Long-Term Care Updates

December 2020

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

By Chad Dicks, PharmD Candidate; Margarita Caraway, PharmD Candidate

PharMerica®

Introduction

Kidney Disease: Improving Global Outcomes (KDIGO) is a global nonprofit organization who develops and implements evidence-based clinical practice guidelines in kidney disease. KDIGO guidelines encompass global scientific evidence and provide practical recommendations for both clinicians and patients. *Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD)* is KDIGO's latest and first guideline on this subject. Although other organizations have published reputable guidelines for diabetes management, such as the American Diabetes Association (ADA) and the American Heart Association (AHA), specific guidelines for patients with CKD are lacking. This newsletter will highlight some major recommendations emphasized by KDIGO pertinent for clinicians to be aware of when managing diabetic patients with CKD.[1]

Approaches to Management and Glycemic Targets

In an effort to reduce the risk of kidney disease progression and future complications, such as cardiovascular disease (CVD), a team-based and integrated approach to the management of patients with diabetes and CKD should consist of regular assessments, control of risk factors, and patient education. As part of this approach, proper glycemic management is advised and should be accomplished by monitoring a patient's hemoglobin A1c (HbA1c). Targets for glycemic control should be individualized and range from < 6.5% to < 8% depending on risk factors such as hypoglycemia, advanced stage CKD, and the type of glucose-lowering medications being taken. However, the reliability of HbA1c decreases should be interpreted with caution in patients with advanced CKD or on dialysis. CKD may cause an A1C to appear higher because of acid build-up or carbamylation which result in protein changes in hemoglobin. A1C may also appear lower in these patients due to a reduction in red blood cell production. This anemia can result in transfusions, addition of iron supplements, and addition of erythropoiesis-stimulating agents which make hemoglobin look healthier than it actually is. Patients may benefit the most from continuous glucose monitoring (CGM) or self-monitoring blood glucose (SMBG).[1] Unlike testing for A1C, which is usually done every three months in a clinical setting, CGM or SMBG is done daily, usually by the patient. It can give a more accurate reading of the day to day and hour to hour fluctuations in blood glucose levels for this patient population.

Comprehensive Care and Nutrition Intake

Management of patients with diabetes and CKD should also include lifestyle interventions, such as a healthy diet, exercise, tobacco avoidance, and pharmacologic risk-factor management of glucose, lipids, and blood pressure (see *Pharmacological Treatments*).

Consumption of a healthy, individualized, well-balanced diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts is recommended, while processed meats, refined carbohydrates, and sweetened beverages should be consumed more sparingly. Sodium intake should be less than 2 g/day, and protein intake should be 0.8 g/kg/day. For patients on dialysis, protein intake should be increased to 1 to 1.2 g/kg/day. Furthermore, patients should be encouraged 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. However, an evidence review did not provide convincing data to show clinical benefits of weight loss among patients with diabetes and CKD. Thus, additional research is needed, and specific recommendations for clinical care of weight loss in this patient population were not made. For smoking cessation, little data is available evaluating its effect in patients with diabetes and CKD. It is recommended though, that all tobacco products be avoided, because smokers are at high risk for CKD progression and CVD.[1]

Pharmacological Treatments

Glucose control

In addition to lifestyle therapy, patients with type II diabetes (T2D) and CKD should use glycemic control medications to further reduce HbA1C to their target goal. The United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glycemic therapy resulted in a statistically significant lower risk of microvascular complications than diet alone. *The New England Journal of Medicine* published a follow-up study that monitored the continued benefits of therapy, and they found a continued reduction in risk in microvascular complications as well as a significant risk reduction for myocardial infarction and death from all causes ten years after treatment had been started.[2]

The ADA recommends metformin as first-line therapy in T2D patients and that it be continued as long as it is well tolerated and not contraindicated. KDIGO recommends the use of both metformin and a sodium-glucose transport protein 2 inhibitor (SGLT2) be used as long as the patient's estimated glomerular filtration rate (eGFR) remains > 30 mL/min/1.73 m^2 in diabetic patients with CKD. The EMPA-REG OUTCOME trial for empagliflozin, CANVAS trial for canagliflozin, and DECLARE-TIMI 59 trial for dapagliflozin are referenced as the basis of proof that SGLT2 inhibitors can reduce major adverse cardiovascular events (MACE). Additionally, the CREDENCE trial showed that SGLT2s can also slow the progression of CKD. Only the CREDENCE trial was specifically conducted in the CKD population. A great benefit of SGLT2s is they can be continued after initiation when the patient's eGFR worsens. If further glucose control is needed or an SGLT2 is not tolerated, KDIGO recommends the addition of a glucagon-like peptide-1 receptor agonist (GLP-1). In a systematic review and meta-analysis consisting of seven trials with over 56,000 subjects, GLP-1s reduced MACE by 12% (HR 0.88, 95% CI 0.82–0.94; $p<0.001$) and hospital admissions for heart failure by 9% (0.91, 0.83–0.99; $p=0.028$) in patients with type 2 diabetes.[3] The cardiovascular outcomes trial included patients with eGFR > 15 ml/min per 1.73 m^2. Data with GLP-1 in more advanced CKD are limited.

RAS Blockade

KDIGO recommends a renin-angiotensin system inhibitor (RASi), such as an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), be used in patients who meet certain criteria based on hypertension status and albumin-creatinine ratio. In a meta-analysis of 119 randomized controlled trials, Xie et al. concluded that RASi in patients with CKD reduced the risk of kidney failure and adverse cardiovascular events. A total of 64,768 patients were included, and the reduction in odds of kidney failure with a RASi was found to be 30% with an ACEi and 38% with an ARB compared to placebo. Additionally, both ACEs and ARBs produced odds reductions of major cardiovascular events by 0.82 and 0.76 compared to placebo respectively. The authors also concluded that ACEis reduced the risk for all-cause mortality compared to ARBs.[4]

Additional therapies

Additionally, aspirin should be used lifelong for secondary prevention among patients with established CVD and may be considered for primary prevention among high-risk patients, patients on dual antiplatelet therapy after acute coronary syndrome, or patients with a percutaneous coronary intervention.[1]

Conclusion

These are the first guideline recommendations from KDIGO for diabetic management in patients with CKD. Overall, care should be comprehensive and tailored to each individual patient. Lifestyle modification, metformin, and SGLT2 are first line therapies plus the management of glucose, lipids, and blood pressure control. Additional therapies may be needed depending on the unique patient's needs and other risk factors or current disease state. The recommendations provide clear guidance for clinicians and should help influence facility implementations of treatment as well as improved outcomes.

References

1. de Boer IH, et al. Diabetes in CKD. KDIGO. https://kdigo.org/guidelines/diabetes-ckd/. Published June 29, 2020. Accessed November 10, 2020.

2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589. https://pubmed.ncbi.nlm.nih.gov/18784090/

3. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials [published correction appears in Lancet Diabetes Endocrinol. 2020 Mar;8(3):e2]. *Lancet Diabetes Endocrinol*. 2019;7(10):776-785. https://pubmed.ncbi.nlm.nih.gov/31422062/

4. Xie X, Liu Y, Perkovic V, et al. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. *Am J Kidney Dis*. 2016;67(5):728-741. https://pubmed.ncbi.nlm.nih.gov/26597926/