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Comparison of Concurrent Complications of CKD by 2 Risk Categorization Systems

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Abstract

Background—Using both estimated glomerular filtration rate (eGFR) and proteinuria to classify the severity of chronic kidney disease (CKD) has been proposed. The utility of a staging system incorporating both eGFR and proteinuria for guiding evaluation of concurrent CKD complications is not known.

Study design—Cross-sectional analysis

Setting & participants—30,528 participants in the US National Health and Nutrition Examination Survey conducted in 1988–1994 and 1999–2006 (n=8,242 for hyperparathyroidism).

Predictors—Classification system that uses both eGFR and proteinuria (alternative) and a system that primarily uses eGFR (NKF-KDOQI; the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative)

Outcomes—Prevalence of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism and hypertension

Measurements—GFR estimated from the CKD-Epidemiology Collaboration (CKD-EPI) equation and proteinuria assessed using urine albumin-creatinine ratio (ACR)

Results—The prevalence of hypoalbuminemia, hypertension and hyperparathyroidism increased with more severe CKD using the NKF-KDOQI system. For example, the prevalence of hyperparathyroidism was 9.1%, 11.1%, 28.2% and 72.5% for Stages 1, 2, 3 and 4, respectively.

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Supplementary Material

Table S1: Prevalence of CKD complications by stage using the NKF-KDOQI guidelines and an alternative system.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Descriptive Text for Online Delivery

Hyperlink: Supplementary Table S1 (PDF)

About: Prevalence of CKD complications by stage using the NKF-KDOQI guidelines and an alternative system.

Similarly the prevalence of anemia, acidosis and hyperphosphatemia increased progressively from Stage 2 through 4. With the alternative system, the prevalence of anemia, hyperphosphatemia, hypertension and hyperparathyroidism was lower in Stage 3 compared to Stage 2. For example, the prevalence of hyperparathyroidism was 13.5%, 40.3%, 22.2%, and 63.4% for stages 1, 2, 3 and 4, respectively. Applying the alternative system, participants without each complication were more likely to be appropriately reclassified to lower stages (for example, overall net reclassification index of -6.5% for hyperparathyroidism). However, participants with complications (except for hypoalbuminemia) were more likely to be inappropriately reclassified to lower stages.

Limitations—Use of single creatinine to estimate GFR and single measure to assess ACR. Small number of participants with CKD Stage 4.

Conclusions—The NKF-KDOQI system may better identify patients with certain concurrent CKD complications compared to systems using eGFR and proteinuria.

The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF-KDOQI) defines chronic kidney disease (CKD) by the presence of reduced estimated glomerular filtration rate (eGFR) or markers of kidney damage, generally determined by elevated proteinuria. However, the severity of CKD has been primarily classified by level of eGFR(1, 2). Although this classification system led to improved awareness of CKD(3–5), it has been criticized on the grounds that it does not sufficiently differentiate among patients who are and are not likely to have adverse outcomes(6). Recently, a KDIGO (Kidney Disease International Global Outcomes) consensus conference proposed that CKD be classified using both proteinuria and eGFR(7). The potential advantages of such an alternative system includes improved specificity for classifying people at low risk of adverse outcomes, including progressive kidney disease and mortality, into lower CKD stages(8).

While a system using both proteinuria and eGFR may more accurately stage individuals with respect to their risk for future adverse outcomes, it is unknown whether such an approach would classify people with concurrent CKD complications better than eGFR alone. We previously demonstrated, in a general population sample, that albuminuria, a specific type of proteinuria, and eGFR are differentially associated with certain concurrent CKD complications (anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism and hypertension), and that other than hypoalbuminemia, eGFR had a stronger association with each of these CKD complications than albuminuria(9). We sought to evaluate the effect of using both eGFR and proteinuria to classify patients with respect to concurrent complications of CKD. Therefore, we calculated the prevalence of these complications of CKD across categories of a recently published CKD risk stratification system that incorporates both eGFR and proteinuria using data from the US National Health and Nutrition Examination Survey (NHANES)(8). For comparison, the prevalence of these six complications were calculated by CKD stage defined using the NKF-KDOQI classification system.

Methods

Study Population

The NHANES are cross-sectional, multistage, stratified, clustered probability samples of the US civilian non-institutionalized population conducted by the National Center for Health Statistics. The NHANES included in the current analysis were conducted from 1988–1994 in 2 phases (1988–1991 and 1991–1994) and from 1999–2006 in 4 phases (1999–2000, 2001–2002, 2003–2004, 2005–2006). Data from all phases were combined herein following National Center for Health Statistics recommendations(10). The current analysis was restricted to participants aged 20 years or older who completed both an interview and

medical evaluation (n=39,136). Those who were pregnant or missing measurements of urinary albumin or creatinine excretion, serum creatinine, phosphorous, hemoglobin, bicarbonate, serum albumin or blood pressure were excluded from the current analyses. Participants with an eGFR < 15 mL/min/1.73m² were also excluded because the small number of individuals available in this group. After these exclusions, data for 30,528 participants were available for the analysis of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, and hypertension. Intact parathyroid hormone (iPTH) was measured only in NHANES 2003–2004 and NHANES 2005–2006. Data were available for 8,242 participants for the analysis of iPTH.

