Proposed Scope of Work for
KDIGO Clinical Practice Guideline on the
Management of Diabetes and Chronic Kidney Disease

Introduction

Kidney Disease: Improving Global Outcomes (KDIGO) is a not-for-profit organization established to develop and implement global clinical practice guidelines for patients with kidney disease. Since its inception in 2003, KDIGO has published ten guidelines, beginning with the KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease (CKD). This proposed Scope of Work is designed to briefly describe the rationale for development of a guideline on the management of patients with diabetes and CKD and to outline the topics that this guideline intends to address. We are now seeking public comments on the proposed Scope of Work presented here to ensure that feedback from all relevant stakeholders of this global guideline is duly considered before a formal systematic review of the literature is undertaken.

Background

The prevalence of diabetes around the world has reached epidemic proportions. While diabetes is already estimated to affect more than 8% of the global population – more than 425 million people— this is projected to grow to over 629 million people by 2045.\(^1\) It has also been estimated that 40% or more of people with diabetes will develop CKD, including a significant number who will develop end-stage kidney disease (ESKD) requiring dialysis and transplantation.\(^2\) Prevention of CKD in diabetes is therefore a high priority. Diabetes is already the leading cause of ESKD in most developed countries, and the growth in the number of people with ESKD around the world over recent decades has been driven primarily by growth in the number of people with diabetes as the underlying cause.\(^3,4\) In people with diabetes, increasing albuminuria and declining GFR
can be due to classic diabetic glomerulopathy. However, reduced GFR without albuminuria is an increasingly recognized phenotype that may have different underlying mechanisms, and people with diabetes can develop kidney disease for reasons other than diabetes itself. As such the need for diagnostic and prognostic kidney biopsies in people with diabetes remains a matter of discussion. The presence of kidney disease is associated with a markedly increased risk of cardiovascular disease and death in people with diabetes.\textsuperscript{5,6} Therefore aggressive intervention against cardiovascular risk factors is very important in people with diabetes and CKD.\textsuperscript{7} Recent data demonstrate decline in incidence of cardiovascular and other complications in some populations probably due to better screening for and treatment of risk factors, but despite this, a decline in ESKD is much less apparent.\textsuperscript{8}

As provision of dialysis to people with ESKD consumes approximately 6\% of all health care costs in the US and more in some other countries,\textsuperscript{4} there is a strong economic imperative to improve outcomes for people with diabetes and kidney disease in addition to the strong personal and societal health rationale. While the identification of renin-angiotensin blockade as an effective strategy for the prevention of ESKD in type 1 and type 2 diabetes mellitus almost 2 decades ago was a major step forward,\textsuperscript{9-11} subsequent research has had limited success at most in building upon these gains. A number of promising treatments have been found to be ineffective or harmful, many of which have now been abandoned in this population. On the other hand, a number of new agents are currently being tested, which may hopefully improve outcomes for people with diabetes and kidney disease. Treating hyperglycemia in people with diabetes and CKD is challenging due to the risk of hypoglycemia and the need to adjust selection and dosing of medications according to level of GFR. Furthermore, assessing mean blood glucose is complicated in advanced CKD because of limitations of hemoglobin A1c (HbA1c).

Importantly some of the new drug classes now available for reducing blood glucose in type 2 diabetes such as sodium-glucose cotransporter type 2 (SGLT2) inhibitors and glucagon-like-peptide-1 (GLP-1) receptor agonists have turned out to have beneficial effects on cardiovascular outcome in people with previous cardiovascular disease, including patients with moderate CKD.\textsuperscript{12,13} In addition, some of these agents exerted beneficial effects on renal outcome parameters measured as secondary endpoints.\textsuperscript{14,15} This included reduction in progression of albuminuria, a surrogate for a potential renal benefit, but for SGLT2 inhibitors a reduction in loss of GFR was also demonstrated.\textsuperscript{16,17}

Given the high prevalence of diabetes and CKD, the large health impact of ESKD, and the strong relationships of CKD with cardiovascular morbidity and death, KDIGO has
determined that the development of a clinical practice guideline for this patient population is timely and appropriate in view of recent development in various management and treatment options.

**Topic 1: Primary prevention of CKD among people with diabetes**

CKD, as represented by albuminuria or reduced GFR, is a common complication of type 1 and type 2 diabetes. Duration of diabetes, glycemic control, and other CKD risk factors are known to be associated with the prevalence and incidence of CKD. Randomized controlled trials have shown that intensive glycemic control and specific glucose-lowering agents reduce the risk of developing CKD or new-onset albuminuria, while results of trials of lifestyle interventions and RAS blockade for primary CKD prevention are less clear.

*Relevant key questions:*

How can we prevent onset of CKD in patients with diabetes? What is the evidence for glycemic control and are there other effective strategies?

Is RAS blockade indicated in patients with albuminuria A1 category (< 30 mg/g or < 3 mg/mmol) for CKD prevention, regardless of blood pressure?

What is the definition of diabetic kidney disease (DKD)? How is DKD diagnosed and what is the role of kidney biopsy in diagnosis? Is there utility in the staging of DKD?

**Topic 2: Secondary prevention of CKD progression among people with diabetes**

Patients with diabetes and either albuminuria or reduced GFR are at risk of progressing to ESKD. In fact, diabetes is the most common cause of ESKD in many countries. In addition, risk of CKD complications (including cardiovascular disease) increases with severity of CKD. Therefore, interventions to halt or slow progression of CKD are important to improve the outcomes of people with diabetes and CKD. Current therapeutic targets include renin-angiotensin system and blood pressure control, as well as glycemic control. Other therapeutic agents under development now target the role of endothelial function, oxidative stress, and fibrosis.
Relevant key questions:

For which patients with diabetes and prevalent CKD is there a strong indication for RAS inhibition?

