Introduction

From editorial in American Journal of Kidney Disease

Definition and classification of chronic kidney disease –
the debate should be about patient prognosis

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In 2002 the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) published a guideline on Chronic Kidney Disease: Evaluation, Classification and Stratification of Risk [1]. The workgroup developing this guideline provided a new conceptual framework for a diagnosis of chronic kidney disease (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 had historically mainly been categorized by cause. The definition is based on three 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 three months duration of structural and/or functional alterations). The diagnosis of CKD relies on markers of kidney damage and/or a reduction in GFR; stage 1 and 2 define conditions of kidney damage in the presence of an GFR ≥ 90 or 60-89 ml/min/1.73 m^2, stages 3 - 5 define conditions of moderately and severely reduced GFR irrespective of markers of kidney damage (Table 1).

The impact that this classification system has had in only six 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 chronic 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.

Nevertheless, there are limitations to this classification system, which is by its nature simple and necessarily arbitrary in terms of defining 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 Kidney Disease: Improving Global Outcomes (KDIGO), an independent non-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 electronic mail to assess their opinion on 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 reanalyse the CKD classification and address questions of CKD screening and surveillance, public policy for CKD and associations of CKD with CVD, 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 dialysis or transplantation, using the suffix “T” for all kidney transplant recipients at any level of GFR and “D” for dialysis for CKD stage 5 patients treated by dialysis (Table 1).

**Table 1. Classification of chronic kidney disease, as defined by KDOQI and modified and endorsed by KDIGO.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Classification by severity GFR ml/min/1.73 m²</th>
<th>Classification by treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ in GFR</td>
<td>60-89</td>
<td>T if kidney transplant recipient</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ in GFR</td>
<td>30-59</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ in GFR</td>
<td>15-29</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
<td>D if dialysis</td>
</tr>
</tbody>
</table>

Abbreviations are: GFR, glomerular filtration rate

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 specialty 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, 6, 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 as 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 stage 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 the 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 CVD outcomes 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 has also been questioned whether a GFR below 60 ml/min/1.73 m² alone, in the absence of other markers of kidney disease, is sufficient to define CKD [6, 9-11, 24], in particular since epidemiological studies show a high proportion of elderly and female individuals 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 as a prerequisite for having CKD [7, 11], lowering the threshold GFR value for stage 3 from 60 to 45 ml/min/1.73m² [9], adding two subcategories to stage 3 CKD corresponding to GFR values of 45-59 and 30-44 ml/min/1.73 m² [26], introducing age- and gender-specific GFR reference values [6-10, 15, 24] and introducing age- and gender dependent 5th percentiles as thresholds [8, 9]. Obviously the latter proposal would create precedence for a new form of “reverse epidemiology” by defining a disease stage on the basis of a fixed prevalence rate [13].

These issues vary significantly in their relevance and implications and a detailed analysis of the concerns and proposals as well as counter-arguments is far beyond the scope of this commentary. However, leadership of KDOQI, as the organisation that issued the CKD guideline in 2002, and of KDIGO, as 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 two aspects generally considered to be relevant in staging the severity of a disease are (1) symptoms and (2) 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 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, gender, ethnicity and co-morbidity? In particular, is the prognosis of elderly individuals who fulfil 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 “Chronic Kidney Disease: Definition, Classification and Prognosis”

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 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 was 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 (US), P. de Jong (NL) M. El Nahas (UK), and A. Levey (US), who will work together with the KDIGO co-chairs K.-U. Eckardt (Ger) and B. Kasiske (US) to develop the scope of work, the analytical framework and the agenda.

The purpose of the planned conference is to address five topics outlined in table 2. 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 cardiovascular disease risk factors will be assessed. Wherever possible variables, such as eGFR and level of albuminuria will be analysed in a continuous fashion in addition to predefined and necessarily arbitrary categories. The analysis will include published and unpublished data derived form analyses of prospective cohorts. To this end a study a registry of ongoing CKD and population cohort studies is currently being established and principal investigators of such studies are being invited to perform predefined analysis prior to the meeting and share their data at this conference.

