The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report

Andrew S. Levey[1], Paul E. de Jong[2], Josef Coresh[3], Meguid El Nahas[4], Brad C. Astor[3], Kunihiro Matsushita[3], Ron T. Gansevoort[2], Bertram L. Kasiske[5] and Kai-Uwe Eckardt[6]

[1]Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts, USA; [2]Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [4]Sheffield Kidney Institute, University of Sheffield, Sheffield, UK; [5]Hennepin County Medical Center, Minneapolis, Minnesota, USA and [6]Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany

The definition and classification for chronic kidney disease was proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and endorsed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2004. This framework promoted increased attention to chronic kidney disease in clinical practice, research and public health, but has also generated debate. It was the position of KDIGO and KDOQI that the definition and classification should reflect patient prognosis and that an analysis of outcomes would answer key questions underlying the debate. KDIGO initiated a collaborative meta-analysis and sponsored a Controversies Conference in October 2009 to examine the relationship of estimated glomerular filtration rate (GFR) and albuminuria to mortality and kidney outcomes. On the basis of analyses in 45 cohorts that included 1,555,332 participants from general, high-risk, and kidney disease populations, conference attendees agreed to retain the current definition for chronic kidney disease of a GFR <60 ml/min per 1.73 m^2 or a urinary albumin-to-creatinine ratio >30 mg/g, and to modify the classification by adding albuminuria stage, subdivision of stage 3, and emphasizing clinical diagnosis. Prognosis could then be assigned based on the clinical diagnosis, stage, and other key factors relevant to specific outcomes. KDIGO has now convened a workgroup to develop a global clinical practice guideline for the definition, classification, and prognosis of chronic kidney disease.

Kidney International (2011) **80,** 17–28; doi:10.1038/ki.2010.483; published online 8 December 2010

KEYWORDS: albuminuria; chronic kidney disease; classification; definition; glomerular filtration rate; prognosis

In 2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) introduced a conceptual model for the definition and classification of chronic kidney disease.[1,2] The model included antecedents associated with increased risk for development of chronic kidney disease, earlier stages of disease that could progress to later stages or lead to complications, and kidney failure as the end-stage (Figure 1). Chronic kidney disease was defined based on the presence of kidney damage or glomerular filtration rate (GFR <60 ml/min per 1.73 m^2) for $\geqslant 3$ months, irrespective of cause, and was classified into five stages based on the level of GFR. This framework advanced a uniform nomenclature for chronic kidney disease, objective diagnostic criteria irrespective of cause that could be assessed in most cases from readily available clinical laboratory data, and a simple classification scheme linked to a clinical action plan. In 2004, Kidney Disease: Improving Global Outcomes (KDIGO) endorsed this framework with minimal modifications.[3] In less than a decade, this framework has had enormous effects on clinical practice, research and public health policy.

During this time, there has also been increasing recognition of limitations of the definition and classification, leading to a heated debate and calls for revisions, mainly in nephrology subspecialty journals. This debate reflects critical self-appraisal of changing knowledge and practice within the discipline and provides opportunities for improvement. However, revisions should be based on a carefully defined rationale, should follow a defined process, and in line with policies for disease definitions and classification in other medical disciplines, should use the best-available evidence.

Correspondence: *Andrew S. Levey, Division of Nephrology, Department of Medicine, Tufts Medical Center, 800 Washington Street, Boston, Massachusetts, USA. E-mail: alevey@tuftsmedicalcenter.org*

The Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference took place on 4–6 October 2009 in London, England.
Presented in part at the 42nd Annual Meeting of the American Society of Nephrology, 1 November 2009, San Diego, California and Spring Clinical Meetings of the National Kidney Foundation, 15 April 2010, Orlando, Florida, USA

Received 3 June 2010; revised 4 October 2010; accepted 19 October 2010; published online 8 December 2010

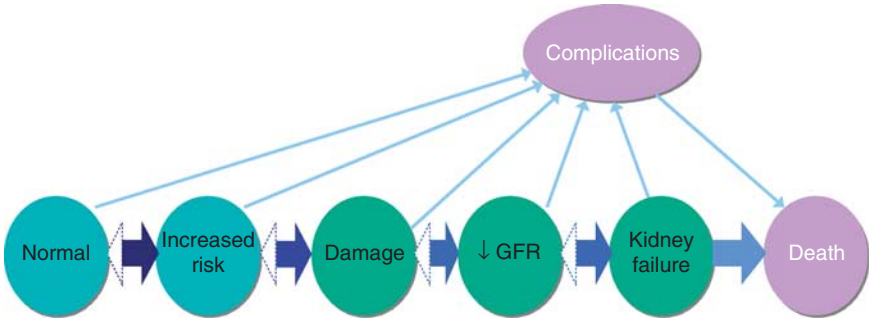

Figure 1 | Conceptual model (updated). This diagram presents the continuum of development, progression, and complications of chronic kidney disease.[1,2] Green circles represent stages of chronic kidney disease; aqua circles represent potential antecedents, lavender circles represent consequences, and thick arrows between ellipses represent risk factors associated with the development, progression, and remission of chronic kidney disease. 'Complications' refers to all complications of chronic kidney disease and interventions for its treatment and prevention, including complications of decreased glomerular filtration rate (GFR) and cardiovascular disease.

The ultimate goal is that application of a definition and classification for kidney disease will lead to improved patient outcomes.

The leadership of KDIGO, with the endorsement of KDOQI, convened a Controversies Conference to provide a forum for an open discussion.[4] A structured format was used to examine the validity of the existing system, as well as to evaluate proposed alternatives. It was the position of KDIGO and KDOQI that the definition and classification of chronic kidney disease should reflect patient prognosis and that a comprehensive analysis of outcomes by estimated GFR (eGFR) and albuminuria would shed light on the key underlying questions. The Conference was held in London in October 2009 and was attended by 98 people, including representatives from 50 cohorts with data on estimated eGFR, albuminuria, and mortality and kidney outcomes. By the end of the conference, participants reached consensus on a proposal to maintain the definition and revise the classification of chronic kidney disease. The purpose of this report is to describe the controversy, the conference, the data, and the proposed revisions and their implications.

Percentage of US population by eGFR and albuminuria category: KDOQI 2002, KDIGO 2004 and NHANES III (1988–1994)				Albuminuria (mg/g)	
				<30	>30
GFR stages, description and range (ml/min per 1.73 m^2)	1	Normal or increased	>90	87.9	3.7
	2	Mild	60–89		3.4
	3	Moderate	30–59	4.7	
	4	Severe	15–29	0.2	
	5	Kidney failure	<15	0.0	

Figure 2 | Percentage of US population by estimated glomerular filtration rate (eGFR) and albuminuria category using the definition and classification of chronic kidney disease (Kidney Disease Outcomes Quality Initiative (KDOQI) 2002 and Kidney Disease: Improving Global Outcomes (KDIGO) 2004) and prevalence estimates from National Health and Nutrition Examinations Survey III (NHANES III; 1988–1994) based on Modification of Diet in Renal Disease (MDRD) Study eGFR and standardized serum creatinine. Albuminuria ascertained by single measurement of albumin-to-creatinine ratio. Values in cells do not total to 100% because of rounding.

