Using Proteinuria and Estimated Glomerular Filtration Rate to Classify Risk in Patients With Chronic Kidney Disease

A Cohort Study

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Background: The staging system for chronic kidney disease relies almost exclusively on estimated glomerular filtration rate (eGFR), although proteinuria is also associated with adverse outcomes.

Objective: To validate a 5-category system for risk stratification based on the combination of eGFR and proteinuria.

Design: Retrospective cohort study.

Setting: A provincial laboratory registry in Alberta, Canada, and a representative sample of noninstitutionalized U.S. adults.

Patients: A derivation data set of 474 521 adult outpatients, 2 independent internal validation cohorts with 51 356 and 460 623 patients, and an external validation cohort of 14 358 patients.

Measurements: Glomerular filtration rate, estimated by using the Modification of Diet in Renal Disease Study equation, and proteinuria, measured by using urine albumin-to-creatinine ratio or dipstick urinalysis. Outcomes included all-cause mortality and a composite renal outcome of kidney failure or doubling of serum creatinine level.

Results: Over a median follow-up of 38 months in the internal validation cohorts, higher risk categories (indicating lower eGFR or more proteinuria) were associated with a graded increase in the risk for the composite renal outcome. The projected number of U.S. adults assigned to risk categories 3 and 4 in the alternate system was 3.9 million, compared with 16.3 million assigned to stage 3 and 4 in the current staging system. The alternate system was more likely to correctly reclassify persons who did not develop the renal outcome than those who did, although some persons developed the renal outcome despite reclassification to a lower category. However, all analyses of patients reclassified to a lower category showed that substantially fewer such patients developed the renal outcome than did not. Correct reclassification by the alternate system was more likely when proteinuria was measured by using albumin-to-creatinine ratio than with dipstick testing, and also more likely for the composite renal outcome than for mortality.

Limitation: The study had a short follow-up time.

Conclusion: Using proteinuria in combination with eGFR may reduce unnecessary referrals for care at the cost of not referring or delaying referral for some patients who go on to develop kidney failure.

Primary Funding Source: Alberta Heritage Foundation for Medical Research interdisciplinary research team grant.

Ann Intern Med. 2011;154:12-21. www.annals.org

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In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) clinical practice guidelines (1) proposed that chronic kidney disease (CKD) be categorized into 5 stages, largely on the basis of estimated glomerular filtration rate (eGFR) (**Figure 1**). This important initiative permitted a common nomenclature for clinicians and researchers (2) and facilitated an international effort to educate the public about CKD.

See also:

Print

Editors' Notes 13
Editorial comment. 65

Web-Only

Appendix
Appendix Tables
Appendix Figures
Supplement
Conversion of graphics into slides

On the basis of the NKF KDOQI system, approximately 26 million adults in the United States have CKD. Nearly one half (10.1 million) have stage 1 or stage 2 CKD, in which eGFR is not significantly reduced but CKD is considered to be present because of kidney damage, defined as proteinuria or abnormal renal imaging (3). Another 15 million adults are classified as having stage 3 CKD, although most of these have an eGFR of 45 to 59 mL/min per 1.73 m^2 without proteinuria, which is associated with lower rates of clinical outcomes than normal eGFR with heavy proteinuria (stage 1 CKD) (4).

Despite its benefits, the current NKF KDOQI staging system does not incorporate information about how the presence and severity of proteinuria might affect prognosis for important clinical outcomes in each CKD stage (5–8). Kidney Disease: Improving Global Outcomes (KDIGO), an organization that develops international practice guidelines for CKD care, recently sponsored an international conference to discuss modifications to the existing staging system, and a working group has been assembled to revise the NKF KDOQI guidelines accordingly. Conference attendees reached a consensus that incorporating proteinuria would improve the current system (9). However, data on

the clinical and health services implications of such a change are lacking.

To help inform future revisions to the CKD classification system, we developed an alternate classification system based on the risk for clinically significant renal function loss and all-cause mortality among persons at varying eGFRs and proteinuria levels. We hypothesized that this system would more accurately predict risk for mortality and renal outcomes than the existing staging system and would prove valid in populations other than the one in which it was developed.

Context

Stages of chronic kidney disease (CKD) are currently defined by estimated glomerular filtration rate (eGFR).

Contribution

These researchers developed a new CKD staging system that used information about renal outcomes and mortality and was based on proteinuria as well as eGFR. It classified more patients into lower stages of disease and seemed to be more accurate for patients who did not develop the outcomes.

Caution

Validation for renal outcomes was internal. Follow-up time was limited.

Implication

This new CKD staging system might be more accurate than the current staging system and avoid unnecessary referrals for care for many patients at low risk for adverse outcomes.

—The Editors

METHODS

We studied 3 populations by using 3 data sets: the Alberta Kidney Disease Network (AKDN) database (10), the Third National Health and Nutrition Examination Survey (NHANES III) (11), and NHANES 1999 to 2006 (12).