Information on age, sex, and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican American, or all other) was based on self-report collected during the interview portion of the survey. Participants who reported having smoked 100 or more cigarettes during their lifetime were classified as current smokers if they reported currently smoking in NHANES III or smoking “some days” or “most days” in NHANES 1999–2006. Diabetes mellitus was defined as a self-report of a previous diagnosis, not during pregnancy, with concurrent use of insulin or oral hypoglycemic medication or blood glucose $\geq$ 126 mg/dL among participants who fasted 9 or more hours prior to their study visit or $\geq$ 200 mg/dL among non-fasting participants.

Measures of Kidney Function and Damage

Serum creatinine was assayed using the Synchron AS/Astra Analyzer (Beckman Coulter, Fullerton, California) in NHANES III and a LX20 analyzer (Beckman Coulter, Fullerton, California) in NHANES 1999–2006 and was recalibrated to standardized creatinine measurements.(11) eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation(12). Urine albumin and creatinine concentrations were measured on random spot urine samples obtained using a clean-catch technique and sterile containers in the same laboratory during each phase of NHANES. Urine albumin was measured by solid phase fluorescence immunoassay and urine creatinine was measured by the modified kinetic Jaffe method using a Synchron AS/Astra Analyzer (Beckman Coulter, Fullerton, California) in NHANES III and a CX3 analyzer (Beckman Coulter, Fullerton, California) in NHANES 1999–2006. Urinary albumin-creatinine ratio (ACR) was computed and is reported in milligrams per gram (mg/g; 1 mg/g = 0.131 mg/mmol). Participants were classified according to NKF-KDOQI CKD staging, which primarily uses level of eGFR, and an alternative classification system, which uses the level of both eGFR and ACR (Fig 1A)(2, 8).

Assessment of CKD complications

Complications that reflect different biological mechanisms were included. Hemoglobin was measured by Coulter Splus J in NHANES III and Beckman Coulter MAXM in the later surveys. Anemia was defined by as hemoglobin levels less than 12 g/dL for women and less than 13.5 g/dL for men(13–15). Bicarbonate, phosphate, and serum albumin were assayed using Hitachi 737 in NHANES III, Hitachi 704 in NHANES 1999–2000 and Beckman-Synchron than 22 mEq/L (16, 17). LX20 in the NHANES 2001–2006. Acidosis was defined as serum bicarbonate less Hyperphosphatemia was defined as serum phosphate greater than or equal to 4.5 mg/dl (16). Hypoalbuminemia was defined as serum albumin less than 3.5 g/dL. Serum iPTH was measured at the University of Washington, in Seattle, WA on an Elecsys 1010 autoanalyzer (Roche Diagnostics, Mannheim, Germany), using a electrochemiluminescent process. This second generation method employs a biotinylated monoclonal PTH-specific antibody and monoclonal PTH-specific antibody labeled with a ruthenium complex to form a sandwich complex. Hyperparathyroidism was defined as iPTH levels greater than or equal to 70 pg/mL(18, 19). To standardize the laboratory values across

all NHANES phases, the age, sex, and race/ethnicity adjusted difference in the mean level for hemoglobin, bicarbonate, phosphate, serum albumin and iPTH for participants 20–39 year olds without diabetes and hypertension, and with eGFR > 60 ml/min/1.73m² and ACR < 10 mg/g for each survey was calculated. Differences from the mean value for NHANES 2005 – 2006 was then added/subtracted for values for all participants in the other NHANES phases. This approach has been used in prior analyses of NHANES data(20). Blood pressure was measured six times in NHANES III and three times in NHANES 1999–2006. Using the average of all available blood pressure measurements, hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication.

Statistical Analyses

Demographic and clinical characteristics were summarized as means or proportions by each stage in the NKF-KDOQI classification system and the alternative classification system, separately. For each system, the prevalence of anemia, acidosis, hyperphosphatemia, hyperparathyroidism, hypoalbuminemia, and hypertension was calculated by CKD stage. Additionally, using log-linear generalized estimating equations, the prevalence ratios for all six complications were calculated for each stage; participants without CKD served as the referent (21). Prevalence ratios were adjusted for age, race-ethnicity, sex, body mass index, total and HDL-cholesterol, diabetes mellitus, a history of cardiovascular disease, hypertension (except for the models with hypertension as the outcome) and NHANES phase. The effect of reclassification of participants with and without concurrent CKD complications using the alternative versus NKF-KDOQI system was quantified using the net reclassification improvement (NRI) statistic. Specifically, the NRI was used to assess the reclassification of people with complications to higher versus lower stages and for those without complications to lower versus higher stages (22). The current recommendation is to monitor CKD complications at eGFR less than 60 ml/min/1.73 m² (Stage 3 or 4 CKD by NKF-KDOQI) (2). We therefore calculated the prevalence and prevalence ratio of each complication comparing individuals with NKF-KDOQI Stage 1 and 2 and alternative system Stage 3 or 4 to their counterparts with (1) Stage 1 and 2 by both systems, (2) Stage 3 or 4 by both systems and (3) alternative system Stage 1 or 2 and NKF-KDOQI Stage 3 or 4.

