Global Action. Local Change.

KDIGO Controversies Conference on Prognosis and Optimal Management of Patients with Advanced CKD

December 2-5, 2016
Barcelona, Spain

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. The recommendations from these conferences may 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

Chronic kidney disease (CKD) is defined by a persistent reduction in GFR and/or the presence of other signs of kidney damage, in particular- presence of albuminuria- and is categorized based on eGFR and albuminuria. Research performed over the last two decades has shown that:

- The prevalence of CKD tends to decrease with increasing severity, indicating that only a proportion of affected patients in a specific stage progress to a more

advanced stage, because (a) their kidney function remains relatively stable or (b) they die before reaching the next stage.

- There is variation in the rate of CKD progression, even within a single country.
- The adverse health consequences associated with CKD increase with increasing severity (i.e., decline in GFR and increase in albuminuria).
- Although the overall prevalence of CKD is similar in different parts of the world, the distribution by eGFR and albuminuria category is variable, and varies by ethnicity.
- Acute kidney injury has increased substantially, is more prevalent in those with existing CKD and is now recognized as an important driver of CKD and kidney failure.
- Renal replacement therapy (RRT), which includes dialysis and transplantation, has been established to mitigate the consequences and improve the prognosis of patients with kidney failure. However, the availability and access to both modes of RRT varies widely between countries and potentially also within countries.
- The level of kidney function and other patient conditions and symptoms at which dialysis should be initiated or pre-emptive transplantation be performed are difficult to define and remain controversial.
- There is dramatic variation in the incidence of ESRD by country, but to what extent this reflects differences in rates of CKD progression or differences in practice patterns (i.e., the likelihood of initiating a patient on RRT) is unknown.
- The first months on dialysis have been identified as a very high-risk period, but it is unknown to what extent this risk is influenced by dialysis initiation. Late referral, defined as referral to renal services within 3 months of dialysis initiation ('crash landing onto dialysis'), is known to exacerbate this risk.

- Work within the CKD field has tended to focus on the prognosis of patients with "earlier" stages and those on RRT (i.e., ESRD). Less attention has been paid to patients with "advanced" CKD (category G4+; i.e., GFR < 30 ml/min/1.73 m^2) not receiving RRT.
- In particular the variation in outcomes of patients in CKD category G4+ (eGFR < 30 ml/min/1.73 m^2) remains poorly defined, although cardiovascular disease (particularly heart failure) remains the leading cause of morbidity and mortality.

A better understanding of the prevalence and prognosis of patients with CKD G4+ and the factors associated with different outcomes may help to generate hypotheses about optimal treatment strategies in this high risk population, including decision making about initiation of RRT. KDIGO has therefore chosen to organize a conference focusing on patients with CKD G4+.

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) that will identify key issues relevant to the prognosis and optimal management of patients with advanced CKD. The goal is to assess our current state of knowledge related to prognosis and management, as well as explore novel analyses provided by the CKD-Prognosis Consortium (CKD-PC). CKD-PC will be presenting their original analyses of 270,000 advanced CKD patients from 29 CKD cohorts and examining how variation in prognosis could be influenced by cohort, demographic, or health characteristics. The conference will summarize outstanding knowledge gaps and propose a research agenda to resolve outstanding controversial issues. Importantly this conference will inform clinicians of the evidence base for current treatment options and identify areas in critical need of future studies. In addition to "hard" outcomes that are captured in observational studies, the discussion will be extended to symptom burden and patient priorities for research and clinical management.

Drs. Kai-Uwe Eckardt (Friedrich-Alexander University Erlangen-Nürnberg, Germany) and Brenda Hemmelgarn (University of Calgary, Canada) will co-chair this conference. The format of the conference will involve topical plenary session presentations, presentation of novel analyses by the CKD-PC commissioned specifically for this conference, 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 Conference**. 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.