THE CONTROVERSY

In clinical practice, clinicians have the opportunity to make a detailed clinical assessment over time, including history, physical examination, and laboratory and imaging studies, to establish the clinical diagnosis of chronic kidney disease, including a search for its cause and determination of the pathological features. In epidemiological studies, kidney damage is usually ascertained as albuminuria estimated from the albumin-to-creatinine ratio (ACR) in a random ('spot') urine sample, GFR is estimated from serum creatinine, all measurements are made at a single point in time, and clinical diagnosis is not ascertained. Application of only these two criteria leads to a simple two-dimensional grid, in which all people with urine ACR $\geqslant$30 mg/g (the threshold commonly accepted for 'microalbuminuria') or eGFR $<$60 ml/min per 1.73 m^2 are defined as having chronic kidney disease, and staged according to the level of GFR (Figure 2). When applied in the US population studies, $\sim$12% (25 million) are estimated to have chronic kidney disease, whereas $<$0.2% ($>$500,000) have kidney failure treated by dialysis or transplantation.[5,6] The prevalence of chronic kidney disease is especially high in the elderly, affecting $>$40% of people over the age of 70 years. Similar prevalence estimates have been reported around the globe, and some reports note an increasing prevalence over time.[5,7–9] Numerous studies show that chronic kidney disease, defined according to these criteria, is a risk factor for cardiovascular disease[10] and is associated with increased costs of care.[11] These prevalence estimates are not higher than for other chronic diseases primarily affecting the elderly in the United States and leading to an increased risk for cardiovascular disease

mortality, such as hypertension (33.3%, 73.6 million), diabetes (10.6%, 23.4 million), and clinical cardiovascular disease (36.3%, 80.0 million).[12]

Rising prevalence, poor outcomes, and high costs of chronic kidney disease have led to its recognition as a public health threat.[13] Fundamentally, this recognition represents a paradigm shift in the perception of kidney disease, especially for nephrologists, from a life-threatening condition affecting few people who require treatment by dialysis or transplantation to a common condition that is the target for prevention, early detection, and management by non-nephrologist physicians and public health agencies.[14] However, given the wide implications, concerns over the definition and classification of chronic kidney disease have also arisen.

The perceived limitations focus on several areas (Table 1).[4] The high prevalence estimates of early stages of disease, especially compared with later stages, may represent overdiagnosis and misdiagnosis of kidney disease, particularly in the elderly, leading to the potential for overuse of subspecialty resources. Use of the term 'disease' to describe asymptomatic laboratory conditions, rather than 'pre-disease' or 'risk factor' may cause unnecessary concern in patients and clinicians. Methodological issues in GFR estimation and ascertainment of albuminuria may not be refined well enough to permit their use in clinical laboratory reporting or screening. The classification system may lack coherence; stage does not reliably predict prognosis. Finally, the threshold values for eGFR and urine ACR, without other evidence of disease, may not be appropriate for disease definition, especially when applied without regard to age, sex, and race.

A number of alternative proposals for the definition and classification have been suggested.[4] Some have proposed a lower eGFR threshold (30 or 45 vs 60 ml/min per 1.73 m^2), a higher urine ACR threshold (300 vs 30 mg/g), or age-specific thresholds. These modifications to the definition would limit the identification of chronic kidney disease to fewer individuals with more severe disease and a higher risk for adverse outcomes. Some have proposed combining stages 1–2 and subdividing stage 3 because of the nonlinear relationship between GFR estimated from serum creatinine and risk. Others have proposed incorporating albuminuria into disease staging across all levels of GFR. This would enable greater stratification of risk, as a growing body of evidence suggests that albuminuria is strongly associated with the risk of adverse outcomes independently of GFR, even in general populations.

Table 1 | Recent concerns with KDOQI definition and classification

Overdiagnosis	Prevalence of earlier stages of chronic kidney disease is too high compared with incidence of treated kidney failure, especially in the elderly
Terms	Earlier stages of chronic kidney disease should be labeled 'risk factor' or 'pre-disease' rather than 'disease'
Methods	GFR estimation compared with measured GFR. Spot urine albumin-to-creatinine ratios compared with timed albumin excretion rates. Single vs repeated measurements over 3 months
Coherence	Some patients at earlier stages are at higher risk of adverse outcomes than those at later stages
Threshold values	GFR and albuminuria vary according to age, sex, or race

Abbreviations: GFR, glomerular filtration rate; KDOQI, Kidney Disease Outcomes Quality Initiative.
Source: Eckardt *et al.*[4]

It is instructive to compare the current classification of chronic kidney disease with classification systems for other diseases. The chronic kidney disease classification is based primarily on severity of functional impairment, as assessed from the level of GFR. Other possible axes for classification of disease include cause, structure, symptoms, treatment, and prognosis. Nephrology has well-developed systems of classification based on cause and pathology of kidney disease. Symptoms in chronic kidney disease are nonspecific and uncommon until late stages and thus are not useful for classification. Classification of chronic kidney disease by treatment has limited utility, as there are few treatments for the underlying clinical diagnosis, and most treatments are directed at preventing progression or complications. The KDIGO Conference in 2004 suggested adding a notation to identify treatment by dialysis (D) or transplantation (T).[3] Prognosis is central to most of the concerns in the current debate, but is not captured well in the current classification system. Prognosis is important to patients, clinicians, public health, and health policy, and better information on prognosis could inform the debate. In particular, estimates of the risks for adverse events based on eGFR and urine ACR could enable assessment of the current definition and classification and determine what, if any, revisions to the current system are appropriate.

THE CONFERENCE

The scope of the Conference was to address the following topics: What are the key outcomes of chronic kidney disease? What progress has been made in testing for chronic kidney disease, focusing on eGFR and albuminuria? What are the key factors determining prognosis? Should the current *classification* (based on eGFR) be modified to include additional factors associated with prognosis? Should the current *definition* be modified?

The Planning Committee structured critical aspects of the debate on the definition and classification of chronic kidney disease to focus on prognosis. The goals were to assemble data on prognosis from a wide variety of cohorts and to use a transparent process and rigorous methods to analyze these data to answer five specific questions about the definition and classification (Box 1). The Planning Committee concluded that there are insufficient data at this time to answer questions about the causes of albuminuria and decreased GFR in the elderly, whether these findings represent 'aging' vs pathological processes, the benefit of screening for early detection of disease vs the harm of 'disease' labeling, and costs. Thus, these issues were not included in the Conference agenda.

Box 1 | Prognosis as a tool: questions for the conference to answer

Definition
Should the threshold value for eGFR be lower than 60 ml/min per 1.73 m^2 or differ by age >65 years?
Should the threshold value for albuminuria be higher than 30 mg/g or differ by age >65 years?

Classification
Should stages 1–2 be combined, divided by level of albuminuria, or both?
Should stage 3 be divided by eGFR <45 ml/min per 1.73 m^2, divided by level of albuminuria, or both?
Should stage 4 be divided by level of albuminuria?

Although the lack of data to answer these latter questions is an important shortcoming, there are few diseases for which the definitions and classification are based on such data.

The Planning Committee identified all-cause and cardiovascular disease mortality and kidney outcomes as the highest priority outcomes for this analysis. In addition to kidney failure treated by dialysis or transplantation (end-stage renal disease), acute kidney injury was included, because it is increasingly recognized as a complication as well as a cause of chronic kidney disease.[15,16] Kidney disease progression based on eGFR decline was included because of its clinical importance, owing to a high risk of complications and potential for further progression to kidney failure.

The Planning Committee considered three types of cohorts: general population cohorts, high-risk cohorts (subjects selected because of hypertension, diabetes, clinical cardiovascular disease, or a history of kidney disease), and chronic kidney disease cohorts (subjects selected because of chronic kidney disease), and identified investigators with access to published or unpublished data from research studies or clinical populations. Cohorts were identified from a systematic search of published articles from general population cohorts and from Committee members' knowledge of published and unpublished data from all three types of cohorts. The search was enhanced by calls for participation at the World Congress of Nephrology in Milan (May, 2009), a published position statement of KDOQI and KDIGO,[4] and an announcement on the KDIGO website.[17]

A survey was conducted to determine ascertainment of eGFR, albuminuria, and key clinical outcomes. Serum creatinine assay calibrated to isotope dilution mass spectrometry was preferred for estimation of GFR using the Modification of Diet in Renal Disease (MDRD) Study equation for standardized creatinine,[18] but calibration methods were not uniform. ACR was the preferred measure of albuminuria,[19] but dipstick urine protein and total urine protein-to-creatinine ratio were accepted if ACR was not available. Investigators from cohorts with adequate baseline measures and number of events in follow-up were invited to perform predefined analyses developed by the Analytic Team led by two members of the Planning Committee (PEdJ and JC). Investigators who agreed to perform the analyses and share results before the Conference were invited to attend. The Analytic Team assembled data from individual cohorts using a standardized format for 'slides'. For cohorts with sufficient number of outcomes that agreed to pool data, the Analytic Team performed a series of meta-analyses. A total of 1704 slides from individual cohorts and 454 slides from the meta-analyses were distributed to all meeting participants at the beginning of the Conference.