Does treatment of glycemia prevent progression of established CKD to ESKD?

What is the optimal approach to implement RAAS blockade in diabetes and CKD?

Is there a remaining role for dual RAS blockade among patients with diabetes and CKD?

What is the role of mineralocorticoid receptor antagonists in the treatment of diabetes and CKD?

Are there additional treatments that should be considered for preventing progression of CKD in diabetes (e.g., SGLT2 inhibitors, dipeptidyl peptidase-4 inhibitors, endothelin antagonists, bardoxolone, pentoxifyline, anti-inflammatory agents, etc.)?

Topic 3: Measurement of glycemia in CKD

HbA1c is the accepted therapeutic target for titrating glucose control among people with diabetes. In advanced CKD, changes to hemoglobin kinetics complicate interpretation of HbA1c. Alternative biomarkers of mean glycemia have now been developed and evaluated in observational studies. However, it is unclear whether using these alternative biomarkers improves glycemia management. With the advance of continuous glucose monitoring technology, measuring glucose itself has been shown to improve glycemic control among people with diabetes (without CKD). Of these options for measuring glycemia, the optimal approach among people with diabetes and CKD is not clear.

Relevant key questions:

Does CKD modify the accuracy and precision of HbA1c in ascertaining glycemia among people with diabetes?

In CKD and those on dialysis therapy, do alternative biomarkers such as glycated albumin or fructosamine correlate more precisely with glycemia than HbA1c?
In CKD and those on dialysis therapy, do alternative biomarkers such as glycated albumin or fructosamine correlate more precisely with clinical diabetes complications or better guide glucose-lowering treatment intensity compared with HbA1c?

Is self monitored blood glucose or continuous glucose monitoring of added value in patients with diabetes and CKD?

**Topic 4: Glycemia management in CKD**

In general, intensive glycemic control reduces the risk of diabetes complications (e.g., CKD, retinopathy, neuropathy, and cardiovascular disease) at the expense increased risk of hypoglycemia. In addition, individual glucose-lowering medications have specific benefits and risks. For example, some SGLT2 inhibitors and GLP-1 receptor agonists reduce the risk of CKD or cardiovascular events with other beneficial effects (e.g., blood pressure and weight reduction), though adverse effects (e.g., hypoglycemia, bone disease) could also vary. In CKD, benefits and risks of intensive glycemic control in general and specific glucose-lowering drugs may vary, and some drugs require dose reductions or are contraindicated. The impact of CKD on glycemia management also differs across the spectrum of CKD severity, being largest among patients on dialysis therapy. Therefore, among people with diabetes and CKD, optimal glycemia targets and the preferred agents used to achieve them are not clear.

*Relevant key questions:*

What is the optimal target range for HbA1c (or alternative glycemia markers) in CKD?  
Do targets vary in accordance to severity of CKD (e.g., GFR categories)?

Are there preferred classes/agents for treating hyperglycemia in patients with diabetes and CKD? How does the selection of agents differ by severity of CKD? Are there preferred classes/agents in patients with diabetes and CKD to prevent renal, cardiovascular and other microvascular complications?

What is the impact of hypoglycemia in patients with diabetes and CKD?

To what extent should insulin doses be modified in advanced CKD?

Should treatment be changed when patients with CKD G5 transition/start dialysis?
Topic 5: **Lifestyle and nutrition among people with diabetes and CKD**

Exercise, weight loss, smoking cessation, and modification of dietary protein, sodium, and potassium are often advised to prevent CKD progression and cardiovascular complications. However, effectiveness of these interventions remains unclear.

**Relevant key questions:**

- Is there evidence for a benefit of lifestyle intervention (e.g., weight loss, exercise, physical activity) on decline in GFR or cardiovascular risk among patients with diabetes and CKD?

- Is there an optimal dietary protein, sodium and potassium intake in patients with diabetes and CKD?

- What is the role of potassium binders in patients with diabetes and CKD?

**Topic 6: Cardiovascular risk reduction among people with diabetes and CKD**

Patients with diabetes and CKD are at high risk of cardiovascular events, including coronary heart disease, stroke, peripheral vascular disease, heart failure, and arrhythmia. In addition to glycemic control and lifestyle interventions, blood pressure lowering, lipid lowering, and antiplatelet medications are commonly used to reduce cardiovascular risk. Blood pressure lowering also affects CKD progression. It is not clear whether diabetes alters optimal blood pressure targets. RAS inhibitors are recommended for blood pressure lowering among patients with albuminuria, but it’s not clear for exactly which patients RAS inhibitors should be recommended over other antihypertensive medications. Questions surrounding blood pressure management in CKD patients with diabetes will be addressed by the upcoming KDIGO Blood Pressure guideline updating Work Group. Recent clinical trials have also demonstrated cardiovascular benefit to intensifying lipid-lowering therapy beyond typical statin therapy, targeting low LDL cholesterol concentrations or adding additional agents to statin therapy. The extent to which this approach may be useful for patients with DKD is not clear.
Relevant key questions:

What is the optimal treatment for CVD risk reduction in CKD G3a-G5D patients with diabetes?

What is the optimal lipid intervention strategy in CKD G3a-5D patients with diabetes?

What is known about the risk-benefit ratio of anti-platelet agents and anticoagulants in patients with CKD and diabetes?

Are there new agents in development (e.g., CETP inhibitors, PCSK9 inhibitors, mineralocorticoid-receptor antagonists) that might be particularly promising for people with diabetes and CKD?
References


