in range of 70 to 180 mg/dL) may serve as treatment targets in addition to or instead of HbA_{1c} (14).

LIFESTYLE INTERVENTIONS

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).

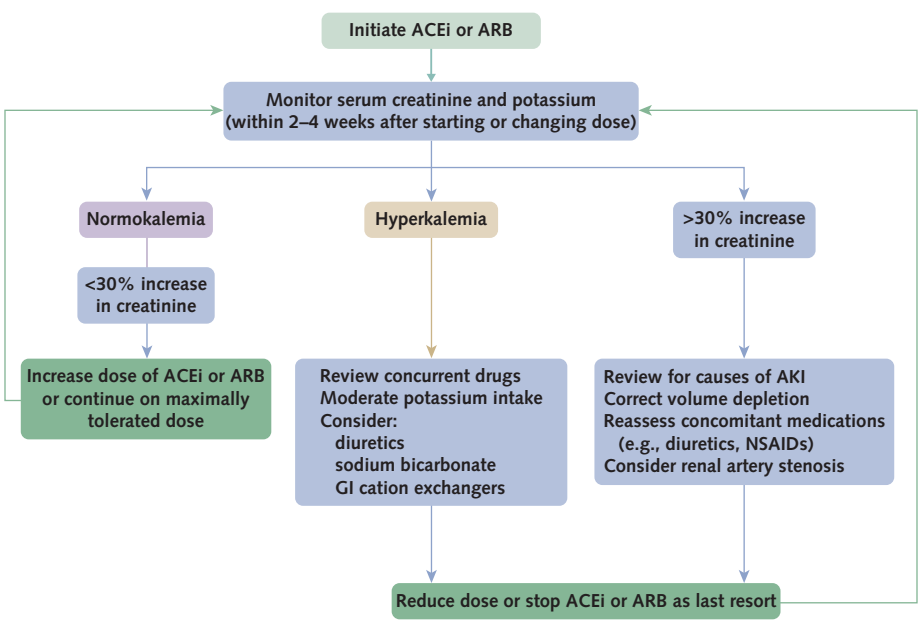
We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD (2C).

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).

Dietary Modifications

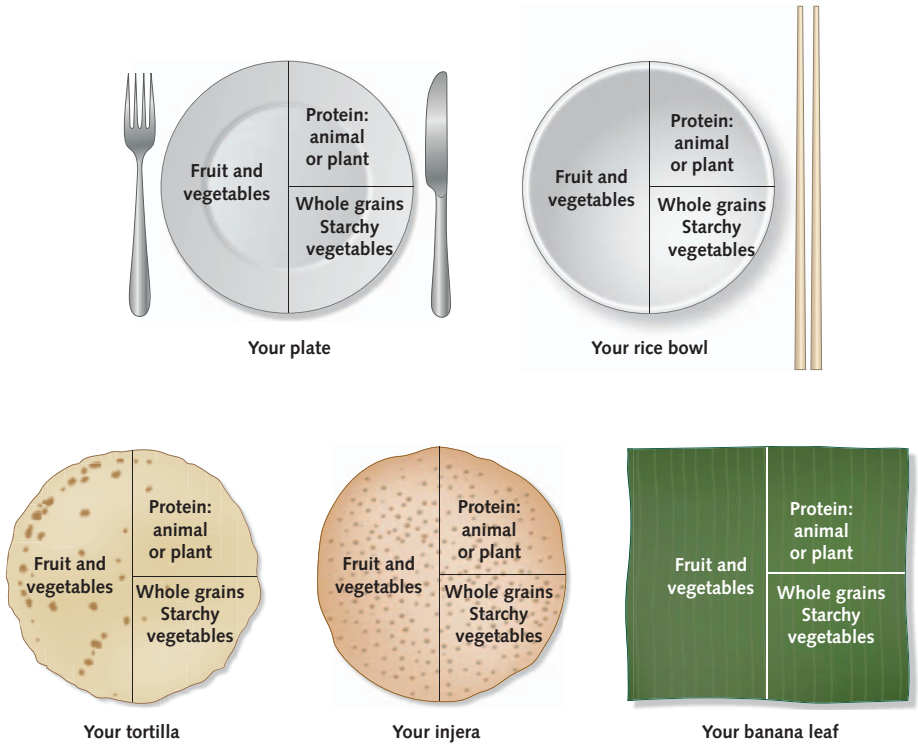
Compared with the general population, patients with diabetes and CKD often have complex nutritional requirements that include increasing or restricting intake of certain nutrients. Several barriers must be considered while attempting to accomplish desired dietary goals. Recommendations for patients with diabetes (and normal kidney function) also differ from those for patients with CKD. Patients' cultural or personal values and preferences often conflict with these recommendations, leading to substantial confusion among patients and their families. Therefore, the primary dietary advice for patients should include consumption of a balanced, healthy diet that is high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts and is lower in processed meats, refined carbohydrates, and sweetened beverages (**Figure 2**).