APPENDIX: SCOPE OF CONFERENCE

Questions to be addressed during plenary sessions:

1. Prevalence of CKD category G4+, and variation by country / regions of the world

2. Prognosis of patients with CKD G4+ in different regions of the world: Novel analyses from the CKD-PC:
    a. ESRD
    b. Death
    c. Cardiovascular events
    d. Hospitalizations

3. Factors associated with inter- and intra-regional variation of prognosis in patients with CKD category G4+

4. Biomarkers to predict prognosis in patients with CKD category G4 +

5. Variation in conditions and practice patterns in patients initiating dialysis

6. Strategies to hold / retard progression of CKD in patients with CKD category G4

7. Models of care – the nephrologists as the general manager vs one member of a larger team

8. Impact of patient history on prognosis of incident dialysis patients (mortality, CV events [including HF], hospitalizations) during the first 6 months post-dialysis initiation

9. Impact of the level of renal function at the time of dialysis initiation on the prognosis of incident dialysis patients

10. Strategies for “conservative” (supportive) management of renal failure (if RRT is either not chosen as a therapy or is unavailable)

Breakout Groups will focus on the discussion of four topics:

1. Risk-based management of patients with CKD G4+

2. Heart failure in CKD G4+

3. Informed decision-making for treatment of kidney failure (i.e., dialysis initiation, transplantation, or conservative care)

4. Needs, opportunities and challenges for clinical trials in patients with advanced CKD

DETAILED BREAKOUT GROUP QUESTIONS

Group #1: Risk-Based Management of Patients with CKD G4+

This breakout group will discuss the identification/assessment, prioritization, and management of patients with CKD G4+ in order to prevent and/or mitigate CKD-associated risks. Questions for further discussion will include:

1. How should the prognosis of patients with CKD G4+ be determined, for key outcomes, including kidney-specific, cardiovascular, and non-cardiovascular outcomes?
2. How should variation in kidney function be distinguished from progression?
3. Does age modify outcomes and how should this be accounted for in risk-based care?
4. What are important racial, geographic, and social determinants of risk and how can these determinants be addressed?
5. How can we weigh the risk/benefit strategies of common medical and surgical interventions in people with CKD G4+ (e.g., stringencies of controlling blood pressure, glycemic control, major surgery, and other medical procedures or exposures?)
6. How should competing risks of non-kidney outcomes, patient preferences, and quality of life be incorporated into risk-based management?
7. What is the best model of care for patients with CKD 4+ and how can this be implemented? What are the implications of multi-morbidities in CKD G4+ and how should different guidelines for managing comorbidities be addressed in people with CKD and how can diverse care providers be alerted to risks of complications?
8. What are the remaining uncertainties about medical therapeutic targets to reduce risk in CKD – e.g., treatment of asymptomatic hyperuricemia, acidosis, use of aspirin, and other cardiovascular prevention strategies?

9. How should patients who develop advanced CKD following AKI be identified and managed? How can the risk of AKI in people with CKD4+ be best mitigated against (e.g., tablet holidays with inter-current illness, temporary cessation of RAAS blockade, etc.)?

10. What is the role of biomarkers to improve prognostication in CKD G4+, above and beyond eGFR and albuminuria?

11. Are there subclinical events (e.g., tubulointerstitial injury, inflammation, fibrosis, unrecognized episodes of AKI, short lived prescription and non-prescription medication exposures, etc.) associated with progression and can these be identified and targeted to reduce risk of adverse outcomes?

12. How can risk prediction strategies be incorporated to time key elements of care delivery for advanced CKD care (i.e., intensity of follow-up, timing of psychosocial and educational interventions for RRT modality selection, or end-of-life care)?

