

POSITION STATEMENT

Definition and Classification of CKD: The Debate Should Be About Patient Prognosis—A Position Statement From KDOQI and KDIGO

AQ: 2 In 2002 the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) published a guideline on chronic kidney disease (CKD) covering evaluation, classification, and stratification of risk.¹ The workgroup developing this guideline provided a new conceptual framework for a diagnosis of CKD independent of cause, and developed a classification scheme of kidney disease severity based on the level of glomerular filtration rate (GFR). Before this new system for defining and staging CKD was developed, vague and variable terminology, such as "chronic renal failure," "chronic renal insufficiency," "pre-dialysis," and "pre-end-stage renal disease" prevented the use of a common and precise language.² The new system also represented a significant conceptual change, since kidney disease historically had been categorized mainly by cause. The definition is based on 3 components: (1) an anatomical or structural component (markers of kidney damage, including albuminuria), (2) a functional component (based on GFR), and (3) a temporal component (at least 3 months' duration of structural and/or functional alterations). The diagnosis of CKD relies on markers of kidney damage and/or a reduction in GFR. Stages 1 and 2 define conditions of kidney damage in the presence of a GFR of at least 90 mL/min/1.73 m² or 60 to 89 mL/min/1.73 m², respectively, and stages 3 to 5 define conditions of moderately and severely reduced GFR irrespective of markers of kidney damage (Table 1).

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The impact that this classification system has had in only 6 years on the awareness of CKD in individuals and populations, on research activities, research support, and public health policy has been tremendous. There has been an exponential increase in the amount of research performed in patients with kidney disease not receiving long-term dialysis therapy since the guidelines were released, and the common definition of CKD has facilitated comparisons between studies. Thus, this new diagnostic classification of CKD has likely been one of the most profound conceptual developments in the history of nephrology.

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Nevertheless, there are limitations to this classification system, which is by its nature simple and necessarily arbitrary in terms of specifying the thresholds for definition and different stages. When the classification system was developed in 2002, the evidence base used for the development of this guideline was much smaller than the CKD evidence base today. It is the growth of this CKD database that has, ironically, stimulated recent discussions questioning the value of current CKD guidelines.

GLOBAL ENDORSEMENT OF A COMMON SYSTEM FOR DEFINITION AND STAGING OF CKD

In 2004, KDIGO (Kidney Disease: Improving Global Outcomes), an independent not-for-profit foundation governed by an international Board of Directors with the stated mission of improving the care and outcomes of kidney disease patients worldwide, hosted its first Controversies Conference devoted to the definition and classification of CKD.³ In preparation for this conference, a survey was sent to approximately 10,000 nephrologists worldwide via e-mail to assess their opinion of the KDOQI definition and classification of CKD. The responses to this survey provided a broad basis for the discussion. In 2006, KDIGO convened a second Controversies Conference to reanalyze the CKD classification and address questions of CKD screening and surveillance, public policy for CKD, and associations of CKD with cardiovascular disease, infections, and cancer.⁴ After extensive discussion, participants of both conferences endorsed the global use of the definition and staging system for CKD originally developed by KDOQI. The only modification recommended at the 2004 conference was the addition of a classification for treatment by

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Table 1. Classification of CKD as Defined by KDOQI and Modified and Endorsed by KDIGO

Stage	Description	Classification by Severity	Classification by Treatment
1	Kidney damage with normal or ↑ GFR	GFR ≥ 90	} T if kidney transplant recipient
2	Kidney damage with mild ↓ in GFR	GFR of 60-89	
3	Moderate ↓ in GFR	GFR of 30-59	
4	Severe ↓ in GFR	GFR of 15-29	
5	Kidney failure	GFR < 15 (or dialysis)	D if dialysis

Note: GFR is given in mL/min/1.73 m².

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative.

transplantation or dialysis, using the suffix “T” for all kidney transplant recipients at any level of GFR and “D” to indicate dialysis for CKD stage 5 patients treated by dialysis (Table 1).