Figure 1. Monitoring of serum creatinine and potassium levels during ACEi or ARB treatment-dose adjustment and monitoring of side effects.



ACEi = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug. (Reproduced from reference 4.)

Figure 2. What does a healthy kidney diet look like?



(Reproduced from reference 4.)

Two key nutritional issues (protein and sodium intake) are discussed in detail in the guideline. Compared with a standard dietary protein intake of 0.8 g/kg of body weight per day, lower intake has been hypothesized to reduce glomerular hyperfiltration and slow progression of CKD (15). However, clinical trial evidence has not supported restricting dietary protein intake to lower levels to improve kidney or other clinical outcomes. Therefore, we recommend that daily dietary protein intake be maintained at the level recommended by the World Health Organization for the general population (approximately 0.8 g/kg) (16). Patients receiving dialysis, particularly peritoneal dialysis, can increase daily dietary protein intake to 1.0 to 1.2 g/kg to offset catabolism and negative nitrogen balance.

As kidney function declines, ensuing sodium retention leads to an increase in blood pressure, kidney function decline, and higher risk for cardiovascular events. On the basis of data from the general population of patients with and without diabetes, sodium intake is probably best limited to less than 2 g/d (or <5 g of sodium chloride). This is consistent with the upcoming KDIGO guideline on blood pressure management in CKD and international guidelines on the prevention and treatment of CVD (17).

Physical Activity

Patients with diabetes and CKD are often sedentary and have lower levels of physical activity than the general population. Physical inactivity and insufficient levels of activity have been associated with adverse clinical outcomes (18). Despite this, clinical trial evidence of the effect of various exercise programs, such as aerobic training, resistance exercises, and a combination of the two, in patients with diabetes and CKD is limited. An improvement in physical activity levels likely offers cardiometabolic, kidney, and cognitive benefits as well as enhanced overall well-being and quality of life in those with diabetes. Similar benefits are also anticipated in those with diabetes and CKD. Therefore, similar to the general population, moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week is recommended for patients with diabetes and CKD, and patients should be counseled to avoid sedentary behavior (19).

ANTIHYPERGLYCEMIC THERAPIES

We recommend treating patients with type 2 diabetes, CKD, and an eGFR ≥30 mL/min per 1.73 m^2 with metformin (1B).

We recommend treating patients with type 2 diabetes, CKD, and an eGFR ≥30 mL/min per 1.73 m^2 with an SGLT2i (1A).

In patients with type 2 diabetes 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).

Type 2 Diabetes

Glycemic management for patients with type 2 diabetes (T2D) and CKD should include lifestyle therapy, first-line treatment with metformin and an SGLT2 inhibitor, and additional drug therapy as needed for glycemic control (Figure 3).