Analyses were performed incorporating the NHANES sampling weights to obtain unbiased estimates for the US population using SUDAAN version 10 (Research Triangle Institute, Research Triangle Park, NC). Sampling weights were combined across all survey phases from NHANES 1988–2006. The standard errors for all estimates were obtained using the Taylor series (linearization) method accounting for the complex, multi-stage recruitment of NHANES participants.

Results

A total of 86.6% of the population were classified as being free of CKD by both systems, with no change in status of CKD versus no CKD between the two systems. Of those with CKD, 31.9% of individuals were categorized into the same stage using both systems (27.8% with Stage 1; 0%, 2.6% and 1.5% with Stages 2, 3 and 4, respectively); 14.7% moved to a higher stage using the alternative system (indicating their disease would be classified as being more severe), and 53.4% moved to a lower stage using the alternative system (indicating their disease would be classified as being less severe)(Fig 1). A total of 34.5% of the population with CKD was classified as having Stage 1 by the NKF-KDOQI system, compared to 69.5% by the alternative system, whereas 38.6% of the population with CKD was classified as Stage 3 by the NKF-KDOQI system compared to 14.7% for the alternative system.

Table 1 shows the characteristics of the population according to the two staging systems. There was a progressive increase in age and a higher prevalence of a history of cardiovascular disease with higher NKF-KDOQI stages, whereas for the alternative system, mean age and the prevalence of cardiovascular disease were lower for participants with Stage 3 compared to Stage 2. In contrast, the prevalence of diabetes mellitus was higher at higher CKD stages for the alternative system, but its prevalence was higher in Stage 2 versus stage 3 for the NKF-KDOQI system. Level of eGFR and albuminuria differed by classification system. Mean eGFR was progressively lower at higher NKF-KDOQI stages, but was higher in Stage 3 compared to Stage 2 for the alternative system. The median ACR was higher in NKF-KDOQI Stages 1 and 2 compared to Stages 3 and 4. The median ACR was over ten-fold higher in alternative system Stages 3 and 4 compared to the NKF-KDOQI Stages 3 and 4, but did not show a graded increase in the alternative system.

Figure 2 and Table S1 (available as online supplementary material) shows the prevalence of the six complications according to each system. There was a progressive increase in the prevalence of hypoalbuminemia, hyperparathyroidism, and hypertension with the NKF-KDOQI Stages. The prevalence of anemia, acidosis and hyperphosphatemia was lower at NKF-KDOQI Stage 2 compared to Stage 1 but highest at Stages 3 and 4. For the alternative system, there was a lower prevalence of anemia, hyperphosphatemia, hyperparathyroidism, and hypertension in Stage 3, compared to Stage 2. Acidosis and hypoalbuminemia increased progressively at higher CKD stages using the alternative system. After adjustment for age, race-ethnicity, sex, body mass index, total and HDL-cholesterol, diabetes mellitus, hypertension, a history of cardiovascular disease, and NHANES phase, the prevalence ratios for anemia, acidosis, hyperphosphatemia, and hyperparathyroidism were higher for NKF-KDOQI Stages 3 and 4 compared to Stages 1 and 2 (Table 2). Using the alternative system, Stage 4 was associated with an increased multivariable adjusted prevalence ratio for each complication except hypertension. However, using the alternative system, the prevalence ratio was higher in Stage 2 than Stage 3 for anemia, acidosis, hyperphosphatemia, and hyperparathyroidism.

Participants without each complication were more likely to be appropriately reclassified into lower stages using the alternative versus NKF-KDOQI system (Table 3). Except for hypoalbuminemia, participants with each complication were more likely to be reclassified to lower stages with the alternative system. A similar percentage of individuals with hypoalbuminemia were reclassified to higher and lower stages. Reclassification to the alternative system led to more appropriate classification for acidosis and hypoalbuminemia and less appropriate classification for hypertension, and less appropriate classification for hypertension.

The prevalence of each complication was highest among participants classified as having Stage 3 or 4 by both systems (Table 4). With the exception of acidosis and hypoalbuminemia, the prevalence of each complication was higher among individuals with Stage 3 or 4 by the NKF-KDOQI system and Stage 1 or 2 by the alternative system compared to individuals with Stage 1 or 2 by the NKF-KDOQI system and Stage 3 or 4 by the alternative system. After multivariable adjustment and compared to Stage 1 or 2 by the NKF-KDOQI system and Stage 3 or 4 by the alternative system, being classified into Stage 3 or 4 by the NKF-KDOQI system and Stage 1 or 2 by the alternative system was associated with increased prevalence ratios for anemia, acidosis, hyperphosphatemia, and hyperparathyroidism.