Both conferences acknowledged shortcomings of the current classification scheme and concluded that additional clinical information is required for the evaluation and management of individual cases of CKD. However, the potential benefits of adding information and granularity to the classification system was thought to be outweighed by added complexity that would limit its applicability, in particular to disciplines outside of nephrology.⁴ Importantly, both conferences also defined research and public policy recommendations, several of which have subsequently been successfully addressed.^{3,4}

DISCUSSION ABOUT THE NEED FOR REVISION

Recently, discussions on the limitations of the current system for the definition and classification of CKD, and the benefits and disadvantages of a possible modification to this system, have led to a passionate debate primarily in the editorial and correspondence pages of nephrology subspecialty journals and in public forums.⁵⁻²⁰ The perceived limitations focus on several areas.

First, proponents of a change in the current system are generally concerned that the application of the current system leads to over- and misdiagnosis of CKD and possible overuse of speciality resources.^{6,7,9,15-17,19} Moreover, reported CKD prevalence rates, based on the use of some, although usually not all, of the components of the current definition and classification system are considered to be too high in comparison to incidence rates for treated kidney failure (end-stage renal disease).^{6,7,9,16,17,19}

Second, there is discomfort with the terminology used to define kidney disease and its different stages. This issue revolves around the question of when and how to use the term “disease” and how to separate it from “pre-disease states” and “risk factors.”^{5-7,9,16,19,21} The use of the general term “chronic kidney disease”, without further specification across the entire spectrum of CKD, and without regard to etiology, has also been considered problematic.

Third, there are methodological issues of concern, which include the use of estimated GFR (eGFR) computed from estimating equations, especially in the elderly and in diverse ethnic and racial populations, for the initial diagnosis and staging of CKD and for determining changes in kidney function over time.^{5-9,22,23} There are also uncertainties about the methodology and cut-off values to diagnose abnormal urinary albumin and protein excretion.³

Fourth, the appropriateness of the definitions and threshold values for different stages of CKD has been questioned. Some argue that CKD stages 1 and 2 are not associated with sufficiently adverse outcomes to justify their labelling as a “disease,”^{5,6,15} while others point out that the cardiovascular event rate is equally increased in stage 1 and 2 CKD as in stage 3 CKD.¹¹ In addition, it has been argued that so-called microalbuminuria, which is sufficient to diagnose CKD stage 1 or 2 in the presence of a GFR above 60 mL/min/1.73 m², is more a cardiovascular disease outcome risk factor rather than a kidney disease outcome risk factor and reflects vascular rather than kidney disease,^{6,15,17} but the lack of proof for this assumption has also been pointed out.⁵ It also has been questioned whether a GFR below 60 mL/min/1.73 m² alone, in the absence of other markers of kidney disease, is sufficient

AQ: 4 to define CKD,^{6,9-11,24} in particular since epidemiological studies show a high proportion of elderly individuals and women in the stage 3 category.^{7-10,25}

Numerous suggested revisions to the classification system have been offered. These include elimination of stages 1 and 2,¹⁵ collapsing stages 1 and 2 into a single stage,⁶ the need for additional evidence of kidney damage in the presence of GFR levels greater than 30 mL/min/1.73 m² as a prerequisite for having CKD,^{7,11} lowering the threshold GFR value for stage 3 from 60 to 45 mL/min/1.73 m²,⁹ adding 2 subcategories to stage 3 CKD corresponding to GFR values of 45 to 59 and 30 to 44 mL/min/1.73 m²,²⁶ introducing age- and sex-specific GFR reference values,^{6-10,15,24} and setting age- and sex-dependent thresholds at the fifth percentile level.^{8,9} Obviously, the latter proposal would create a precedent for a new form of “reverse epidemiology” by defining a disease stage on the basis of a fixed prevalence rate.¹³

AQ: 5 These issues vary significantly in their relevance and implications, and a detailed analysis of the concerns and proposals as well as counterarguments is far beyond the scope of this commentary. However, the leadership of KDOQI, the organization that issued the CKD guideline in 2002, and of KDIGO, the foundation that endorsed the global use of the current definition and staging system of CKD, both believe that an open discussion needs to be continued in a structured way and that a rationale should be developed on how to validate the existing system as well as proposed alterations to this system.