The Conference included introductory remarks on the current definition and classification of chronic kidney disease, limitations of the current scheme, and the questions to be answered. Updates were presented on progress in standardization of creatinine, cystatin C and urine albumin assays, GFR-estimating equations, assessment of albuminuria, and novel outcomes of chronic kidney disease. Preliminary results from the meta-analyses and application of these results to the questions of interest were presented by the Analytic Team in plenary sessions and discussed further in breakout sessions. In the final plenary session, attendees were asked to participate in a non-binding vote on each question. There was agreement by greater than two-thirds of conference participants on all questions. At the end of the Conference, attendees were invited to participate in an ongoing research project, the Chronic Kidney Disease Prognosis Consortium, led by the Analytic Team, to develop manuscripts from the final meta-analyses and to design new analyses to answer additional questions about prognosis of chronic kidney disease. The agenda of the conference and slide presentations can be accessed at the KDIGO website.[17]

THE DATA

Analytic plan

For the analysis plan, the '*a priori*' hypothesis was that both eGFR and albuminuria would be associated with mortality and kidney disease outcomes, independent of traditional cardiovascular risk factors and independent of each other, and despite inclusion of diverse study populations. The Analytic Team provided definitions of study populations and outcomes as defined above, predictors (eGFR and measures of albuminuria), adjustment variables (age, sex, race, history of clinical cardiovascular disease and cardiovascular disease risk factors (smoking, systolic blood pressure, diabetes, and serum total cholesterol), and treatment assignment for clinical trials), and statistical code for survival and logistic regression analyses using continuous and categorical definitions of predictor variables.

For continuous analysis, splines for eGFR at multiple points were used to allow for nonlinearity. For the general population and high-risk population, comparisons were made with reference points of eGFR of 95 ml/min per 1.73 m^2 and ACR of 5 mg/g. These values were considered optimal, as higher values of eGFR are associated with higher risk, presumably because of confounding from chronic conditions associated with decreased creatinine generation, and urine ACR even below the threshold for microalbuminuria is already associated with increased risk. For the

chronic kidney disease population, there were insufficient events at the reference points; hence, relative risks were computed per 15 ml/min per 1.73 m^2 lower eGFR and eightfold higher ACR or protein-to-creatinine ratio. Analyses were performed for interactions of eGFR and ACR and of eGFR vs age as a continuous variable. Additional analyses were performed stratified by age <65 or $\geqslant 65$ years.

For categorical analysis, eGFR and albuminuria were classified into more categories than that used in the chronic kidney disease definition and classification (eight categories for eGFR and five categories for albuminuria, not all categories were reported for each population). For the general population and high-risk population, mortality comparisons were made with a reference group with eGFR 90–104 ml/min per 1.73 m^2 and ACR <10 mg/g or dipstick negative, and kidney outcome comparisons were made with a reference group with eGFR >60 ml/min per 1.73 m^2 and ACR <30 mg/g or dipstick negative or trace. For the chronic kidney disease population, comparisons were made with a reference group with eGFR 45–75 ml/min per 1.73 m^2 and ACR <30 mg/g, dipstick negative or trace, or protein-to-creatinine ratio <50 mg/g. Heterogeneity among cohorts was investigated in categorical and continuous analyses using standard meta-analytic methods.

Study populations

Altogether, 90 cohorts were invited to participate, 69 completed the survey and 53 completed the request analyses (Figure 3). A total of 45 cohorts, including 1,555,332 people, were included in the meta-analyses, grouped into four study populations: a general population with ascertainment of albuminuria as ACR, a general population with ascertainment of albuminuria by dipstick, a high-risk population, and a chronic kidney disease population. Table 2 shows the number of events for each outcome in each population, stratified by age. In studies that reported multiple outcomes, cardiovascular disease mortality accounted for approximately one-third of all-cause mortality, and there were fewer kidney

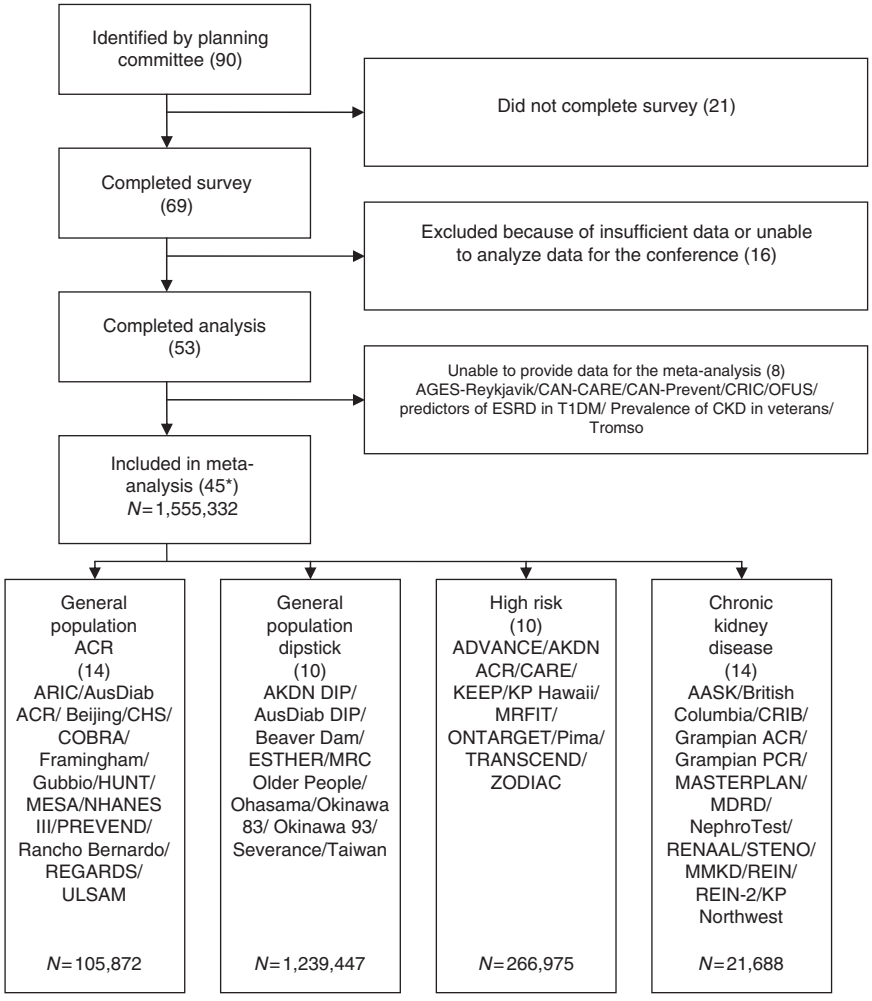

Figure 3 | Flow diagram of cohorts. *Three cohorts (AKDN, AusDiab, Grampian) were divided into two subcohorts for meta-analysis according to ascertainment of albuminuria with variable overlap between subcohorts. *Note*: The study name expansions are provided in the Appendix.

