Diabetes and CKD: New Approaches to Managing a Common Condition

By Ian H. de Boer

Diabetes treatment has advanced rapidly over the past decade, with new drugs and technologies developed and translated into clinical care. Many of these treatments affect the kidney, are affected by chronic kidney disease (CKD), or carry both effects. In addition, new data have been published on foundational elements of care for people with diabetes and CKD, including lifestyle, ascertainment of glycemia, glycemic targets, and use of renin-angiotensin system (RAS) inhibitors. Providers and patients rightly ask how to apply the new treatments and integrate them into tailored existing care paradigms.

KDIGO has initiated a new clinical practice guideline to help guide medical management for people with diabetes and CKD. The goal of the new clinical practice guideline is to provide evidence-based recommendations for the care of people with diabetes and CKD. The guideline arose from a KDIGO Controversies Conference held in 2015 that outlined critical areas in need of evidence-based recommendations (1). The scope of the guideline was then refined by the KDIGO diabetes and CKD guideline writing group, with input through open commentary from the broad community engaged in managing diabetes and CKD.

The new guideline will take a comprehensive approach, covering lifestyle, glycemia assessment and targets, use of medications that target both glycemia and other intermediate targets, self-management, and systems of care (see box). The guideline is designed to apply to people with diabetes and any stage of CKD, from elevated urine albumin excretion and normal estimated GFR (eGFR) to severely reduced eGFR to ESKD treated with dialysis or kidney transplantation, highlighting the aspects of care that are common across the CKD spectrum and also those that should differ by severity of CKD. Similarly, the guideline will address care for people with both type 1 and type 2 diabetes, highlighting common and differential approaches where appropriate. The guideline will be informed by a systematic literature review performed by an expert evidence review team, focusing on high-level evidence from clinical trials.

New drugs will be addressed by this new diabetes and CKD guideline. Three new classes of drugs are revolutionizing diabetes care: sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors (2). All three classes reduce blood glucose, with a low risk of hypoglycemia. In addition, SGLT2 inhibitors and GLP-1 receptor agonists have shown substantial benefits in terms of cardiovascular and kidney outcomes (Table 1). These benefits were first demonstrated in large cardiovascular outcomes trials that were mandated by regulatory agencies to ensure cardiovascular safety of new diabetes drugs. SGLT2 inhibitors and GLP-1 receptor agonists proved to be not only safe but beneficial. In each of these drug classes, several specific drugs reduced cardiovascular events in high-risk populations (2). SGLT2 inhibitors also substantially reduced GFR loss in secondary analyses (3)—an effect confirmed in the recent CREDENCE trial (4). GLP-1 receptor agonists may also have renal benefits (5). However, all of these drugs do have adverse effects, most are restricted below certain eGFR thresholds and in kidney failure, and combinations with other glucose-lowering drugs remain poorly developed (3). Therefore, further guidance is needed on the implementation of these promising new drugs in clinical nephrology practice.

Table 1. Summary of the benefits and harms of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, by class, as observed in large, placebo-controlled clinical outcomes trials

		Cardiovascular effects		Kidney effects		
Drug	**HbA_{1c} lowering**	**Major atherosclerotic cardiovascular events**	**Heart failure**	**Albuminuria or albuminuria-containing composite outcome**	**GFR loss***	**Notable adverse effects**
SGLT2 inhibitors	↓ 0.6–0.9% (CKD G1–G2) ↓ 0.3–0.5% (CKD G3a) ↔ (CKD G3b–G4) NA (CKD G5)	↓/–	↓↓	↓↓	↓↓	Genital mycotic infections, diabetic ketoacidosis, possibly amputations (canagliflozin)
GLP-1 receptor agonists	↓ 1.0–1.2% (CKD G3a–4)	↓/–	–	↓	↓/–	Gastrointestinal, primarily nausea and vomiting
DPP-4 inhibitors	↓ 0.5–0.7% (CKD G3a–4)	–	–/↑	↓	–	Possibly heart failure (saxagliptin)

Notes: ↓ = significant reduction in risk, with HR estimate > 0.7 and 95% confidence interval not overlapping 1; ↓↓ = significant reduction in risk, with HR estimate ≤ 0.7 and 95% confidence interval not overlapping 1; ↔ = no change; ↑ = increase; - = no significant effect; * = variable composite outcomes that include loss of eGFR, ESKD, and related outcomes.