Table 2. Questions to be addressed at the planned KDIGO Controversies Conference

<table>
<thead>
<tr>
<th>Question</th>
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<tr>
<td>What are the key outcomes of CKD?</td>
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<tr>
<td>What progress has been made in CKD testing (eGFR and albuminuria)?</td>
</tr>
<tr>
<td>What are the key factors determining prognosis (eGFR, albuminuria, others?)</td>
</tr>
<tr>
<td>Should the current CKD classification (based on eGFR) be modified to include additional factors associated with prognosis?</td>
</tr>
<tr>
<td>Should the current CKD definition be modified?</td>
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</tbody>
</table>

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 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 KDIGO following the conference 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 conference, participation will be by invitation only, in order to limit the group of participants to a number that will ensure an intense interactive debate.

**References**

11. de Jong PE, Gansevoort RT. Fact or fiction of the epidemic of chronic kidney disease – let us not squabble about estimated GFR only, but also focus on albuminuria. Nephrol Dial and Transpl 23: 1092-5, 2008
KDIGO - Controversies Conference
Definition, Classification, and Prognosis in CKD
4-6 October, 2009
London, England

CONFERENCE AGENDA

Saturday, 3 October
18:00 – 22:00 hrs

18:00 – 20:30 hrs  Planning Committee Dinner Meeting
20:30 – 22:00 hrs  Welcome Reception

Day 1 – Sunday, 4 October
08:00 – 19:00 hrs

07:30 – 08:00 hrs  Continental Breakfast

Introduction: Meeting Overview

08:00 – 08:20 hrs  Welcome and Introductions
  Presenter: Bert Kasiske

Plenary Sessions: Overview of CKD Definition and Classification
  Session Moderators: Joe Coresh, Paul de Jong, Meguid El Nahas, & Andrew Levey

  08:20 - 08:40 hrs  The 2002 CKD definition and classification system: concept, impact, criticisms and opportunities to move forward
  Presenter: Kai-Uwe Eckardt

  08:40 – 09:00 hrs  The 2002 CKD definition and classification system: limitations and problems
  Presenter: Richard J. Glassock
09:00 – 09:30 hrs  Prognosis matters - the concept and general objectives of the conference - the analytical plan
Presenter: Andrew Levey

09:30 – 09:50 hrs  Break

**Plenary Sessions: The Methodological Background**
**Session Moderators:** Joe Coresh, Paul de Jong, Meguid El Nahas, & Andrew Levey

09:50 – 10:50 hrs  Measures of kidney function and damage
- Laboratory and measurement issues
- eGFR based on creatinine and cystatin C
- Proteinuria and albuminuria
Presenters: Greg Miller, Lesley Stevens, Ron Gansevoort

10:50 – 11:30 hrs  Analytical Methodology
- Selection and characteristics of cohorts
- Data analysis
Presenters: Meguid El Nahas, Josef Coresh, Paul de Jong

**Plenary Sessions: Population-Based Cohort Studies and Non-Refereed Clinical Populations**
**Session Moderators:** Joe Coresh, Paul de Jong, Meguid El Nahas, Andrew Levey

11:30 – 12:00 hrs  Summary of Pooled Data (30 minutes)
Presenters: Paul de Jong and Josef Coresh

12:00 – 12:20 hrs  Discussion

12:20 – 13:00 hrs  Lunch

13:00 – 14:50 hrs  Presentations of Individual Studies (10 minute presentation per speaker; *cohort participation and order of presentations are not yet confirmed)
- **AKDN Study** - Brenda Hemmelgarn
- **Kaiser Pacific Northwest** – David Smith
- **AGES-Reykjavik Study** - Ólafur Skúli Indriðason
- **ARIC** – Josef Coresh
- **AusDiab**- Robert Atkins
- **Beaver Dam CKD Study** - Anoop Shankar
14:50 - 15:10 hrs  Break

15:10 – 17:00 hrs  Presentations of Individual Studies (Continued)
•  Cardiovascular Health Study -- Michael Shlipak
•  MESA – Michael Shlipak
•  Kaiser Northern California – Alan Go
•  CKD and Mortality Risk in Older People - Paul Roderick
•  Control of BP and Risk Attenuation – Tazeen Jafar