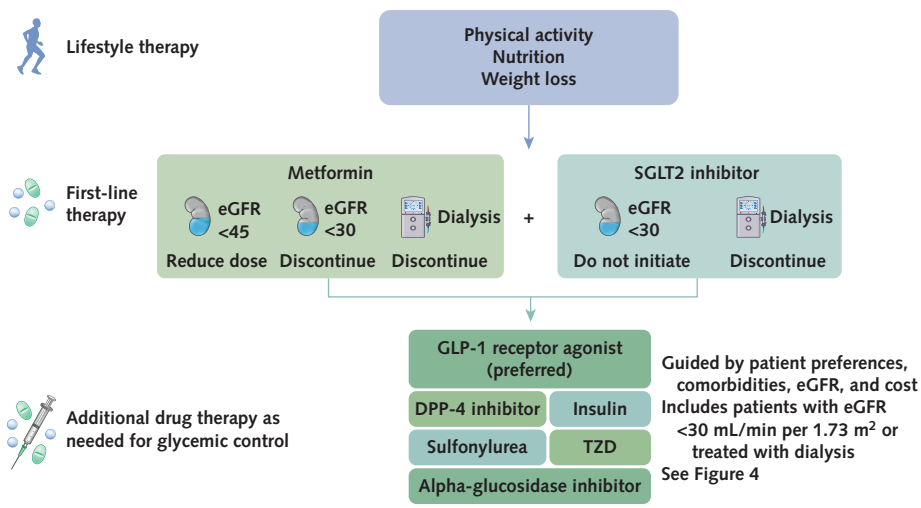
Most patients with diabetes, CKD, and an eGFR of 30 mL/min/1.73 m^2 or more would benefit from receiving both metformin, an inexpensive and generally well-tolerated medication that effectively lowers blood glucose, and an SGLT2 inhibitor, which has been shown to offer substantial benefits in reducing risks for CKD and CVD. When these drugs are not available or not tolerated or when they are insufficient to attain individualized glycemic goals, additional drugs should be selected on the basis of patient preferences, comorbidities, eGFR, and costs (Figure 4). In general, GLP-1 RAs are preferred additional agents because of their demonstrated beneficial effects in reducing cardiovascular events, particularly among persons with prevalent atherosclerotic CVD, and their potential to prevent macroalbuminuria or reduction in eGFR decline.

Metformin may accumulate with reduced kidney function and may increase risk for lactic acidosis, although this risk is very low in absolute terms (20). Patients receiving metformin should have their eGFR monitored, and the dose should be reduced when the eGFR is less than 45 mL/min/1.73 m^2 (or 45 to 59 mL/min/1.73 m^2 in some patients at high risk for acute kidney injury) or withdrawn when the eGFR is less than 30 mL/min/1.73 m^2 or kidney failure develops (Figure 3). In addition, metformin may cause vitamin B_{12} deficiency; therefore, monitoring of levels is advised with long-term use (>4 years) (21).

Sodium–glucose cotransporter-2 inhibitors have been evaluated in patients with diabetes in cardiovascular outcomes trials and in 1 dedicated kidney outcomes trial done in a CKD population (22–24). These trials reported consistent reductions in cardiovascular events (22–28) for major adverse cardiovascular events and CKD progression (22–24, 28). Similar findings from a second dedicated kidney outcomes trial (DAPA-CKD) were also reported at the writing of this guideline but were not included in the guideline systematic review. In addition, the benefits of SGLT2 inhibitors for cardiovascular death, hospitalization for heart failure, or urgent heart failure visit were confirmed in a trial of patients with heart failure and reduced ejection fraction, with more than 80% of participants receiving RAS inhibitors (29). Another trial (EMPEROR-Reduced) published at the writing of this guideline also confirmed the benefits of SGLT2 inhibitors for heart failure. Adverse events included genital mycotic infections; diabetic ketoacidosis; and, in 1 study, a concern about increased risk for lower-extremity amputation. Rates of severe hypoglycemia were not increased, except in subsets of participants receiving insulin or a sulfonylurea (30). Cardiovascular and kidney benefits were seen across all categories of albuminuria (including normal albumin excretion) and CKD (eGFR as low as 30 to 44 mL/min/1.73 m^2), despite reduced glucose-lowering efficacy at lower eGFR. Of note, the cardiovascular and kidney benefits were out of proportion to the reductions in HbA_{1c}, suggesting that these effects could not be fully ascribed to glucose lowering.