Table 2 | Number of outcomes (% of outcomes in age < and ⩾65 years) in the meta-analysis by population

Population	All-cause mortality	Cardiovascular disease mortality	Kidney failure (ESRD)	Acute kidney injury (AKI)	Kidney disease progression
General population ACR	11,209 (21.1, 78.9)	3823 (15.0, 85.0)	147 (36.7, 63.3)	427 (38.9, 61.1)	173 (26.0, 74.0)
General population dipstick	35,042 (30.9, 69.1)	5980 (19.6, 80.4)	713 (58.8, 41.2)	3438 (33.2, 66.8)	4624 (27.1, 72.9)
High risk	16,009 (52.2, 47.8)	5656 (59.5, 40.5)	1319 (71.8, 28.2)	1074 (37.3, 62.7)	6347 (35.3, 64.7)
Chronic kidney disease	4374 (26.4, 81.6)	NA	4157 (62.8, 36.2)	NA	NA

Abbreviations: ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICD-9, international classification of disease-9; NA, not available.
Definitions: Cardiovascular disease mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death or stroke. ESRD was defined as initiation of dialysis or transplantation or death coded as due to kidney disease other than AKI. AKI was defined as ICD-9 code 584 as primary or additional discharge code. Kidney disease progression was defined as an average annual decline in eGFR during follow-up of at least 2.5 ml/min per 1.73 m^2 per year and a last eGFR value of <45 ml/min per 1.73 m^2, independent of the level of baseline eGFR. The average annual decline in eGFR was calculated as last available eGFR minus baseline eGFR divided by follow-up time (in years, minimum 2) between the two observations.

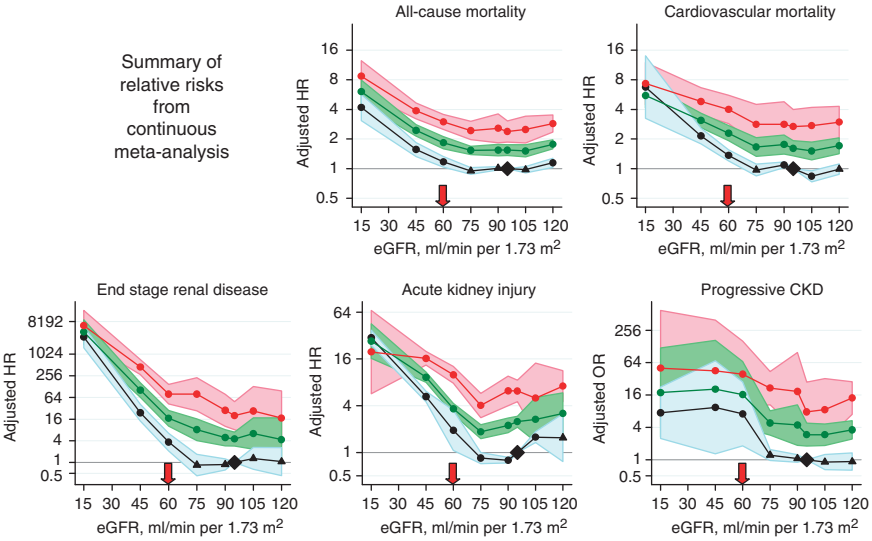

Figure 4 | Summary of continuous meta-analysis (adjusted relative risk (RR)) for general population cohorts with albumin-to-creatinine ratio (ACR). Mortality is reported for general population cohorts assessing albuminuria as urine ACR. Kidney outcomes are reported for general population cohorts assessing albuminuria as either urine ACR or dipstick. Estimated glomerular filtration rate (eGFR) is expressed as a continuous variable. The three lines represent urine ACR of <30 mg/g or dipstick negative and trace (blue), urine ACR 30–299 mg/g or dipstick 1+ positive (green), and urine ACR ⩾300 mg/g or dipstick ⩾2+ positive (red). All results are adjusted for covariates and compared with reference point of eGFR of 95 ml/min per 1.73 m^2 and ACR of <30 mg/g or dipstick negative (diamond). Each point represents the pooled relative risk from a meta-analysis. Solid circles indicate statistical significance compared with the reference point ($P<0.05$); triangles indicate non-significance. Red arrows indicate eGFR of 60 ml/min per 1.73 m^2, threshold value of eGFR for the current definition of chronic kidney disease (CKD). HR, hazards ratio; OR, odds ratio.

outcomes than deaths. As expected, in cohorts that reported acute kidney injury or in which kidney disease progression could be computed, these events were more numerous than end-stage renal disease events. This report summarizes selected results on mortality and kidney outcomes from the general population. Detailed presentations on all four populations are being reported in this issue of *Kidney International*[20–22] and elsewhere.[23]

Summary of results from meta-analyses

Figures 4 and 5 summarize the pooled relative risks of varying levels of eGFR and albuminuria, expressed as continuous or categorical variables, respectively, for all five outcomes. The relative risk for each eGFR and urine ACR combination represents the point estimate from a meta-analysis. The analyses are complimentary and provide a comprehensive description of the joint associations of these two variables with risk. Several key findings relate to the questions in Box 1.

First, the incidence rates were higher for mortality than kidney outcomes, but the risk relationships have a similar shape (Figure 4) and color pattern (Figure 5) for all outcomes, with higher relative risks associated with lower eGFR and higher levels of albuminuria, suggesting that groups at increased risk for one outcome are at increased risk for all outcomes. In general, the relative risks are higher for kidney outcomes than for mortality, reflecting a greater specificity of association of eGFR and ACR with these outcomes. Not surprisingly, measures of kidney disease are more dominant factors in kidney outcomes than in mortality

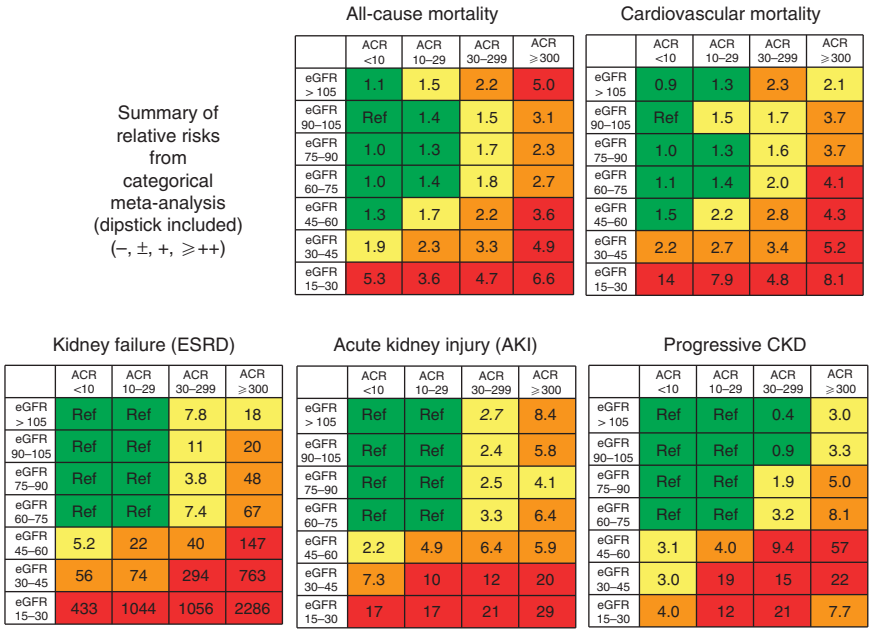

Figure 5 | Summary of categorical meta-analysis (adjusted relative risk (RR)) for general population cohorts with albumin-to-creatinine ratio (ACR). Mortality is reported for general population cohorts assessing albuminuria as urine ACR. Kidney outcomes are reported for general population cohorts assessing albuminuria as either urine ACR or dipstick. Estimated glomerular filtration rate (eGFR) and albuminuria are expressed as categorical variables. All results are adjusted for covariates and compared with the reference cell (Ref). Each cell represents a pooled relative risk from a meta-analysis; bold numbers indicate statistical significance at $P<0.05$. Incidence rates per 1000 person-years for the reference cells are 7.0 for all-cause mortality, 4.5 for cardiovascular disease mortality, 0.04 for kidney failure, 0.98 for acute kidney injury (AKI), and 2.02 for kidney disease progression. Absolute risk can be computed by multiplying the relative risks in each cell by the incidence rate in the reference cell. Colors reflect the ranking of adjusted relative risk. The point estimates for each cell were ranked from 1 to 28 (the lowest RR having rank number 1, and the highest number 28). The categories with rank numbers 1–8 are green, rank numbers 9–14 are yellow, the rank numbers 15–21 are orange, and the rank numbers 22–28 are colored red. (For the outcome of kidney disease progression, two cells with RR <1.0 are also green, leaving fewer cells as orange.)