POSITION OF KDOQI AND KDIGO

Both KDOQI and KDIGO acknowledge that the ongoing debate is important and is a reflection of a self-critical appraisal of changing knowledge and practice within our discipline. The risk of overdiagnosis of CKD and inappropriate diagnosis of a kidney “disease” needs to be taken very seriously, since it may easily blunt preventive and therapeutic strategies and impair the credibility of a whole discipline. On the other hand, opportunities for improvement of patient care and appropriate recognition of patient risks should not be dismissed.

The currently used definitions of CKD and of different stages of CKD are considered working definitions. Similarly, the currently available

methods to estimate GFR and ascertain kidney damage are evolving. The appropriateness of these definitions, methods, and the recommendations linked to them need to be regularly reviewed as experience with their implementation is gained and in light of new knowledge, and revised as necessary. Such revisions, however, should be based on a carefully defined rationale, should follow a defined process, and should be in line with policies for disease definition and staging in other medical disciplines. The ultimate goal is that the application of a definition and staging system for kidney disease will lead to improved patient outcomes as compared to not applying it. Testing whether this goal is achieved and which CKD definition and staging system serves this purpose best is obviously not straightforward. While using common language and definitions is an indispensable initial step, the identification of therapeutic targets and strategies for intervention, followed by the vigorous validation and implementation of these strategies, are the critical steps that will eventually justify any definition and staging system. There are many examples in other areas of medicine where progress towards this goal has taken decades of stepwise iterative adaptations. It has rightly been pointed out that there is still a long way to go to make a compelling case that increased attention to measures of kidney structure and function can add substantially to the prevention of kidney failure and cardiovascular disease,⁵ but we believe that nephrology as a discipline has started along a path that is well worth continuing to travel.

Disease classification systems that have been successfully employed in other fields of medicine also frequently classify different disease stages by severity. The 2 aspects generally considered to be relevant in staging the severity of a disease are symptoms and adverse consequences for patient outcomes (in other words, “prognosis”). Since CKD, unless it is far advanced, is not regularly associated with symptoms, but may have a significant impact on patient prognosis, we believe that carefully and accurately defining the prognosis of patients with CKD is an important prerequisite to move the debate on CKD definition and staging forward. Knowledge about the prognosis of patients fulfilling certain diagnostic criteria will be vital in assessing the current

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CKD classification system and determining what, if any, modifications to the current system are appropriate.

There are many vitally important questions about the outcome of CKD that need to be considered. What is the prognosis of patients with reduced kidney function and/or markers of kidney damage in terms of survival, progressive loss of kidney function, and other relevant outcomes, including cardiovascular disease? And how does this relationship between indicators of CKD and patient prognosis differ depending on age, sex, ethnicity, and comorbid conditions? In particular, is the prognosis of elderly individuals who fulfill the current definition for CKD different from that of individuals of the same age group without reduced eGFR and/or albuminuria? Does the current system of staging CKD match with differences in patient prognosis so that a disease stage defined as more severe is associated with poorer prognosis? And if it does not, or does so only imperfectly, how could it be improved? We believe that questions such as these are of central relevance. Although data that became available during recent years have already greatly informed the debate and provided some answers, many of these questions have not yet been clarified with certainty. Of particular importance, the increasing awareness of kidney disease as a public health issue has led to the establishment of several CKD cohorts in different parts of the world that are being studied prospectively, and should provide far more solid and detailed information about CKD and patient prognosis than the many retrospective and secondary analyses that are currently available to us. In addition, large population-based cohorts should also be able to answer questions about the prognosis of individuals who fulfil the current definitions of early stages of CKD.