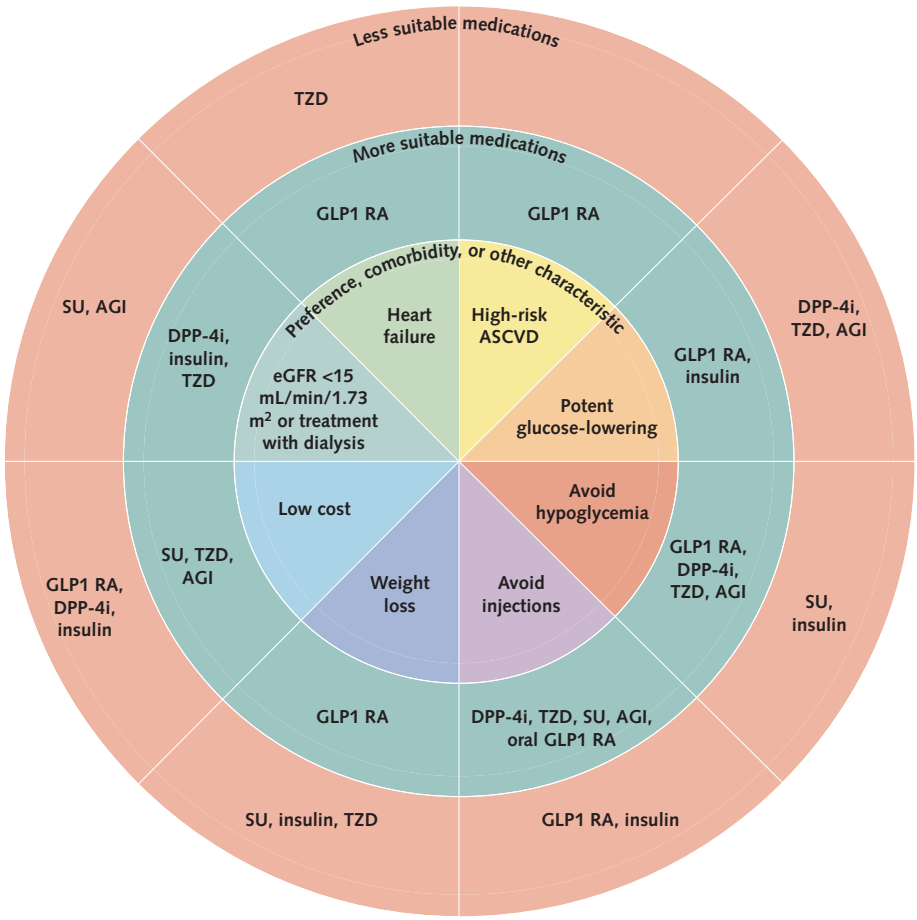
From a practical perspective, SGLT2 inhibitors can simply be added to other antihyperglycemic medications when glycemic targets are not met or when they are met but can safely be lowered (for example, patients with HbA_{1c} at goal who are receiving metformin alone or other drugs with low risk for hypoglycemia). For patients in whom additional glucose lowering with

Figure 3. Treatment algorithm for selecting antihyperglycemic drugs for patients with type 2 diabetes and CKD.



Kidney icon indicates eGFR (mL/min/1.73 m^2); dialysis machine icon indicates dialysis. CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium–glucose cotransporter-2; TZD = thiazolidinedione. (Reproduced from reference 4.)

Figure 4. Patient factors influencing selection of glucose-lowering drugs other than SGLT2 inhibitors and metformin in type 2 diabetes and CKD.



AGI = α-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione. (Reproduced from reference 4.)

SGLT2 inhibitors may increase risk for hypoglycemia (for example, those receiving insulin or sulfonylureas and meeting glycemic targets), reducing or withdrawing the insulin dose or sulfonylurea may be necessary.

