Global Action. Local Change.

KDIGO Controversies Conference on Management of Patients with Diabetes and Chronic Kidney Disease

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Vancouver, Canada

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

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 350 million people), this is projected to grow to over 550 million people by 2035.[1] It has been estimated that 40% or more of people with diabetes will develop chronic kidney disease,[2] including a significant number who will develop end-stage kidney disease (ESKD) requiring dialysis and transplantation.

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 addition, the presence of kidney disease is associated with a markedly increased risk of cardiovascular disease and death in people with diabetes.[5] In fact, data from the FinnDiane study suggest that the excess mortality associated with the presence of type 1 diabetes is observed entirely among those with kidney disease, while people with diabetes who do not have markers of kidney disease had outcomes similar to those observed in the general population.[6]

Relevance of the topic and the conference

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[7], 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 more than a decade ago was a major step forward,[8-10] 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. These include dual renin-angiotensin-system blockade, [11-14] bardoxolone methyl,[15] the endothelin antagonist avosentan[16] and a number of others. A common feature of many of these failures was the emergence of unexpected adverse effects, highlighting the importance

of specific attention to this aspect for new therapies in future trials and also the importance of reconsidering what is known about the safety of existing treatments in this patient population.

With a number of new agents targeting a variety of mechanistic approaches to improving outcomes for people with diabetes and kidney disease, it is timely to reflect on what has been learned in order to ensure that as much as possible is gained from previous studies and to better optimize both the care of affected patients, as well as the design of future research. This conference will therefore explore these issues in detail.

CONFERENCE OVERVIEW

The objective of this KDIGO conference is to gather a global panel of multi-disciplinary clinical and scientific expertise (e.g., nephrology, cardiology, endocrinology) that will identify key issues relevant to the optimal management of diabetes in CKD. The goal is to assess our current state of knowledge related to antidiabetic agents for glycemic control and other potential therapies aiming to improve outcomes for people with diabetes and CKD; address key controversial issues concerning optimal management for the reduction of comorbidities such as cardiovascular diseases; summarize the outstanding knowledge gaps; and to propose a research agenda to resolve standing controversial issues. It is hoped that this conference will inform clinicians of the evidence base for present treatment options and help pave the way for future studies in this area.

Drs. Per-Henrik Groop (Helsinki University Central Hospital, Finland) and Vlado Perkovic (George Institute for Global Health, Australia) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus-building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research in this area.

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APPENDIX: SCOPE OF COVERAGE

A. Safety of treatments in diabetes and kidney disease

What is known (and what needs to be known) about the safety of:

- Diverse pharmacologic treatments in the diabetic patient, particularly in relation to GFR. Is the diabetic CKD patient in any way different compared to other CKD patients at equivalent renal function?

- Glucose-lowering agents used in diabetes and kidney disease, including:
  - Metformin
  - Sulfonylureas
  - Thiazolidinediones
  - Insulin

- Novel and recently approved treatments:
  - DPP-4 inhibitors
  - GLP-1 agonists
  - SGLT2 inhibitors

- Treatments under development, including:
  - Endothelin receptor antagonists
  - Pirfenidone
  - Others

- Cardiovascular and other therapies in diabetes and kidney disease, including:
  - Blood pressure-lowering agents
  - Lipid-lowering therapies
  - Antiplatelet agents and antithrombotics
  - Treatments for anemia
  - Novel and in development approaches: Vitamin D, antioxidants, other agents

- How should the safety of agents being developed in this population be studied in the future?
    - How do we select patients who are most likely to have a positive benefit-risk profile
    - What are the most important outcomes to be considered?
    - What should be required to achieve regulatory approval, and/or guideline recommendations?

B. Efficacy of glycemic control

- Does glucose lowering *per se* prevent ESKD in people with diabetes and kidney disease? At what stage of kidney disease might this be best known or studied?
- Do specific classes of agents have particular nephroprotective or harmful effects?
- What is the impact of more intensive glycemic control on cardiovascular events in this population? Is there a similar or different effect on mortality?
- What is the importance of hypoglycemia in this population?
- What is the effect of lifestyle measures on diabetic nephropathy?
- How does one assess glycemic control in diabetic subjects with chronic kidney disease?

C. Therapies for protecting kidney function

- What treatments are proven to be effective at improving kidney function?
- What is the relevance of short-term changes in kidney function induced by treatment?
- Should surrogate endpoints (e.g., albuminuria) be used in clinical trials and proposed to regulatory agencies?
- How should GFR be measured in clinical trials?
- Use of new biomarkers in monitoring potential nephroprotective effects
- Can renal structure be used as primary endpoint in clinical trials?
- What are ideal patients to test the nephroprotective effects of a new agent? (i.e., prevention of development vs. prevention of progression)

- Which are the most promising agents or approaches that should be prioritized for future study?
- How should promising agents be identified and selected for outcome studies?

D. Therapeutic effects on cardiovascular risk and other outcomes of interest

- What is the impact of lifestyle intervention on CV outcomes in patients with DKD?
- Why are effects of metabolic control on micro- & macro-vascular outcomes different?
- Is there any new information that might change the conclusions of recent guidelines on blood pressure lowering and lipid modification in diabetes and CKD?
- Are there still options for using dual blockade in DKD?
- Is lower the BP target the better in DKD?
- How are residual risk and unmet medical need defined for the increased CVD risk in DKD patients?
- What is known about the risk-benefit ratio of antithrombotic agents and anticoagulants in CKD?
- 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?
- Do any new agents in development have important caveats that require specific study in people with diabetes and CKD?
- Are there any CKD-specific therapies that are effective at reducing cardiovascular risk in diabetes and CKD (e.g., iron therapy)?