outcomes. Second, there is a graded increase in risk for higher levels of albuminuria categories, independent of eGFR, without an apparent threshold value. Increased relative risk is statistically significant for urine ACR >30 mg/g for mortality and kidney outcomes, even when GFR is >60 ml/min per 1.73 m^2, consistent with the current threshold value for albuminuria (>30 mg/g) as a marker of kidney damage. Increased relative risk at urine ACR of 10–29 mg/g is also apparent, suggesting that levels below the threshold may also warrant increased attention. Third, within each category of albuminuria, the risk for all outcomes is relatively constant between eGFR of 75 and 105 ml/min per 1.73 m^2, with a suggestion of a U-shaped curve for some outcomes. Even for the group with the lowest value of albuminuria, the increased relative risk for all outcomes is significant for eGFR of 60 ml/min per 1.73 m^2 in the continuous analysis and in the range of 45–59 ml/min per 1.73 m^2 for the categorical analysis, consistent with the current threshold value of GFR for the definition of chronic kidney disease (<60 ml/min per 1.73 m^2). Fourth, in the range of eGFR 30–59 ml/min per 1.73 m^2, there is a steep rise in risk with lower eGFR, consistent with suggestions to subdivide stage 3 into two stages. In the range of eGFR $\geqslant 60$ ml/min per 1.73 m^2, the risk for most outcomes is higher for lower eGFR between 60 and 74 ml/min per 1.73 m^2, which does not support the suggestion to combine stages 1 and 2. Before making a change, it would be prudent to re-examine this issue with improved GFR estimation equations, as the MDRD Study equation is known to be biased in this range, compared with measured GFR, and less accurate than the new Chronic Kidney Disease Epidemiology equation.[24] In addition, non-GFR determinants of serum creatinine may blunt the risk relationship in this range of GFR, as evidenced by steeper risk relationship with eGFR computed from cystatin C than estimated (data not shown). Fifth, the predictive ability of albuminuria at levels of eGFR, as previously noted by others,[25–31] supports the suggestion to add albuminuria stages at all GFR stages. Although there is a tendency for the relative risks for higher levels of albuminuria to converge at low eGFR, most subjects at very low eGFR had higher levels of albuminuria, and tests for interactions between eGFR and albuminuria were not significant. Sixth, age-stratified analyses showed qualitatively similar patterns in subjects with age <65 and $\geqslant 65$ years. In general, incidence rates were higher in older subjects, whereas relative risks were higher in younger individuals, as is the pattern for cardiovascular disease risk factors. The interaction between eGFR and age as a continuous variable was significant in some cohorts, but was not consistent. Table 3 shows the adjusted relative risks for all outcomes stratified by age for

the category of eGFR of 45–59 ml/min per 1.73 m^2 and optimal albuminuria, compared with the reference group. With the exception of all-cause mortality, the relative hazards are similar above and below the age of 65 years. Overall, these data do not support the suggestion for age-specific GFR thresholds for the definition of chronic kidney disease. Finally, numerical estimates for heterogeneity were high, but qualitative results were generally consistent across cohorts. These data suggest that the overall pattern of relative risks that we observed was consistent across most cohorts.

In general, results from the other populations were similar to the general population with albuminuria ascertained by ACR, with a few differences. In the general population with albuminuria ascertained by dipstick, the U-shaped relationship between eGFR and mortality was more prominent and 'shifted to the left.' In contrast, in the high-risk population, the U-shaped curve relationship between eGFR and mortality was less apparent. The relationship between albuminuria and mortality was similar in all three populations. In the chronic kidney disease population, the risk relationships for eGFR and albuminuria with mortality were less strong than in the other three populations, but the relationships with kidney failure were as strong as in the other populations. Analyses in the chronic kidney disease population report lower levels of eGFR and higher levels of albuminuria than in the other three populations, and report highest risks for these most extreme categories.

Strengths and limitations

The strengths of this analysis are the large number of cohorts, including participants with a wide range of clinical and demographic characteristics from Asia, Europe, North America, and Oceania. The general population cohorts were assembled from a systemic search, and supplemented by high-risk and chronic kidney disease cohorts to increase the number of kidney events and assess the generalizability of the findings across varied clinical settings. Uniform definitions of study populations, outcomes, predictors, covariates, and methods for regression analysis were used in individual and group-level meta-analysis, including testing for interactions. The pooled relative risks were qualitatively consistent across the study populations and across cohorts within study populations.

However, there are important limitations. By necessity, the results include only the outcomes that have been studied. The meta-analyses focus primarily on relative risk. Other important metrics, such as population prevalence, absolute risk and attributable risk have not been modeled. It was necessary to use different reference ranges for different outcomes and for different populations. The analyses of results from high-risk and chronic kidney disease populations may be affected by bias in selecting the cohorts for inclusion in the meta-analyses and bias in selecting participants for inclusion in the cohorts. There are also important measurement issues, which may affect the validity of results from each cohort and harmonization across cohorts. These issues include the use of single measurements for eGFR and albuminuria, the calibration of serum creatinine assays, estimation of GFR using the MDRD Study equation, uniformity of urine albumin assay, reliability of spot urine samples and total urine protein for ascertainment of albuminuria, and independent effects of urine creatinine on mortality and kidney outcomes. Finally, there was substantial quantitative heterogeneity in the point estimates for the observed pooled relative risks, which requires additional investigation.

Table 3 | Adjusted relative risks for mortality and kidney disease outcomes stratified by age for eGFR of 45–59 ml/min per 1.73 m^2 in the categorical meta-analyses[a]

Outcomes	Age <65 years Adjusted hazards ratio or odds ratio (95% confidence interval)[b]	Age >65 years Adjusted hazard ratio or odds ratio (95% confidence interval)[b]
All cause mortality	1.9 (1.4–2.5)	1.2 (1.0–1.5)
Cardiovascular disease mortality	1.3 (0.6–3.2)	1.4 (1.2–1.8)
Kidney failure (ESRD)	3.1 (1.1–8.3)	3.4 (1.6–7.2)
Acute kidney injury	1.8 (1.4–2.2)	2.0 (1.8–2.3)
Kidney disease progression	2.5 (0.8–8.1)	3.4 (1.9–5.9)

Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
[a]Includes general population cohorts with ascertainment of albuminuria by ACR for mortality and by ACR or dipstick for kidney disease outcomes.
[b]For mortality, comparison is for the group with eGFR 45–59 ml/min per 1.73 m^2 and urine ACR <10 mg/g or dipstick negative to the reference group with eGFR 90–105 ml/min per 1.73 m^2 and urine ACR <10 mg/g or dipstick negative. For kidney outcomes, comparison is for the group with eGFR 45–59 ml/min per 1.73 m^2 and urine ACR <30 mg/g or dipstick 1+ or greater to the reference group with eGFR >60 ml/min per 1.73 m^2 and urine ACR <30 mg/g or dipstick negative or trace.