All patients initiating SGLT2 inhibitors should be educated on potential adverse effects, which may include modest volume contraction, blood pressure reduction, and weight loss. For patients at risk for hypovolemia (for example, due to concomitant diuretic use), clinicians should consider decreasing the diuretic dose and advising patients about symptoms of volume depletion and low blood pressure. Within the first few weeks of use, SGLT2 inhibitors may cause a modest reduction in eGFR that is hemodynamic in nature and reversible. This is generally not considered a reason to discontinue therapy because long-term eGFR preservation has been reported with continuation of these agents. Even when the eGFR falls below 30 mL/min/1.73 m^2, SGLT2 inhibitors may be continued as long as they are well tolerated and kidney replacement therapy is not imminent. Follow-up to assess glycemia, volume status, and experience of other adverse effects is essential, with consideration of the need for the addition of glucose-lowering therapy if blood glucose levels remain elevated.

Several long-acting GLP-1 RAs (mostly injectables) have been shown to reduce cardiovascular events in patients with T2D and high cardiovascular risk (31–35). Although not specifically done in CKD populations, these trials included patients with eGFRs as low as 15 mL/min/1.73 m^2 and reported reduced albuminuria as well as preserved eGFR (34, 36). For patients with CKD not achieving individualized glycemic targets despite use of metformin and an SGLT2 inhibitor or for those unable to use these medications, a long-acting GLP-1 RA is recommended.

Type 1 Diabetes

Studies evaluating new oral glucose-lowering medications added to different insulin regimens are sparse for patients with type 1 diabetes and CKD. Therefore, antihyperglycemic management in patients with type 1

diabetes should follow the recommendations of general diabetes guidelines (37, 38).

APPROACHES TO MANAGEMENT

We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (1C).

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).

Self-management Education Program

Diabetes self-management educational programs aim to empower and enable persons to develop self-management knowledge and skills to improve long-term clinical outcomes and quality of life (39). They can be delivered face-to-face as one-to-one or group-based programs or via technology platforms by members of health care teams (40). Group-based education programs for persons with T2D result in improvements in biochemical outcomes (HbA_{1c} and fasting glucose) and clinical outcomes (body weight and psychosocial outcomes [for example, self-efficacy and patient satisfaction]) (41). The best approach is tailored to individual preferences and learning styles (39). Although no studies examined the utility of self-management education in patients with diabetes and CKD, systematic reviews in the general population with diabetes have shown that the reduction of clinical risk factors with these programs is likely to be cost-effective in the long term (42–44).

Despite the lack of high-quality evidence specifically in persons with diabetes and CKD, a strong recommendation was made because the WG believed that well-informed patients would choose self-management as the cornerstone of any chronic care model; therefore, a high value was placed on the potential benefits of self-management education programs in persons with diabetes and CKD.

Team-Based Integrated Care

The chronic care model focuses on team management, data collection, and care integration, which is analogous to care in clinical trials where participants often have considerably better outcomes than peers with similar or lower risk profiles in real-world practice (45, 46). Despite a paucity of direct evidence, the WG judged that multidisciplinary integrated care for patients with diabetes and CKD would represent a good investment.

A team-based, integrated approach includes regular assessment, control of multiple risk factors, and self-management to protect kidney function and reduce risk for complications (47, 48). Care organization, empowered and informed patients, and proactive care teams are essential for the chronic care model (49). Team-based chronic care models that focus on treatment to multiple targets and self-management are cost-effective and cost-saving (50, 51) and are likely to achieve multiple treatment targets (39, 52–54) and improve clinical outcomes (9, 52, 55).

This recommendation recognizes potential resource and capacity constraints in delivering team-based care, especially in low- and middle-income countries. However, these countries are often the least able to provide expensive care for advanced disease, so prevention through care reorganization and "train the trainer" patient education is vital to prevent CKD onset and progression. In high-income countries, system and financial barriers often lower the quality of diabetes and kidney care; thus, policymakers, planners, and payers need to build capacity, strengthen the system, and reward preventive care (56, 57).