DPP-4, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

Key questions to be addressed by the new KDIGO guideline on diabetes and CKD

1. Do lifestyle interventions (exercise/physical activity, and smoking cessation) versus usual care improve clinically relevant outcomes and intermediate outcomes and reduce clinically relevant harms?
2. Do dietary interventions (caloric restriction diet, low-potassium diet, low-sodium diet, low-phosphate diet, low-protein diet and whole food diets) versus usual diet improve clinically relevant outcomes and intermediate outcomes and reduce clinically relevant harms?

   What is the equivalency of HbA1c compared with freqently measured blood glucose (continuous glucose monitoring or mutiple capillary blood glucose measurements)?
4. Compared with blood glucose monitoring and/or HbA1c determination, do alternative biomarkers (glycated albumin, fructosamine) improve clinically relevant outcomes and decrease clinically relevant harms?
5. Compared with HbA1c determination, does blood glucose monitoring (continuous interstitial glucose monitoring, self-monitoring blood glucose) improve clinically relevant outcomes and decrease harms?
6. Does reducing blood glucose to a lower versus higher target improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?
7. What are the most effective education, self-management, and healthcare delivery programs to improve clinically relevant and intermediate outcomes, and reduce clinically relevant harms?
8. What are the effects of metformin on clinically relevant outcomes, intermediate outcomes, and clinically relevant harms?
9. What are the effects of other glucose-lowering medications (sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, insulin) on clinically relevant outcomes, intermediate outcomes, and clinically relevant harms?
10. Do renin-angiotensin system (RAS) inhibitors improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?
11. Does dual RAS inhibition compared with single RAS inhibition improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?
12. Does the addition of a medication blocking the production or action of aldosterone to RAS inhibitors compared with RAS inhibition alone improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms?

Technology has also advanced in diabetes care. In particular, continuous glucose monitoring is facilitating more intensive glycemic control, particularly in type 1 diabetes (6). New biomarkers, such as glycated albumin and fructosamine, have also been proposed to assess glycemia in CKD, because hemoglobin A1c may be biased or imprecise when red blood cell turnover increases with low eGFR and the use of erythropoietin-stimulating agents.

Of course, new drugs and technologies cannot treat diabetes and CKD on their own. These new treatments must be added to and integrated with established therapies, including lifestyle interventions and proven therapies, such as metformin and RAS inhibitors. Of lifestyle interventions, dietary sodium, dietary protein, and physical activity have been best studied. All treatments must be applied in a manner that engages and is acceptable to patients and is delivered in care models that acknowledge local patterns of care and local resources. Importantly, diabetes has grown most rapidly in low-income countries. Treatment paradigms must take into account the cultural values and resources of diverse contexts.

The care of people with diabetes and CKD makes large demands on patients and is necessarily multidisciplinary in nature. Effective guidelines must therefore reflect patient priorities and the perspectives of multiple approaches to care. Such guidelines must also acknowledge and account for the large range of care settings across the world. For these reasons, the KDIGO diabetes and CKD guideline writing group includes patients along with members from diverse professional backgrounds (nephrology, endocrinology, primary care, cardiology, pharmacology, nutrition) and from across the globe (United States, United Kingdom, Netherlands, Germany, India, Nigeria, Singapore, Hong Kong, and Brazil). It is anticipated that KDIGO and this writing group will release a draft set of recommendations for public commentary in December 2019, with a final guideline published in early 2020.

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KDIGO Hypertension Guideline

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In 2012, KDIGO issued a clinical practice guideline for the management of blood pressure in chronic kidney disease (CKD) which excluded patients receiving maintenance dialysis. This guideline is now being revised on the basis of new clinical trial evidence, particularly from SPRINT, SPS3, and others. A multidisciplinary KDIGO guideline panel of clinical and scientific experts has convened in person and over teleconferences to discuss the excellent work of the Evidence Review Team with the aim to publish an update to the 2012 guideline in 2020. This revision will address several major subjects, such as optimal blood pressure (BP) measurement techniques, BP targets, antihypertensive agents, and the role of lifestyle and dietary interventions in CKD patients, including the special populations of pediatric patients and kidney transplant recipients.