Discussion

Goals of a disease classification system are to facilitate clinical decisions that improve patient outcomes and to identify individuals who have more severe illness. In the development of the NKF-KDOQI guidelines, level of GFR was selected as the measure on which CKD was classified, as it is broadly recognized as the best overall measure of kidney function in health and disease, and lower levels of GFR are strongly related to the development of kidney failure and concurrent complications of CKD(2). However, for individuals with CKD, eGFR is not the only relevant factor for all clinical decisions, and other factors such as proteinuria and rate of kidney function loss are also important in determining patient prognosis. Some have advocated incorporating the level of proteinuria into the classification system used for staging the severity of CKD, and alternative systems using both eGFR and proteinuria have been developed to estimate risk for adverse outcomes such as mortality and the progression of kidney disease(8, 23, 24). In the current analysis, we demonstrated that in a general population sample, compared to the NKF-KDOQI system, a classification system based on eGFR and proteinuria led to substantial misclassification of individuals with respect to the presence of concurrent CKD complications including anemia, acidosis, hyperphosphatemia, and hyperparathyroidism.

The NKF-KDOQI CKD classification system has been criticized by some for being too sensitive and not sufficiently specific for identifying patients with CKD who are at risk for adverse outcomes related to CKD (6). Multiple studies have demonstrated strong associations between proteinuria, independent of eGFR, with long-term clinical outcomes(25–29) Therefore, classification systems that use both eGFR and proteinuria as criteria for categorizing individuals may address the criticisms about the low specificity of the NKF-KDOQI CKD classification system. In a prior study, the alternative system evaluated herein was more accurate than the NKF-KDOQI system for the outcomes of kidney disease progression and mortality, for those who did not have subsequent events(8). In a large meta-analysis of general population and high-risk cohorts, both ACR and eGFR were independently associated with risk for all cause and cardiovascular mortality, kidney failure, kidney disease progression and progressive CKD(7, 27–29). This suggests that incorporation of both eGFR and proteinuria into a classification system would improve prediction for these outcomes, but this requires explicit testing. In the current study we considered concurrent complications and while the classification by the alternative system was more accurate for people without complications, it was less accurate for people with complications. If such an alternative classification system were adopted, a substantial proportion of individuals identified by the NKF-KDOQI system as having moderate to severe CKD (Stages 3 or 4) may not be recognized as being at risk for concurrent CKD complications such as those in the current study.

Adopting a classification system with lower sensitivity and higher specificity for identifying adverse outcomes or concurrent complications of CKD may be acceptable. With the exception of hypertension, the prevalence of concurrent complications among individuals with NKF-KDOQI CKD Stages 1 through 3 was well below 50%(8). As such, the improved specificity of classification systems using eGFR and proteinuria may lead to a higher proportion of individuals with adverse outcomes or complications as having high CKD Stages or risk categories. In addition, there are few data that demonstrate the benefit of identifying and treating concurrent complications, and therefore the value of identification of CKD complications is not known. There is sound pathophysiological basis and some clinical trial data for treatment of acidosis(30, 31) and hypertension(32) but trials thus far for treatment of anemia, hyperparathyroidism, hypoalbuminemia, and hyperphosphatemia have not been done or have not demonstrated a benefit on the incidence of clinical events(33, 34). Finally, the threshold for treatment of these conditions may be at a higher or lower level than

is used for the definition of the complication. Nevertheless, even in the absence of clinical trial data, clinicians may wish to evaluate patients with CKD for these complications and to treat patients with extreme values.

As is shown in this analysis and our prior work, decreased eGFR and proteinuria are differentially associated with the concurrent complications of CKD studied herein(9). Together these data suggest there may be value to considering GFR and proteinuria separately when evaluating concurrent complications of CKD, which is consistent with current evidence for treatment strategies for CKD. Even if a revised classification system for CKD incorporates both GFR and proteinuria, it is likely that the recommended clinical action plans will be different for decreased GFR vs increased proteinuria. For example, it may be appropriate for clinicians evaluating patients with decreased GFR, regardless of the level of proteinuria, to screen for, detect and treat complications of CKD, such as anemia, bone and mineral disorders, malnutrition and neuropathy; as well as to counsel avoidance of nephrotoxic drugs or to institute preparation for dialysis and transplant when appropriate(2, 35–39). In contrast, the clinical focus for patients with proteinuria should be on use of medications that block the renin-angiotensin system (40). For patients with either decreased eGFR or proteinuria, it appears appropriate to focus on prevention of kidney disease progression and cardiovascular events. Finally, it is likely the use of CKD stages, regardless of the inclusion of GFR alone or both GFR and proteinuria, may not be sufficient for determining an individual patient's prognosis. Patient factors such as demographics and other comorbid conditions influence the association of eGFR and proteinuria with multiple outcomes (e.g., kidney disease progression, all-cause mortality, anemia, etc.)(7). Multivariable approaches to efficiently evaluate which patients are likely to have concurrent CKD complications may be implemented using computer based instruments and reported by laboratories or electronic medical records. While this was beyond the scope of the current analysis, developing and validating such risk prediction algorithms is worth future study.