DISCUSSION

Globally, more than 450 million persons have diabetes (>8%), with projected growth to more than 700 million by 2045 (58). More than 40% of persons with diabetes develop CKD, and a significant number of them develop kidney failure requiring dialysis or transplant. This first KDIGO guideline for management of diabetes in patients with CKD addresses several key issues relevant for clinical practice and highlights areas that merit further research. Where robust evidence was lacking, practice points were presented to inform clinical practice. The recommendations and practice points have direct relevance for clinicians, especially primary care physicians, nephrologists, cardiologists, and endocrinologists who care for most patients with diabetes and CKD.

The KDIGO guideline recommendations and practice points are similar to other guidelines that pertain to patients with diabetes but extend these by highlighting the specific management differences for those with different severities of CKD. For example, monitoring of glycemic control with HbA_{1c} is recommended, but the limitations of HbA_{1c} when the eGFR is less than 30 mL/min/1.73 m^2 are emphasized, and alternate methods, such as CGM, are described.

Notably, the KDIGO guideline and the American Diabetes Association and European Association for the Study of Diabetes Consensus Report both recommend comprehensive lifestyle therapy, metformin as first-line treatment along with an SGLT2 inhibitor for organ protection (such as the heart and kidneys), and self-management education (59).

Persons with CKD often have complex nutritional requirements, and given the lack of clinical trial evidence supporting protein restriction, the KDIGO guideline recommends a protein intake of 0.8 g/kg per day for those with diabetes and CKD. This is similar to the National Kidney Foundation clinical practice guidelines for nutrition in CKD (60).

In line with recent changes in U.S. Food and Drug Administration guidance on the acceptable use of metformin with kidney disease, the KDIGO guideline recommends metformin use down to an eGFR of 30 mL/min/1.73 m^2 but with specific caution in the setting of rapid decline in kidney function. The KDIGO guideline

also recommends initiating an SGLT2 inhibitor in those with an eGFR of 30 mL/min/1.73 m^2 or greater on the basis of recent clinical trial evidence showing the beneficial effects of SGLT2 inhibitors on kidney disease progression and cardiovascular outcomes. As recent and forthcoming trials allowed enrollment of patients with baseline eGFR greater than 20 and greater than 25 mL/min/1.73 m^2, the eGFR level at which SGLT2 inhibitors can be initiated and maintained will be subject to revisiting pending future trial data. To assist clinicians, several practice points address concerns about initiation of SGLT2 inhibitors and follow-up of patients receiving them (**Appendix Table 3**, available at Annals.org).

Clinical trials examining other novel agents targeting various pathways in patients with diabetes at different severities of kidney disease are under way. Updates of this guideline based on the latest evidence from these trials can be rapidly incorporated into the MAGICapp platform that is freely available online. We are optimistic that this new guideline will help improve the delivery of evidence-based, high-quality care by a multidisciplinary team to those with diabetes and CKD around the globe.

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Acknowledgment: The WG thanks the KDIGO Co-Chairs, Michel Jadoul and Wolfgang C. Winkelmayer, for their invaluable guidance. The WG also acknowledges all who provided feedback during the public review of the draft guideline.

Financial Support: By KDIGO. No funding is accepted for the development of specific guidelines.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-5938.

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Appendix Table 1. Classification for Certainty and Quality of the Evidence