THE PROPOSED REVISIONS AND IMPLICATIONS

On the basis of the review of the data and discussions in plenary and breakout sessions, the five questions about the definition and classification (Box 1) were rephrased and an additional question was added about emphasizing the cause of disease in addition to the stage (Table 4). For the definition, the consensus (>2/3 majority) was not to change the eGFR threshold or the urine ACR threshold

Table 4 | The proposed revisions (answers to questions[a])

Classification	
Emphasize cause of disease as well as stage	Agree
Albuminuria stages at all GFR stages (three stages)	Agree
Subdivide stage 3 (at 45 ml/min per 1.73 m^2)	Agree
Combine stages 1–2	Disagree
Definitions	
Age modification for GFR threshold	Disagree
Retain GFR threshold at 60 ml/min per 1.73 m^2	Agree
Age modification for albuminuria as a marker for kidney damage	Disagree
Retain albuminuria threshold 30 mg/g	Agree

Abbreviation: GFR, glomerular filtration rate.
[a]All answers represented at least a 2/3 majority vote.

for albuminuria as marker of kidney damage. For the classification, the consensus was to add three albuminuria stages at all GFR stages, to subdivide stage 3 at eGFR of 45 ml/min per 1.73 m^2, and to emphasize the clinical diagnosis in addition to GFR and albuminuria stages. The endorsement of the current definition and the revisions to the classification system based on prognosis have important implications.

First, the robust association of the eGFR and albuminuria thresholds used for the current definition, with increased risk for mortality and kidney outcomes, has implications for research. The increased risk for all outcomes for eGFR <60 ml/min per 1.73 m^2 without consistent age interactions is not consistent with the interpretation by others that decreased GFR with aging is 'normal' or 'physiological.'

Table 5 | Proposed revised chronic kidney disease classification (KDIGO 2009)

Clinical Diagnosis	GFR stages (ml/min per 1.73 m^2)	Albuminuria stages (ACR, mg/g)
Diabetes	>90	<30
Hypertension	60–89	
Glomerular disease	45–59	30–299
Many others	30–44	
Transplant	15–29	>300
Unknown	<15	

Abbreviations: ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

The increased risk for all kidney outcomes for urine ACR of 30–299 mg/g is not consistent with the interpretation by others that 'microalbuminuria' is only a marker for increased cardiovascular disease risk. More research is necessary to understand the role of aging and systemic vascular disease in the pathogenesis of decreased GFR and increased albuminuria.

Second, the revised classification (Table 5) is consistent with recommendations for the clinical evaluation and treatment of chronic kidney disease.[1] Although, the classification system identifies many possible combinations of eGFR and urine ACR for each clinical diagnosis, it is unlikely that the clinical action plan would include unique recommendations for each combination. It will be important for future research and clinical practice guidelines to evaluate and recommend clinical action plans for groups of categories according to risk.

Third, the 'heat map' generated by a composite ranking of relative risks enhances communication about prognosis (Figure 6). The colors indicate groups of patients at progressively higher risk for the major outcomes. Clinicians, researchers and the public health agencies can use these risk categories to describe and prioritize efforts for patients and populations. Similar communication tools are used for description of cardiovascular disease risk.[32]

Fourth, because the chronic kidney disease definition is not altered, prevalence estimates based on eGFR and urine ACR will not change. However, an examination of the

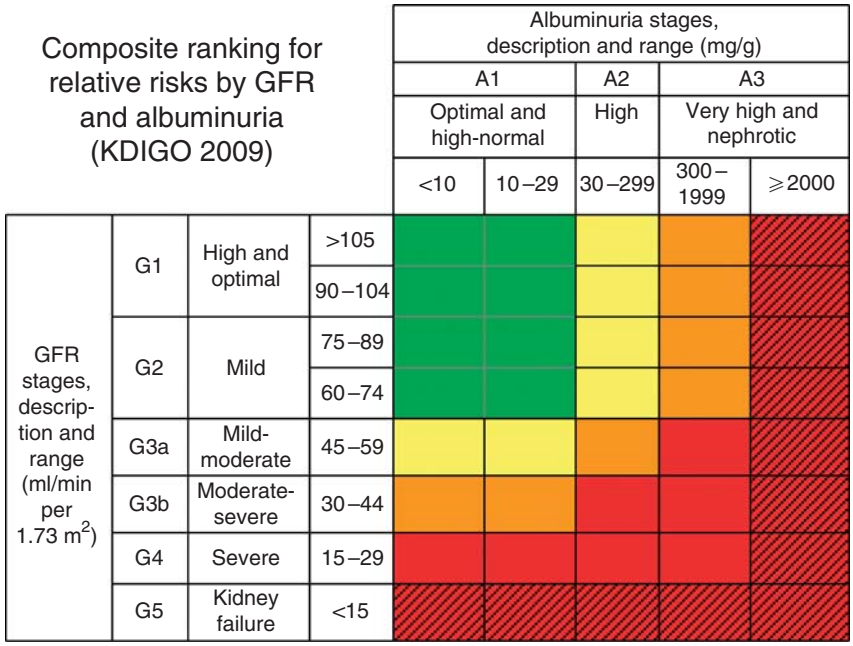

Figure 6 | Composite Ranking for Relative Risks by glomerular filtration rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009). As in Figure 5, colors reflect the ranking of adjusted relative risk. The ranks assigned in Figure 5 were averaged across all five outcomes for the 28 GFR and albuminuria categories. The categories with mean rank numbers 1–8 are green, mean rank numbers 9–14 are yellow, mean rank numbers 15–21 are orange, and mean rank numbers 22–28 are red. Color for twelve additional cells with diagonal hash marks is extrapolated based on results from the meta-analysis of chronic kidney disease cohorts. The highest level of albuminuria is termed 'nephrotic' to correspond with nephrotic range albuminuria and is expressed here as $\geqslant$2000 mg/g. Column and row labels are combined to be consistent with the number of estimated GFR (eGFR) and albuminuria stages agreed on at the conference.

Percentage of US population by eGFR and albuminuria category: KDIGO 2009 and NHANES III (1988–1994)				Albuminuria stages, description and range (mg/g)				
				A1		A2	A3	All
				Optimal and high-normal		High	Very high	
				<10	10–29	30–299	>300	
GFR stages, description and range (ml/min per 1.73 m^2)	G1	Increased and optimal	>105	21.1	4.7	2.0	0.2	28.1
			90–104	21.2	4.2	1.4	0.1	26.9
	G2	Mild	75–89	20.8	4.5	1.7	0.2	27.3
			60–74	8.9	2.5	1.3	0.2	12.8
	G3a	Mild-moderate	45–59	1.8	1.0	0.7	0.2	3.7
	G3b	Moderate-severe	30–44	0.4	0.2	0.3	0.1	1.0
	G4	Severe	15–29	0.0	0.0	0.0	0.1	0.2
	G5	Kidney failure	<15	0.0	0.0	0.0	0.0	0.0
	All			74.2	17.3	7.4	1.1	100.0

Figure 7 | Percentage of US population by estimated glomerular filtration rate (eGFR) and albuminuria category using: definition and classification of chronic kidney disease (Kidney Disease: Improving Global Outcomes (KDIGO) 2009) and prevalence estimates from National Health and Nutrition Examinations Survey III (NHANES III; 1988–1994) based on Modification of Diet in Renal Disease (MDRD) Study eGFR and standardized serum creatinine. Albuminuria ascertained by single measurement of albumin-to-creatinine ratio. Values in cells do not total to values in margins because of rounding. Category of very high albuminuria includes nephrotic range.

prevalence according to the groups used for this analysis allows clearer focus on the cells in which there is most concern for overdiagnosis of chronic kidney disease. Whereas there had been debate about the prognostic significance of stage 3 comprising 4.7% of the US population (Figure 2), with the proposed revised classification, this uncertainty is now focused more narrowly on GFR stage 3a (45–59 ml/min per 1.73 m^2) with urine ACR <10 mg/g, comprising only 1.8% of the US population (Figure 7). Nonetheless, this is an important group, especially in the elderly, in whom reduction in GFR without elevated albuminuria is common and the incidence rates for mortality and kidney outcomes, particularly acute kidney injury, are high.