17:00 – 17:30 hrs  Break

17:30 – 19:00 hrs  Discussion

20:00 – 22:00 hrs  Dinner (Meet in hotel Lobby at 19:30 hrs)
Day Two – Monday, 5 October
8:00 to 19:00 hrs

7:30 - 8:00 hrs  Continental Breakfast

Plenary Sessions: CKD Cohort Studies and Referred Clinical Populations
Session Moderators: Joe Coresh, Paul de Jong, Meguid El Nahas, Andrew Levey

08:00 – 08:30 hrs  Summary of Pooled Data (30 minutes)
                  Presenters: Paul de Jong and Josef Coresh

08:30 – 09:50 hrs  Presentations of Individual Studies (10 minute presentation per speaker; *cohort participation and order of presentations are not yet confirmed)
                  • Beijing Cohort – HaiYan Wang
                  • British Columbia CKD Cohort – Adeera Levin
                  • CANCARE – Adeera Levin
                  • Can Prevent – Brendan Barrett
                  • CKD-JAC - Enyu Imai
                  • CRIB Study – David Wheeler
                  • CRIC Study - Mahboob Rahman
                  • Kaiser – Hawaii – Brian Lee

9:50 – 10:10 hrs  Break

10:10 – 11:40 hrs  Presentations of Individual Studies (Continued)
                  • MASTERPLAN – Jack Wetzels
                  • MDRD Study – Vandana Menon
                  • ASSK – Jackson Wright
                  • MMKD - Florian Kronenberg
                  • NephroTest - Marc Froissart
                  • ORFAN Follow-up study – Marie Evans
                  • REIN Study - Giuseppe Remuzzi
                  • RENAAL - Dick de Zeeuw
                  • USRDS – Allan Collins

11:40 – 12:40 hrs  Discussion

12:40 – 13:30 hrs  Lunch
Plenary Sessions: High Risk Cohort Studies and Clinical Populations (Hypertension, Diabetes & CVD)
Session Moderators: Joe Coresh, Paul de Jong, Meguid El Nahas, Andrew Levey

13:30 – 13:45 hrs  **Summary of Pooled Data** (15 minutes)
Presenters: Paul de Jong and Josef Coresh

13:45 – 15:15 hrs  **Presentations of Individual Studies** (10 minute presentation per speaker; *cohort participation and order of presentations are not yet confirmed)
• CARE – Marcello Tonelli
• Prevalence and Progression of CKD in Veterans – Ann O’Hare
• ONTARGET – Johannes Mann
• MRFIT - Areef Ishani
• ADVANCE – Mark Woodward
• Predictors of ESRD in Type 1 DM - Andreiz Krolewski
• Pima Indian Study – Robert Nelson
• STENO – Peter Rossing
• ZODIAC - Henk Bilo

15:15 – 15:30 hrs  Discussion

15:30 – 16:00 hrs  Break

16:00 – 17:00 hrs  Special Topics
Presenters: TBD

17:00 – 18:30 hrs  **Breakout Sessions**  
**Breakout Group #1**
Discussion Leaders: TBD

**Breakout Group #2**
Discussion Leaders: TBD

**Breakout Group #3**
Discussion Leaders: TBD

18:30 – 19:00 hrs  Discussion leaders develop group presentation

20:00 – 22:00 hrs  **Dinner (Meet in hotel Lobby at 19:30 hrs)**
**Day 3 - Tuesday, 6 October**
8:00 to 15:00 hrs

7:30 - 8:00 hrs  Continental Breakfast

**Presentation and Discussion of Recommendations**
Session Moderators: Joe Coresh, Paul de Jong, Meguid El Nahas, Andrew Levey

8:00 – 8:40 hrs  Group 1 Presentation
8:40 – 9:20 hrs  Group 2 Presentation
9:20 - 10:00 hrs  Group 3 Presentation
10:00 – 10:30 hrs  Break
10:30 – 13:00 hrs  Discussion and consensus on recommendations
12:30 – 13:00 hrs  Working Lunch
13:00 – 14:00 hrs  Wrap up and outline of tasks for drafting of position statement
14:00 hrs  Adjourn (Departures)

14:00 – 16:00 hrs  Planning Committee – Post Meeting