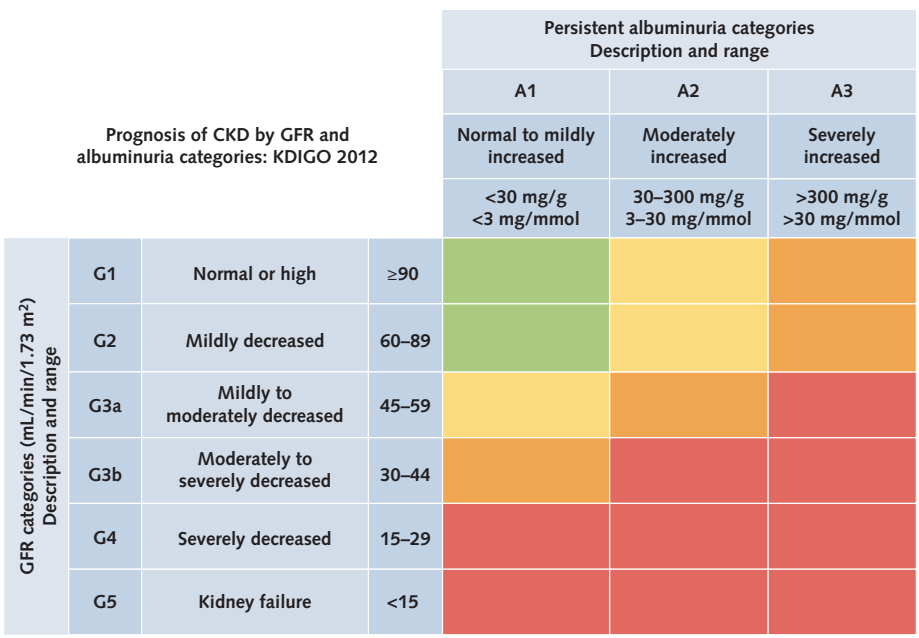
Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain and often will be far from the truth.

Appendix Table 2. KDIGO Nomenclature and Description for Grading Recommendations

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1: "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2: "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO = Kidney Disease: Improving Global Outcomes.

Appendix Figure. Current CKD nomenclature used by KDIGO.



Green, low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes. (Reproduced from reference 4.)

Appendix Table 3. Recommendations and Practice Points From the KDIGO 2020 Clinical Practice Guideline for Management of Diabetes in CKD

Chapter 1: Comprehensive care in patients with diabetes and CKD

Recommendations

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).

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

Practice points

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 1).

Practice Point 1.2.3: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose (Figure 1).

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than by decreasing the dose or stopping the ACEi or ARB immediately (Figure 1).

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 mL/min per 1.73 m^2).

Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

Practice Point 1.2.8: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low eGFR.

Practice Point 1.3.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

Chapter 2: Glycemic monitoring and targets in patients with diabetes and CKD

Recommendations

Recommendation 2.1.1: We recommend using hemoglobin A_{1c} (HbA_{1c}) to monitor glycemic control in patients with diabetes and CKD (1C).

Recommendation 2.2.1: We recommend an individualized HbA_{1c} target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (1C).

Practice points

Practice Point 2.1.1: Monitoring long-term glycemic control by HbA_{1c} twice per year is reasonable for patients with diabetes. HbA_{1c} may be measured as often as 4 times per year if the glycemic target is not met or after a change in antihyperglycemic therapy.

Practice Point 2.1.2: Accuracy and precision of HbA_{1c} measurement declines with advanced CKD (G4–G5), particularly among patients treated by dialysis, in whom HbA_{1c} measurements have low reliability.

Practice Point 2.1.3: A glucose management indicator (GMI) derived from continuous glucose monitoring (CGM) data can be used to index glycemia for individuals in whom HbA_{1c} is not concordant with directly measured blood glucose levels or clinical symptoms.

Practice Point 2.1.4: Daily glycemic monitoring with CGM or self-monitoring of blood glucose (SMBG) may help prevent hypoglycemia and improve glycemic control when antihyperglycemic therapies associated with risk of hypoglycemia are used.

Practice Point 2.1.5: For patients with type 2 diabetes (T2D) and CKD who choose not to do daily glycemic monitoring by CGM or SMBG, antihyperglycemic agents that pose a lower risk of hypoglycemia are preferred and should be administered in doses that are appropriate for the level of eGFR.

Practice Point 2.1.6: CGM devices are rapidly evolving with multiple functionalities (e.g., real-time and intermittently scanned CGM). Newer CGM devices may offer advantages for certain patients, depending on their values, goals, and preferences.