A key issue of this new guideline will be a new chapter on how to measure BP properly. As a rule, casual office BP is 5 to 10 mm Hg higher than both standardized office and automated oscillometric office BP. Still, it is impossible to come up with conversion factors to adjust one measuring technique to another because that difference of 5 to 10 mm Hg refers to population means and those differences may vary vastly in each individual. The variabilities in BP obtained by the use of different techniques of measurements in CKD appear similar to those in the general population, although the available data are more limited. The utility of out-of-office BP is important in CKD because the prevalence of white-coat hypertension, masked hypertension, white-coat effect, and masked uncontrolled hypertension appears to be higher than in individuals without CKD. Nonetheless, there is insufficient literature to support guidelines on how to manage BP based on out-of-office measurements.

When BP targets are discussed, it is of utmost importance that BP measurement be performed in a highly standardized manner, probably using an automated oscillometric device that incorporates, by default, a five-minute rest period and averaging three measurements several minutes apart. This Work Group panel is considering a target systolic BP of less than 120 mm Hg as determined using standardized office BP measurement, based on the new evidence from the SPRINT and recent meta-analyses. Such a low target would obviate separate recommendations for different risk populations such as individuals with diabetes or variable degrees of proteinuria. The targets are mainly chosen based on their effects on cardiovascular events, which are rampant in CKD, and mortality. The effect of intensive BP lowering on kidney outcomes, GFR decline and end-stage kidney disease, is surprisingly small. In fact, in the intensive BP-lowering arms of the SPRINT, SPS3, and ACCORD studies, the decrease in GFR was consistently, albeit only slightly, greater than in the control arms.

In regard to preferred antihypertensive agents of choice, KDIGO will likely recommend, as before, angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) as first-line agents in those with very heavy albuminuria (>300 mg/g or >300 mg/24 h) and in those with diabetes. One unresolved issue is how best to handle an acute decrease in GFR in the first few weeks after antihypertensive therapy has been started, particularly with an ACEi or an ARB. Randomized intervention trials in this area are lacking, and more recent observational studies cast uncertainties on the predictive value of these acute early changes in GFR for long-term renoprotective effects. There is also no randomized trial to inform whether potassium binders would allow better control of hypertension in hyperkalemia-prone CKD by enabling the use of RAAS blockers and thus reduce cardiovascular and kidney complications.

What about the other special groups with CKD, namely older patients, children, or those with a kidney transplant? There is a large unmet need for studying the effects of antihypertensive therapy on cardiovascular and kidney outcomes in older patients with advanced CKD, given the increasing incidence of ESKD in this population. Because the aggregate benefits of antihypertensive therapy require at least one to two years to materialize, clinical judgment and shared decision-making is essential, and should take into consideration such factors as patient preferences, life expectancy, and potential adverse effects of therapy. We also note that the cardiovascular and apparent cognitive benefits of intensive BP lowering in the SPRINT trial persisted in the predefined subgroup above age 75 years and it was not associated with a higher risk of injurious falls or other serious adverse event than with standard BP goal.

Providing advice for the management of hypertension in pediatric CKD is a challenge for a number of reasons. Cardiovascular events, even over a 10-year time frame, are rare in this population. Thus, evidence is based primarily on the ESCAPE trial which examined kidney outcomes or surrogate outcomes such as left ventricular mass. Unfortunately, there is no good evidence to support the use of automated oscillometric BP devices in children with CKD, and normative values for ambulatory BP are available largely for Western populations only. Scientific societies do not agree on whether antihypertensive therapy should be initiated when BP is consistently above the 90th or 95th percentile for a child's age, sex, and height, but the target BP is consistently stated as < 50th percentile.

In kidney transplant recipients, there are no randomized trials to inform the optimal BP target with regard to cardiovascular or kidney allograft outcomes. ACEi, alpha-blockers, beta-blockers and mineralocorticoid receptor antagonists were compared with placebo with no differences in cardiovascular and kidney outcomes. ARBs and dihydropyridine calcium channel blockers (CCB) have been shown to reduce graft loss, compared to placebo. There are also several special aspects, such as renal artery stenosis and the use of vasoactive immunosuppressants (e.g., calcineurin inhibitors) that may complicate BP management in transplant recipients.

Finally, is there any role for nonpharmacologic treatment (e.g., dietary interventions, salt restriction, exercise, alcohol use) of hypertension in patients with CKD? There really is no evidence from randomized studies in CKD with patient-relevant outcomes to answer this question. However, most experts would agree that moderate salt restriction, physical activity, weight reduction in the obese, and attention to healthy diet, as recommended for the general population with the exception of high-potassium-containing food in advanced CKD, would likely to be helpful.

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