Strengths of this analysis include a large ethnically diverse general population sample, rigorous collection of data for multiple CKD complications using standardized protocols and laboratory procedures. However, there are several limitations of this analysis. We evaluated only selected complications, although these were complications that reflect different biological processes. Data from 24 hour urine collections were not available, and albuminuria and eGFR were both assessed in only a single occasion. It is estimated that approximately 50% of individuals with an ACR ≥ 30 mg/g on a single measurement will not have persistent albuminuria(41). Different assays were used across the NHANES for some biochemical measures (e.g., phosphate). However, we conducted an indirect calibration and adjusted for NHANES phase. We only evaluated one alternative system for staging CKD via eGFR and albuminuria, and other such systems that combine eGFR and proteinuria might correlate better with the CKD complications. Despite the large sample size of US adults analyzed, there were a limited number of participants with CKD Stage 4 by NKF-KDOQI (n=157) and the alternative system (n=366). The eGFR levels used to define the NKF-KDOQI classification scheme were chosen in part because of their association with some of the complications evaluated in the current study. However, this does not negate our conclusion that a system based on both eGFR and proteinuria together may be less strongly associated with such complications than the status quo. Finally, we did not evaluate the prevalence of other characteristics such as dyslipidemia that are associated with adverse outcomes and might plausibly be associated with both reduced eGFR and albuminuria.

In conclusion, these analyses demonstrate that classification systems that use both eGFR and proteinuria to define the severity of CKD may be less accurate for identifying certain concurrent complications of CKD, as compared to systems that use eGFR alone.

Modifications to the current NKF-KDOQI classification system should consider the impact of missed opportunities to screen for concurrent complications of CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. 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(6):2089–2100. [PubMed: 15882252]
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39(2):S1–S266. [PubMed: 11904577]
3. Akbari A, Swedko PJ, Clark HD, et al. Detection of Chronic Kidney Disease With Laboratory Reporting of Estimated Glomerular Filtration Rate and an Educational Program. *Arch Intern Med.* 2004; 164(16):1788–1792. [PubMed: 15364673]
4. Jain AK, McLeod I, Huo C, et al. When laboratories report estimated glomerular filtration rates in addition to serum creatinines, nephrology consults increase. *Kidney Int.* 2009; 76(3):318–323. [PubMed: 19436331]
5. Hemmelgarn BR, Zhang J, Manns BJ, et al. Nephrology visits and health care resource use before and after reporting estimated glomerular filtration rate. *JAMA.* 2010; 303(12):1151–1158. [PubMed: 20332400]
6. Eckardt KU, Kasiske BL. Kidney disease: improving global outcomes. *Nat Rev Nephrol.* 2009; 5(11):650–657. [PubMed: 19786993]
7. Levey AS, de Jong PE, Coresh J, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011; 80(1):17–28. [PubMed: 21150873]
8. Tonelli M, Muntner P, Lloyd A, et al. Using Proteinuria and Estimated Glomerular Filtration Rate to Classify Risk in Patients With Chronic Kidney Disease: A Cohort Study. *Ann Intern Med.* 2011; 154(1):12–21. [PubMed: 21200034]
9. Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Concurrent Complications of Chronic Kidney Disease (CKD) by Level of Albuminuria and Estimated GFR (eGFR). *J Am Soc Nephrol.* In press.
10. National Center for Health Statistics. Centers for Disease Control and Prevention: National Health and Nutrition Examination Survey.
11. Selvin E, Manzi J, Stevens LA, et al. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988–1994, 1999–2004. *Am J Kidney Dis.* 2007; 50(6):918–926. [PubMed: 18037092]
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009; 150(9):604–612. [PubMed: 19414839]
13. National Kidney Foundation. K/DOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006; 47:S1–S146.
14. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C. Hematological and iron-related analytes--reference data for persons aged 1 year and over: United States, 1988–94. *Vital Health Stat 11.* 2005(247):1–156.
15. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep.* 1998; 47:1–29.
16. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003; 42(4):S1–S202. [PubMed: 14520607]

17. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. *Kidney Int.* 2004; 65(3): 1031–1040. [PubMed: 14871424]
18. National Kidney Foundation. K/DOQI clinical practice guidelines for anemia of chronic kidney disease: Update 2000. *Am J Kidney Dis.* 2001 suppl 1:S182–S236.
19. Kidney Disease Improving Global Outcomes. Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.* 2009; (113):S1–S130.
20. Kottgen A, Selvin E, Stevens LA, Levey AS, Van Lente F, Coresh J. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis.* 2008; 51(3):385–394. [PubMed: 18295054]
21. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986; 42(1):121–130. [PubMed: 3719049]
22. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008; 27(2):157–172. discussion 207–112. [PubMed: 17569110]
23. Levey AS, Astor BC, Stevens LA, Coresh J. Chronic kidney disease, diabetes, and hypertension: what's in a name? *Kidney Int.* 2010; 78(1):19–22. [PubMed: 20428101]
24. 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(9731):2073–2081. [PubMed: 20483451]
25. Astor BC, Hallan SI, Miller ER 3rd, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol.* 2008; 167(10):1226–1234. [PubMed: 18385206]
26. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA.* 2010; 303(5):423–429. [PubMed: 20124537]
27. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int.* 2011; 79(12):1331–1340. [PubMed: 21289598]
28. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int.* 2011; 80(1):93–104. [PubMed: 21289597]
29. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int.* 2011; 79(12):1341–1352. [PubMed: 21307840]
30. Menon V, Tighiouart H, Vaughn NS, et al. Serum bicarbonate and long-term outcomes in CKD. *Am J Kidney Dis.* 2010; 56(5):907–914. [PubMed: 20605301]
31. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol.* 2009; 20(9):2075–2084. [PubMed: 19608703]
32. Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med.* 2005; 142(5):342–351. [PubMed: 15738453]
33. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *New England Journal Medicine.* 2006; 355(20):2085–2098.
34. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *New England Journal Medicine.* 2009; 361(21):2019–2032.
35. Khurana A, McLean L, Atkinson S, Foulks CJ. The effect of oral sodium phosphate drug products on renal function in adults undergoing bowel endoscopy. *Arch Intern Med.* 2008; 168(6):593–597. [PubMed: 18362251]

36. Kribben A, Witzke O, Hillen U, Barkhausen J, Daul AE, Erbel R. Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J Am Coll Cardiol*. 2009; 53(18):1621–1628. [PubMed: 19406336]
37. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006; 17(9):2359–2362. [PubMed: 16885403]
38. Cutroneo P, Polimeni G, Curcuruto R, Calapai G, Caputi AP. Adverse reactions to contrast media: an analysis from spontaneous reporting data. *Pharmacol Res*. 2007; 56(1):35–41. [PubMed: 17482832]
39. Gooch K, Culleton BF, Manns BJ, et al. NSAID use and progression of chronic kidney disease. *Am J Med*. 2007; 120(3):280, e281–287. [PubMed: 17349452]
40. National Kidney Foundation. K/DOQI clinical practice guidelines for hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004; 43 Suppl 1(5):S1–S268. [PubMed: 15114537]
41. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003; 41(1):1–12. [PubMed: 12500213]

Figure 1.

NKF-KDOQI and an alternative classification system (Panel a) and Prevalence of concurrent complications of CKD by the cross-classification of CKD stages by the two classification systems (Panel b). Percentages represent NHANES (National Health and Nutrition Examination Survey) data weighted to the civilian, non-institutionalized US adult population. Numbers in parentheses are the NHANES sample size in each category/stage. Abbreviations: CKD, chronic kidney disease; NKF-KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative;

Figure 2.
Prevalence of complications according to the 2 classification systems

Table 1

Characteristics of NHANES participants by CKD Stage using the 2 classification systems.

	No CKD	CKD stage/category			p-trend
		1	2	3	
Sample size					
NKF-KDOQI	N=24908	N=1657	N=1437	N=2369	N=157
Alternative system	N=24908	N=3691	N=702	N=861	N=366
Demographics					
Age (y)					
NKF-KDOQI	43.4 +/- 0.2	41.6 +/- 0.6	63.9 +/- 0.6	72.2 +/- 0.4	74.8 +/- 1.2
Alternative system	43.4 +/- 0.2	57.3 +/- 0.5	74.7 +/- 0.6	55.7 +/- 1.3	71.6 +/- 1.0
					<0.001
					<0.001
Women					
NKF-KDOQI	49.7	58.8	53.8	59.5	55.8
Alternative system	49.7	59.3	58.6	52.1	50.8
					<0.001
					<0.001
Non-Hispanic white					
NKF-KDOQI	74.7	61.6	77.9	84.8	75.4
Alternative system	74.7	74.0	82.7	74.4	71.3
					0.08
					0.1
Non-Hispanic black					
NKF-KDOQI	10.0	15.3	10.6	8.1	11.8
Alternative system	10.0	11.0	8.1	13.3	15.9
					<0.001
					<0.001
Hispanic					
NKF-KDOQI	9.1	14.2	6.7	11.8	3.5
Alternative system	9.1	8.8	4.4	7.7	4.9
					0.003
CVD Risk Factors					
Body mass index, kg/m ²					
NKF-KDOQI	27.2 (0.1)	28.4 (0.3)	28.5 (0.3)	28.2 (0.2)	28.3 (0.7)
Alternative system	27.2 (0.1)	28.4 (0.2)	28.1 (0.3)	28.5 (0.4)	28.8 (0.5)
					<0.001
					<0.001
Diabetes mellitus					
NKF-KDOQI	4.3	19.4	23.5	18.7	36.0
					<0.001