Practice Point 2.2.1: Safe achievement of lower HbA_{1c} targets (e.g., <6.5% or <7.0%) may be facilitated by CGM or SMBG and by selection of antihyperglycemic agents that are not associated with hypoglycemia.

Practice Point 2.2.2: CGM metrics, such as time in range and time in hypoglycemia, may be considered as alternatives to HbA_{1c} for defining glycemic targets in some patients.

Chapter 3: Lifestyle interventions in patients with diabetes and CKD

Recommendations

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).

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).

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).

Practice points

Practice Point 3.1.1: Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.

Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis, should consume between 1.0 and 1.2 g protein/kg (weight)/d.

Practice Point 3.1.3: Shared decision-making should be a cornerstone of patient-centered nutrition management in patients with diabetes and CKD.

Practice Point 3.1.4: Accredited nutrition providers, registered dietitians and diabetes educators, community health workers, peer counselors, or other health workers should be engaged in the multidisciplinary nutrition care of patients with diabetes and CKD.

Practice Point 3.1.5: Health care providers should consider cultural differences, food intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to the patients and their families.

Continued on following page

Appendix Table 3–Continued

Practice Point 3.2.1: Recommendations for physical activity should consider age, ethnic background, presence of other comorbidities, and access to resources.
Practice Point 3.2.2: Patients should be advised to avoid sedentary behavior.
Practice Point 3.2.3: For patients at higher risk of falls, health care providers should provide advice on the intensity of physical activity (low, moderate, or vigorous) and type of exercises (aerobic vs. resistance, or both).
Practice Point 3.2.4: Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR ≥30 mL/min per 1.73 m^2.

Chapter 4: Antihyperglycemic therapies in patients with type 2 diabetes (T2D) and CKD

Recommendations

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 mL/min per 1.73 m^2 with metformin (1B).
Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 mL/min per 1.73 m^2 with an SGLT2i (1A).
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).

Practice points

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a sodium–glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control.
Practice Point 4.2: Most patients with T2D, CKD, and eGFR ≥30 mL/min per 1.73 m^2 would benefit from treatment with both metformin and an SGLT2i.
Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred.
Practice Point 4.1.1: Treat kidney transplant recipients with T2D and eGFR ≥30 mL/min per 1.73 m^2 with metformin according to recommendations for patients with T2D and CKD.
Practice Point 4.1.2: Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when the eGFR is <60 mL/min per 1.73 m^2.
Practice Point 4.1.3: Adjust the dose of metformin when eGFR is <45 mL/min per 1.73 m^2, and for some patients when eGFR is 45–59 mL/min per 1.73 m^2.
Practice Point 4.1.4: Monitor patients for vitamin B_{12} deficiency when they are treated with metformin for more than 4 years.
Practice Point 4.2.1: An SGLT2i can be added to other antihyperglycemic medications for patients whose glycemic targets are not currently met or who are meeting glycemic targets but can safely attain a lower target.
Practice Point 4.2.2: For patients in whom additional glucose-lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.
Practice Point 4.2.3: The choice of SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.
Practice Point 4.2.4: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).
Practice Point 4.2.5: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.
Practice Point 4.2.6: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.
Practice Point 4.2.7: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 30 mL/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.
Practice Point 4.2.8: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 4.2.1).
Practice Point 4.3.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.
Practice Point 4.3.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly.
Practice Point 4.3.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.
Practice Point 4.3.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications, such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

Chapter 5: Approaches to management of patients with diabetes and CKD

Recommendations

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (1C).
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 points

Practice Point 5.1.1: Health care systems should consider implementing a structured self-management program for patients with diabetes and CKD, taking into consideration local context, cultures, and availability of resources.
Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dietitians, pharmacists, health care assistants, community workers, and peer supporters) preferably with knowledge of CKD.

ACEi = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; CGM = continuous glucose monitoring; CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GMI = glucose management indicator; HbA_{1c} = glycated hemoglobin; RAS = renin–angiotensin system; SGLT2i = sodium–glucose cotransporter-2 inhibitor; SMBG = self-monitoring of blood glucose.