Fifth, these results suggest that both eGFR and albuminuria should be included in the development of risk-prediction instruments. Prediction of risk in chronic kidney disease will be most useful if it is specific for each specific outcome, such as mortality and kidney outcomes, and it is likely to vary according to the clinical diagnosis.[33] The importance of covariates, such as age, sex, race, cardiovascular disease risk factors, and clinical cardiovascular disease, is also likely to vary for different outcomes. Although not examined at this conference, it seems likely that individuals with eGFR just above and urine ACR just below the threshold values for the definition of chronic kidney disease will be at increased risk for new-onset of chronic kidney disease. Better tools for risk prediction can be helpful to clinicians in making decisions about medical care for individual patients, to researchers in focusing efforts on interventions to reduce risk, and to public health agencies in monitoring the burden of chronic kidney disease.

CONCLUSIONS AND PERSPECTIVES

In summary, the willingness and enthusiasm of a large number of investigators worldwide to collaborate and analyze their data according to a predefined strategy has resulted in a unique database that provides strong epidemiological evidence for the association of eGFR and albuminuria with a broad spectrum of important clinical outcomes. These data allowed the generation of a much more solid evidence base for the debate about the definition and classification of chronic kidney disease than has previously been available, and resulted in a consensus among a large, international group of clinical nephrologists and scientists. Even without a revision of the definition, the consensus on revising the classification indicates the need for an update to the KDOQI clinical practice guidelines on chronic kidney disease[1,2] and KDIGO has already established a workgroup to develop a global guideline. The individual and pooled analyses of the collaborative research effort will be available to the workgroup, with the ongoing assistance of members of the Analytic Team. Although the conference focused on prognosis, a guideline must take all aspects and implications of definition and classification into account, and must consider a broader constituency of stakeholders. Ultimately, the goal of improving global outcomes depends on successful implementation of the updated guidelines worldwide. The value of this or any other proposal for the definition and classification for chronic kidney disease should be judged based on its ability now and in the future to guide medical care and improve global outcomes.

Another outcome of the Conference is the launch of a new research venture, the Chronic Kidney Disease Prognosis Consortium. The Consortium is uniquely suited for ongoing research efforts. At this time, 45 cohorts have agreed for ongoing participation. Publication of separate detailed reports of the meta-analyses as original investigations in this issue of *Kidney International* [20–22] and elsewhere[23] represents completion of the first phase of its research plan. Additional analyses using new GFR-estimating equations, gender and additional age interactions, and alternative definitions for kidney disease progression are planned. A long-term goal includes development of clinically applicable risk-prediction instruments for the onset, progression, and complications of chronic kidney disease. The KDIGO Consensus Conference highlights how clinical practice guideline development and implementation can stimulate research to improve outcomes in chronic kidney disease.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank the following members for their contributions: *Planning committee*: Andrew S Levey, MD, USA; Meguid El Nahas, MD, UK;

Paul E de Jong, MD, PhD, The Netherlands; Josef Coresh, MD, PhD, USA; Kai-Uwe Eckardt, MD, Germany; Bertram Kasiske, USA. *Analytic team*: Josef Coresh, MD, PhD, USA; Brad Astor, PhD, USA; Kunihiro Matsushita, MD, PhD, USA; Priscilla Auguste, MHS, USA; Yaping Wang, ScM, USA; Mark Woodward, PhD, Australia. Paul E de Jong, MD, PhD, The Netherlands; Ron T Gansevoort, MD, PhD, The Netherlands; Marije van der Velde, The Netherlands; Kasper Veldhuis, The Netherlands. *Other invited speakers*: Richard Glassock, MD, MACP, USA; Greg Miller, PhD, USA; Lesley Stevens, MD, MS, USA; Brenda Hemmelgarn, MD, PhD, Canada; William McClellan, MD, MPH, USA; Michael Shlipak, MD, MPH, USA. *Other breakout group leaders*: Marcello Tonelli, MD, Canada; Dick de Zeeuw, MD, PhD, The Netherlands; Adeera Levin, MD, Canada; Tazeen Jafar, MD, MPH, Pakistan. *Others who participated in pilot tests*: Ronit Katz, PhD, USA; Shih-Jen Hwang, PhD, USA, Anita Lloyd, MSc, Canada; Brian J Lee, MD, USA. *Support*: The London Conference was organized by Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO initiatives are supported by a consortium of sponsors, who are listed on the KDIGO website (http://www.kdigo.org/ accessed May 24, 2010). The Chronic Kidney Disease Prognosis Consortium is supported by KDIGO and the US National Kidney Foundation. The meta-analyses work conducted jointly at the Johns Hopkins School of Public Health, Baltimore, USA and the University Medical Center Groningen, Groningen, The Netherlands, was supported by the US National Kidney Foundation and the Dutch Kidney Foundation, respectively. A variety of institutions supported the cohorts contributing to the Chronic Kidney Disease Prognosis Consortium and are described in publications by these cohorts. Some individuals had multiple roles. Except for members of the Planning Committee and Analytic Group, individuals are listed only once.

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1–266.
2. Levey AS, Stevens LA, Coresh J. Conceptual model of CKD: applications and implications. *Am J Kidney Dis* 2009; **53**: S4–16.
3. Levey AS, Eckardt KU, Tsukamoto Y *et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67**: 2089–2100.
4. Eckardt KU, Berns JS, Rocco MV *et al.* Definition and classification of CKD: the debate should be about patient prognosis–a position statement from KDOQI and KDIGO. *Am J Kidney Dis* 2009; **53**: 915–920.
5. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–2047.
6. US Renal Data System. *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2009.
7. Hallan SI, Coresh J, Astor BC *et al.* International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006; **17**: 2275–2284.
8. Chadban SJ, Briganti EM, Kerr PG *et al.* Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 2003; **14**: S131–S138.
9. Imai E, Matsuo S. Chronic kidney disease in Asia. *Lancet* 2008; **371**: 2147–2148.
10. Sarnak MJ, Levey AS, Schoolwerth AC *et al.* Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; **108**: 2154–2169.
11. Smith DH, Gullion CM, Nichols G *et al.* Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. *J Am Soc Nephrol* 2004; **15**: 1300–1306.
12. Lloyd-Jones D, Adams R, Carnethon M *et al.* Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**: e21–181.
13. Levey AS, Schoolwerth AC, Burrows NR *et al.* Comprehensive public health strategies for preventing the development, progression, and complications of CKD: report of an expert panel convened by the Centers for Disease Control and Prevention. *Am J Kidney Dis* 2009; **53**: 522–535.
14. Rettig RA, Norris K, Nissenson AR. Chronic kidney disease in the United States: a public policy imperative. *Clin J Am Soc Nephrol* 2008; **3**: 1902–1910.
15. Hsu CY, Ordonez JD, Chertow GM *et al.* The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int* 2008; **74**: 101–107.
16. Coca SG. Long-term outcomes of acute kidney injury. *Curr Opin Nephrol Hypertens* 2010; **19**: 266–272.
17. KDIGO Controversies Conference. Definition, Classification and Prognosis in CKD, London, October 2009. Accessed 11 April 2010 Available from http://www.kdigo.org/meetings_events/CKD_Controversies_Conference.php.
18. Levey AS, Coresh J, Greene T *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–254.
19. Miller WG, Bruns DE, Hortin GL *et al.* Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem* 2009; **55**: 24–38.
20. The Chronic Kidney Disease Prognosis Consortium. Association of estimated GFR and albuminuria with all-cause and cardiovascular mortality: A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2010 (submitted for publication).
21. The Chronic Kidney Disease Prognosis Consortium. Association of estimated GFR and albuminuria with kidney outcomes: a collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 2010 (submitted).
22. The Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with mortality and end-stage renal disease: a collaborative meta-analysis of kidney disease cohorts. *Kidney Int* 2010 (submitted).
23. Matsushita K, van der Velde M, Astor BC *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–2081.
24. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
25. Hemmelgarn BR, Manns BJ, Lloyd A *et al.* Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010; **303**: 423–429.
26. Hallan SI, Ritz E, Lydersen S *et al.* Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009; **20**: 1069–1077.
27. Astor BC, Hallan SI, Miller 3rd ER *et al.* Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol* 2008; **167**: 1226–1234.
28. Brantsma AH, Bakker SJ, Hillege HL *et al.* Cardiovascular and renal outcome in subjects with K/DOQI stage 1–3 chronic kidney disease: the importance of urinary albumin excretion. *Nephrol Dial Transplant* 2008; **23**: 3851–3858.
29. Ninomiya T, Perkovic V, de Galan BE *et al.* Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009; **20**: 1813–1821.
30. Tonelli M, Jose P, Curhan G *et al.* Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ* 2006; **332**: 1426.
31. Ishani A, Grandits GA, Grimm RH *et al.* Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 2006; **17**: 1444–1452.
32. Conroy RM, Pyorala K, Fitzgerald AP *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; **24**: 987–1003.
33. Levey AS, Coresh J. Should the K/DOQI definition of chronic kidney disease be changed? *Am J Kidney Dis* 2003; **42**: 626–630.