	No CKD	CKD stage/category			p-trend
		1	2	3	
Alternative system	4.3	18.8	21.4	21.8	<0.001
History of CVD, %					
NKF-KDOQI	4.5	5.2	17.7	28.3	<0.001
Alternative system	4.5	14.1	34.5	18.0	<0.001
Total cholesterol, mg/dL					
NKF-KDOQI	201.9 (0.6)	207.7 (1.8)	213.4 (2.0)	217.6 (2.1)	<0.001
Alternative system	201.9 (0.6)	212.1 (1.3)	210.7 (2.7)	216.4 (2.8)	<0.001
HDL-cholesterol, mg/dL					
NKF-KDOQI	51.7 (0.2)	51.2 (0.7)	51.8 (0.7)	51.1 (0.4)	0.2
Alternative system	51.7 (0.2)	52.0 (0.4)	50.0 (0.7)	49.9 (0.8)	0.002
Kidney Markers					
eGFR, ml/min/1.73 m ²					
NKF-KDOQI	99.2 (0.3)	109.2 (0.4)	76.8 (0.3)	50.0 (0.2)	<0.001
Alternative system	99.2 (0.3)	82.5 (0.7)	45.7 (0.3)	82.7 (1.7)	<0.001
eGFR < 60 ml/min/1.73 m ² , %					
NKF-KDOQI	0%	0%	0%	100%	<0.001
Alternative system	0%	31.3%	100%	22.9%	<0.001
ACR, mg/g					
NKF-KDOQI	5.3 (3.6; 8.6)	67.0 (39.9; 182)	67.1 (41.4; 175)	12.0 (5.7; 40.5)	<0.001
Alternative system	5.3 (3.6; 8.6)	38.6 (14.7; 70.4)	29.2 (9.0; 65.1)	985 (312; 995)	<0.001
ACR ≥ 30 mg/g					
NKF-KDOQI	0%	100%	100%	29.2%	<0.001
Alternative system	0%	68.7%	49.1%	94.5%	<0.001

NHANES participants included in this analysis were from NHANES III and NHANES 1999–2006. Continuous variables are given as mean $\pm$ standard error or median (25th; 75th percentile); categorical variables are given as percentage.

Abbreviations: ACR, albumin-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NKF-KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey;

Table 2

Multivariable adjusted prevalence ratios for CKD complications by the 2 staging systems.

	No CKD	CKD stage>				p-trend
		1	2	3	4	
Anemia						
NKF-KDOQI	1 (ref)	1.34 (1.04 – 1.74)	1.02 (0.82 – 1.26)	2.06 (1.79 – 2.37)	5.23 (3.99 – 6.86)	<0.001
Alternative system	1 (ref)	1.33 (1.14 – 1.56)	2.45 (1.99 – 3.01)	1.57 (1.31 – 1.89)	4.37 (3.39 – 5.63)	<0.001
Acidosis						
NKF-KDOQI	1 (ref)	1.34 (1.12 – 1.61)	1.13 (0.85 – 1.51)	1.70 (1.44 – 2.00)	4.89 (3.43 – 6.96)	<0.001
Alternative system	1 (ref)	1.33 (1.14 – 1.55)	1.99 (1.51 – 2.62)	1.39 (1.10 – 1.77)	2.95 (2.27 – 3.82)	<0.001
Hyperphosphatemia						
NKF-KDOQI	1 (ref)	0.91 (0.70 – 1.18)	1.06 (0.75 – 1.50)	1.61 (1.36 – 1.92)	3.64 (2.40 – 5.52)	<0.001
Alternative system	1 (ref)	1.11 (0.93 – 1.33)	1.57 (1.12 – 2.19)	1.16 (0.81 – 1.67)	2.02 (1.28 – 3.18)	0.003
Hypoalbuminemia						
NKF-KDOQI	1 (ref)	1.97 (1.36 – 2.85)	2.25 (1.59 – 3.18)	2.07 (1.25 – 3.43)	3.03 (1.31 – 7.04)	<0.001
Alternative system	1 (ref)	1.11 (0.76 – 1.63)	2.47 (1.27 – 4.78)	5.13 (3.38 – 7.78)	5.61 (3.22 – 9.78)	<0.001
Hypertension						
NKF-KDOQI	1 (ref)	1.47 (1.34 – 1.60)	1.20 (1.12 – 1.28)	1.01 (0.96 – 1.06)	0.97 (0.83 – 1.14)	0.002
Alternative system	1 (ref)	1.19 (1.13 – 1.25)	1.05 (0.98 – 1.12)	1.12 (1.03 – 1.23)	1.07 (0.96 – 1.19)	<0.001
Hyperparathyroidism						
NKF-KDOQI	1 (ref)	1.15 (0.70 – 1.58)	1.00 (0.63 – 1.59)	2.63 (1.97 – 3.51)	6.05 (4.46 – 8.19)	<0.001