Group #2: Heart Failure in CKD G4+

Epidemiology and natural history of heart failure in CKD G4+

1. What is the relative distribution of HFPEF and HFREF as patients transition from CKD G4+ to G5?
2. What is the progression in LVH burden from CKD G4 4+ to G5?
3. What is the contribution of ischemic heart disease to heart failure in CKD G4+? And does it change in the progression/transition to CKD G5 (i.e., is the risk actually higher in CKD G4+ with survival bias/less IHD in CKD G5)?
4. What are the short- and long-term outcomes associated with heart failure in patients progressing to CKD G5?

Screening and diagnosis of heart failure in CKD G4+

5. Does screening for heart failure in CKD G4+ have any evidence-based benefit in patients progressing to CKD G5? If yes, what are the best methods to screen?

Pathophysiology and risk factors for heart failure in CKD G4+

6. Are there CKD-specific risk factors that contribute to the development of heart failure in patients progressing from CKD G4+ to G5?

Strategies for primary and secondary treatment of heart failure in CKD G4+

7. How do we manage a patient with CKD G4+ and heart failure (HFREF and HFPEF as categories) i.e., "conventional" therapy such as ACEi/ARB/MRA? Do we use potassium binders as part of the therapeutic strategy?

8. How do we prepare a CKD G4+/ G5 ND patient with HF for the initiation of renal replacement therapy?

9. Do arteriovenous fistula adversely affect patients with HF? Should patients with HF receive AVF?

10. What modality of renal replacement therapy is best for patients with CKD G4+/G5 with HF (e.g., in-center HD, home HD, PD, preemptive kidney transplant)?

Group #3: Informed Decision-Making for Renal Failure Therapy (i.e., dialysis initiation, transplantation or conservative care)

1. What tools can be used to assess patient prognosis in CKD G4+ and/or incident ESRD? Are the available tools accurate? Generalizable?
2. Is it possible to identify patients for whom dialysis or transplant might be considered "futile"? How should prognostic estimates be used and communicated to patients in decision-making?
3. At what level of kidney function and/or what level of ESRD risk should patients receive counseling about treatment modalities for kidney failure? What are the costs, risks and benefits of early vs. late or liberal vs. more targeted counseling?
4. What considerations do patients consider most important in making treatment modality decisions (i.e., dialysis vs. transplant, dialysis vs. conservative care). How important is life expectancy relative to other considerations?

5. What considerations do clinicians consider most important in making treatment modality decisions (i.e., dialysis vs. transplant, dialysis vs. conservative care). How important is life expectancy relative to other considerations?
6. What are the characteristics of patient education interventions that promote informed decision-making about treatment of kidney failure (e.g., decision aids, group classes, others)? How do studies measure the effectiveness of these interventions?
7. What is the appropriate timing and quantity of nephrologist care to promote informed decision-making for treatment of kidney failure? What is the role of nephrologist care for patients who have expressed a preference for conservative care, and/or patients considered to have a poor prognosis on dialysis?
8. How can informed decision making be promoted among patients with limited health literacy, cognitive impairment, language and/or cultural barriers, etc.?

Group #4: Needs, Opportunities and Challenges for Clinical Trials in Patients with Advanced CKD

How can we increase the number of completed trials in CKD G4+?

1. What are the elements of the "business case" that would encourage industry to support trials in this population?
2. How can patients be engaged to lead and support clinical trials in this population (CKD G4+)?
3. What alternative trial designs or platforms can be used in this population and which should be prioritized?
4. How can we build capacity for trial design and conduct, especially in LMIC?

How to increase the likelihood that trials will demonstrate benefit of the experimental treatment?

5. What are the optimal (non-renal) endpoints (e.g., CV, vascular access, MBD, others) for patients with CKD G4+?
6. How can the most appropriate participants be selected for inclusion?
7. What lessons can be learned from prior trials of advanced CKD?

How can the findings of trials be made more relevant to patients and their families?

8. What interventions and outcomes are most patient-relevant for CKD G4+?
9. What structures/processes are required to ensure ongoing input from patients and families in priority setting for future trials?
10. What is the optimal method for involving patients in increasing the uptake of findings from completed trials?