A KDIGO CONTROVERSIES CONFERENCE ON DEFINITION, CLASSIFICATION, AND PROGNOSIS OF CKD

The Executive Committee and Board of Directors of KDIGO believe that a comprehensive analysis of outcomes in patients with CKD is timely and represents the appropriate strategy to test the validity of the current system for definition and staging of CKD and to define the rationale

Box 1. Questions to Be Addressed at the Planned KDIGO Controversies Conference

- What are the key outcomes of CKD?
- What progress has been made in CKD testing (eGFR and albuminuria)?
- What are the key factors determining prognosis (eGFR, albuminuria, others)?
- Should the current CKD classification (based on eGFR) be modified to include additional factors associated with prognosis?
- Should the current CKD definition be modified?

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

for a possible modification. They have therefore decided that KDIGO will host a Controversies Conference to facilitate a review of the current system and a thorough analysis of the prognosis of patients fulfilling different potential criteria for CKD. Although the current CKD classification and staging schema were produced under the auspices of KDOQI, the KDOQI leadership has endorsed this conference, recognizing that these issues are clearly of global relevance and are best addressed by an international body such as KDIGO.

This KDIGO Controversies Conference will be held in October 2009 and will bring together experts from all over the world with different research and professional backgrounds, including clinical nephrologists, methodologists, epidemiologists, public health specialists, and general practitioners. It will be chaired by Drs J. Coresh (United States), P. de Jong (The Netherlands), M. El Nahas (United Kingdom), and A.S. Levey (United States), who will work together with the KDIGO co-chairs K.-U. Eckardt (Germany) and B. Kasiske (United States) to develop the scope of work, the analytical framework, and the agenda.

The purpose of the planned conference is to address 5 topics outlined in Box 1. The main objective is to analyze the prognosis of patients with CKD, defined according to different criteria, with respect to a range of relevant outcomes, including, but not necessarily confined to, mortality, kidney disease progression, cardiovascular disease events, and acute kidney injury. In addition to those parameters used in the current definition and staging for CKD, the risk-modifying influence of parameters not currently included, in particular albuminuria, age, sex, and

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cardiovascular disease risk factors, will be assessed. Wherever possible, variables such as eGFR and level of albuminuria will be analyzed in a continuous fashion, in addition to predefined and necessarily arbitrary categories. The analysis will include published and unpublished data derived from analyses of prospective cohorts. To this end, a study registry of ongoing CKD and population cohort studies is currently being established and principal investigators of such studies are being invited to perform predefined analyses prior to the meeting and share their data at this conference.

The scope of the conference will also include a review of the progress in methodology with respect to standardization of creatinine measurements, use of existing GFR estimating equations, and consideration of new formulas for estimating GFR. The purpose of this review is to determine how methodological progress will impact the accuracy of estimating GFR, which will inevitably determine the prognostic precision of eGFR-based estimates of kidney function. Based on a similar rationale, progress in standardizing measurements of urinary protein will also be reviewed.

The results of the conference will be summarized, and publication of a conference report, together with technical reports concerning the analysis presented, is being planned. We anticipate that the conference will have a prominent role in shaping the current debate of the CKD definition and classification and that the evidence reviewed at the conference, together with a structured review of the literature since the time of the initial CKD guideline literature review in 2001, will provide a basis for a guideline update. To this end, following the conference KDIGO will appoint a workgroup to develop a revised global guideline on the definition, staging, and management of CKD. The update process is a vital part of both KDOQI and KDIGO and is designed to determine if current guideline statements are still supported by current literature or if recommendations need to be revised based on recent literature.

As with past KDIGO controversies conferences, participation will be by invitation only, in order to limit the group of participants to a number that will ensure an intense interactive debate. Nevertheless, individuals who are inter-

ested in participating in this conference and are willing to present the results of unpublished analyses relevant to the topic of the conference are invited to submit a declaration of interest through the KDIGO website (www.kdigo.org).

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