	No CKD	CKD stage>				p-trend
		1	2	3	4	
Alternative system	1 (ref)	1.38 (1.05 – 1.80)	3.41 (2.44 – 4.76)	2.07 (1.35 – 3.17)	5.01 (3.62 – 6.95)	<0.001

Numbers in table are prevalence ratio (95% confidence interval)

Prevalence ratios are adjusted for age, race-ethnicity, sex, body mass index, total and HDL-cholesterol, diabetes mellitus, hypertension (except for the model with hypertension as the outcome), a history of cardiovascular disease, and NHANES (National Health and Nutrition Examination Survey) survey phase.

Abbreviations: CKD, chronic kidney disease; NKF-KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative;

Table 3

Reclassification of CKD staging for participants with and without complications.

	Without Complication			With Complication			Overall NRI
	Downstaged: appropriate classification	Upstaged: inappropriate classification	Net difference (95% CI)	Downstaged: inappropriate classification	Upstaged: appropriate classification	Net Difference (95% CI)	
Anemia	53.3%	14.7%	38.6% (35.6%, 41.6%)	55.3%	14.2%	-41.1% (-35.4%, -47.1%)	-2.5% (-9.1%, 4.0%)
Acidosis	55.2%	14.4%	40.8% (37.8%, 43.9%)	42.6%	16.1%	-26.5% (-18.9%, -34.2%)	14.3% (6.2%, 22.4%)
Hyperphosphatemia	53.3%	14.8%	38.5% (35.4%, 41.7%)	56.5%	13.2%	-43.3% (-36.1%, -50.6%)	-4.8% (-12.8%, 3.0%)
Hypoalbuminemia	54.1%	13.7%	40.4% (37.1%, 43.7%)	38.2%	40.4%	2.2% (-9.1%, 13.0%)	42.7% (30.9%, 54.0%)
Hypertension	39.5%	16.2%	23.3% (19.1%, 27.5%)	63.7%	13.5%	-50.2% (-47.3%, -53.1%)	-26.9% (-31.9%, -21.9%)
Hyperparathyroidism	60.4%	7.6%	52.8% (47.8%, 57.8%)	67.8%	8.5%	-59.3% (-53.3%, -65.1%)	-6.5% (-14.4, 1.5)

Overall NRI may not equal the sum of net difference with and without complications due to rounding.

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; NRI, net reclassification index

Table 4

Prevalence and prevalence ratios for complications by CKD stage using the 2 staging systems.

	Stage 1 or 2 CKD by NKF-KDOQI		Stage 3 or 4 CKD by NKF-KDOQI	
	Stage 1 or 2 via alternate system	Stage 3 or 4 via alternate system	Stage 1 or 2 via alternate system	Stage 3 or 4 via alternate system
Prevalence of complication				
Anemia	6.8%	5.9%	13.4%	31.4%
Acidosis	13.3%	13.9%	10.8%	20.3%
High phosphorus	6.9%	7.4%	9.5%	11.9%
Hypoalbuminemia	1.8%	9.1%	2.9%	10.8%
Hypertension	47.5%	44.4%	71.5%	83.7%
Hyperparathyroidism	10.4%	6.4%	26.2%	54.7%
Prevalence ratio (95% CI) of complication				
Anemia	1.18 (0.86 – 1.63)	1 (ref)	2.03 (1.41 – 2.91)	4.03 (2.88 – 5.65)
Acidosis	1.17 (0.79 – 1.74)	1 (ref)	1.61 (1.10 – 2.34)	3.07 (2.09 – 4.50)
Hyperphosphatemia	0.92 (0.58 – 1.46)	1 (ref)	1.64 (0.98 – 2.75)	1.84 (1.03 – 3.28)
Hypoalbuminemia	0.22 (0.13 – 0.36)	1 (ref)	0.33 (0.19 – 0.57)	1.15 (0.69 – 1.92)
Hypertension	1.00 (0.96 – 1.04)	1 (ref)	1.00 (0.96 – 1.04)	0.94 (0.90 – 0.98)
Hyperparathyroidism	2.45 (0.73 – 8.22)	1 (ref)	5.57 (1.60 – 19.4)	9.62 (2.89 – 32.0)

Prevalence ratios are adjusted for age, race-ethnicity, sex, body mass index, total and HDL-cholesterol, diabetes mellitus, hypertension (except for the model with hypertension as the outcome), a history of cardiovascular disease, and NHANES (National Health and Nutrition Examination Survey) survey phase.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; NKF-KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative;

Bolded prevalence ratios represents p-value <0.05 compared to the referent group of individuals with stage 1 or 2 CKD by NKF-KDOQI and stage 3 or 4 via the alternative system.