APPENDIX

Cohort representatives

Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) Study: Mark Woodward, PhD, Australia; African American Study of Kidney Disease and Hypertension (AASK) Cohort

Study: Jackson Wright, MD, PhD, USA; Age, Gene, Environment, Susceptibility (AGES)-Reykjavik Study: Ólafur Skúli Indriðason, MD, MHS and Runolfur Palsson, MD, Iceland; Alberta Kidney Disease Network (AKDN): Brenda Hemmelgarn, MD, PhD; Canada; Atherosclerosis Risk in Communities (ARIC): Josef Coresh, MD, PhD and Kunihiro Matsushita, MD, PhD, USA; Australian Diabetes, Obesity and Lifestyle (AusDiab)Study: Robert Atkins, MD and Kevan Polkinghorne, MBChB, MClinEpi, PhD, Australia; Beaver Dam CKD Study: Anoop Shankar, MD, PhD, USA; Beijing Cohort Cohort: HaiYan Wang, MD and Fang Wang, MD, China; Canadian Care Prior to Dialysis (CAN-CARE): Adeera Levin, MD, Canada; Canadian Prevention of Renal and Vascular Endpoints trial (Can-Prevent): Brendan Barrett, MD, Canada; Cardiovascular Health Study (CHS): Michael Shlipak, MD, MPH, USA; Cholesterol and Recurrent Events Study (CARE): Marcello Tonelli, MD, Canada; CKD and mortality risk in older people: a community-based population study in the UK (MRC Older People): Dorothea Nitsch, MD, MSc and Paul Roderick, MD, UK; Chronic Renal Impairment in Birmingham (CRIB) Study: David Wheeler, MD, FRCP, UK; Chronic Renal Insufficiency Cohort (CRIC) Study: Mahboob Rahman, MD, USA; Control of Blood Pressure and Risk Attenuation Study (COBRA): Tazeen Jafar, MD, MPH, Pakistan; ESTHER Study: Dietrich Rothenbacher, MD, MPH, Germany; Framingham Heart Study: Caroline Fox, MD, MPH, USA; Gubbio Population Study: Massimo Cirillo, MD, Italy; Health Study of Nord Trøndelag (HUNT): Stein Hallan, MD, PhD, Norway; Kaiser Pacific Northwest: Developing a Risk Equation to Predict Mortality and Progression to End Stage Renal Disease: David Smith, RPh, MHA, PhD and Jessica Robin Weinstein, MD, USA; Kaiser Permanente—Hawaiian Cohort: Brian Lee, MD, Honolulu, USA; Kidney Early Evaluation Program (KEEP): Alan Collins, MD and Joseph Vassalotti, MD, USA; MASTER-PLAN: Jack Wetzels, MD, PhD, The Netherlands; Mild to Moderate Kidney Disease (MMKD) Study: Florian Kronenberg, MD, Austria; Modification of Diet in Renal Disease (MDRD) Study: Mark Sarnak, MD, MS, USA; Multi-Ethnic Study of Atherosclerosis (MESA): Michael Shlipak, MD, MPH, USA; Multiple Risk Factor Intervention Trial (MRFIT): Areef Ishani, MD, MS,USA; NephroTest: Marc Froissart, MD, PhD and Benedicte Stengel, MD, PhD, France; National Health and Nutrition Examinations Survey (NHANES III): Brad Astor, PhD, USA; Ohasama Study Cohort: Hirohito Metoki, MD, PhD, Japan; USA; Okinawa General Health Maintenance Association (OGHMA) and Okinawa Dialysis Study (OKIDS) Registry: Kunitoshi Iseki, MD, Japan; ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) / Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Study: Johannes Mann, MD, Germany; ORFAN Follow-up Study (OFUS): Marie Evans, MD, Sweden; Pima Indian Longitudinal Study of Diabetes and Its Complications: Robert Nelson, MD, PhD, USA; Prevention of Renal and Vascular End-stage Disease Study (PREVEND): Paul E de Jong, MD, PhD; Ron T Gansevoort, MD, PhD; and Marije van der Velde, The Netherlands; Predictors of End Stage Renal Disease in Patients with Type 1 Diabetes and Proteinuria: Andrzej Krolewski, MD, PhD, USA; Prevalence and Progression of Chronic Kidney Disease in Veterans: Ann O′Hare, MD, USA; Ramipril Efficacy In Nephropathy (REIN and REIN2): Annalisa Perna, Stat.Sci.D, Italy; Rancho Bernardo Study: Simerjot Jassal, MD, USA; RENAAL Study: Dick de Zeeuw, MD, PhD, The Netherlands; Renal - REasons for Geographic And Racial Differences in Stroke (REGARDS) Study: William McClellan, MD, MPH; Paul Muntner, PhD; and David Warnock, MD, USA; Severance Cohort Study: Sun Ha Jee, PhD, MPH, Korea; STENO Diabetes Center Study: Peter Rossing, MD, DMSc, Denmark; Taiwan Cohort: Chi-Pang Wen, MD, MPH, DrPH and Sung-Feng Wen, MD, USA; Tromso Study: Bjørn Odvar Eriksen, MD, PhD, Norway; Uppsala Longitudinal Study of Adult Men: Johannes Ärnlöv, MD, PhD, Sweden; Zwolle Outpatient Diabetes Project Involving Available Care (ZODIAC): Henk Bilo, MD, PhD, FRCP and Hanneke Joosten, MD, Netherlands.

Other participants

Dennis Andress, MD, USA; Shaila Basavappa, MSc, Dphil, USA; Jeffrey Berns, MD, FACP, FACN, USA; Eric Cantor, MD, USA; Brian Copley, MD, USA; Garabed Eknoyan, MD; USA; Armand Famiglietti, USA; Ali Hariri, MD, USA; Alan Hull, MD, USA; Eynu Imai, MD, PhD, Japan; Nathan Levin, MD, USA; Alison MacLeod, MB ChB, MD, UK; Donal O′Donoghue, MB ChB, UK; Miguel Riella, MD, PhD, Brazil; Michael Rocco, MD, MSCE, USA; Robert Schrier, MD, USA; Paul Stevens, MBBS, BSc, UK; Nihad AM Tamimi, MD, UK; Yusuke Tsukamoto, MD, Japan; Katrin Uhlig, MD, MS, USA; Anil Upadhyay, MD, UK; Raymond Vanholder, MD, PhD, Belgium; Desmond Williams, MD, PhD, USA; Dan Wilson, MD, USA; Christopher Winearls, MB, FRCP, Dphil, UK.