Derivation and Internal Validation

The AKDN database contains information about routine laboratory tests for all patients in Alberta, Canada. We used it to derive and internally validate an alternate CKD classification system on the basis of information about renal outcomes (end-stage renal disease [ESRD] or doubling of serum creatinine level) and all-cause mortality. We defined a cohort of 1 530 447 patients aged 18 years or older with at least 1 outpatient measurement of serum creatinine between 1 May 2002 and 31 December 2006 from 7 of the 9 provincial health regions in Alberta (adult population, 2.6 million), and between 1 July 2003 (or 1 January 2005) and 31 December 2006 for the other 2 regions (**Appendix Figure 1**, available at www.annals.org). After we excluded 2345 patients with ESRD and 1383 with an index eGFR less than 15 mL/min per 1.73 m^2 before cohort entry (on the assumption that they would be considered to have the most severe form of CKD [stage 5] in both the current and the alternate system), 282 patients who died or reached end of follow-up on the same day as their initial creatinine measurement, and 577 114 with no dipstick or albumin–creatinine ratio (ACR) measurement, data were available for 949 323 patients (102 701 with at least 1 ACR measurement and 920 985 with at least 1 urine dipstick measurement).

We calculated baseline eGFR for each patient as reported elsewhere by using a standardized serum creatinine assay (10, 13) and the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation (14). For patients with multiple creatinine measurements, the mean of all measures taken within 6 months of the first measurement in the observation period was used, with the date of the last measurement in that 6-month period used as the baseline date (10). The non–isotope-dilution mass spectrometry traceable 4-variable MDRD equation (14) was used to estimate GFR for creatinine levels measured before 2003. In 2003, laboratories began using creatinine assays calibrated against an isotope-dilution mass spectrometry reference standard; the new version of the MDRD equation was used to determine eGFR for levels calculated since then (15).

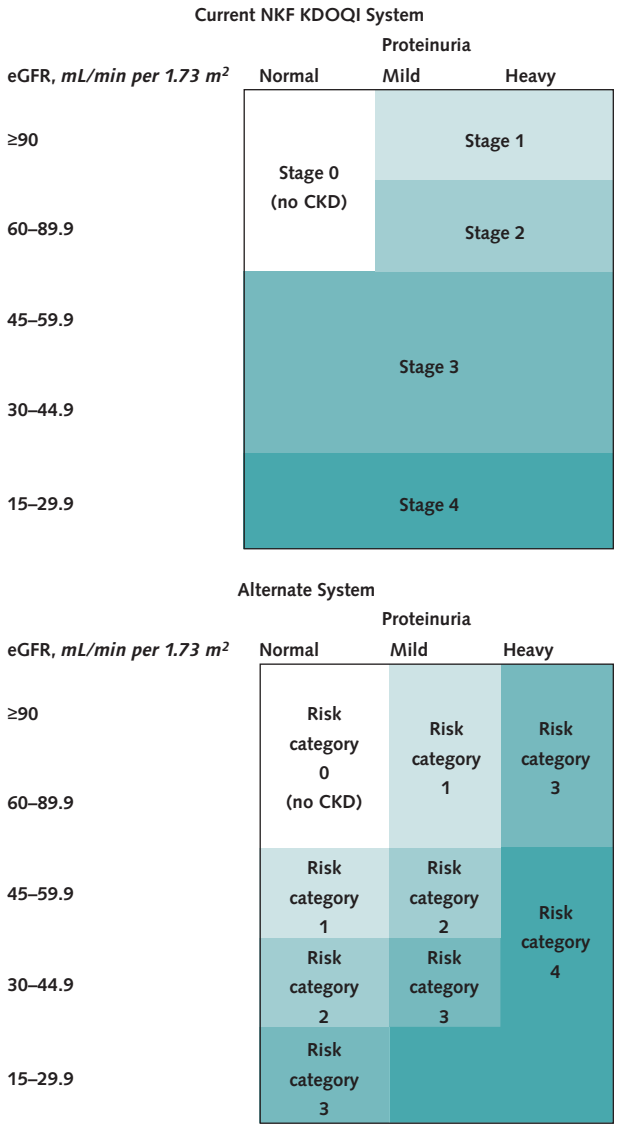
Proteinuria was measured by using ACR or urine dipstick testing, on the basis of outpatient random spot urine measurements. All outpatient ACR and urine dipstick measurements in the 6 months before and after the baseline eGFR were used to establish baseline proteinuria and albuminuria. If multiple measurements were done during this period, the median level (using ordinal numbers for dipstick protein categories) was selected for each patient (4).

Demographic data, date of dialysis initiation, and socioeconomic status for patients in the AKDN were determined from the administrative data files of the provincial renal programs and health ministry (16). The presence of diabetes mellitus, hypertension, or other comorbid conditions was identified by using validated coding algorithms from the International Classification of Diseases, 9th Edition, Clinical Modification, or International Classification of Diseases, 10th Edition (17–19).

External Validation and Prevalence Estimates

We used the NHANES III (1988 to 1994) data set to externally validate the ability of our new classification system to predict all-cause mortality (11). Serum creatinine level was measured in patients according to a standardized protocol and calibrated to the assay used to develop the MDRD formula (20). Proteinuria was measured by using ACR on a spot urine specimen. Of 18 825 adults aged 20 years or older, 14 358 were included in the external validation cohort after we excluded 2998 patients with missing creatinine values, 690 patients with missing ACRs, 25 patients with an eGFR less than 15 mL/min per 1.73 m^2, 15 patients with unknown follow-up status, and 749

Figure 1. **Current NKF KDOQI CKD staging system and alternate system of CKD risk categories.**



The composite renal outcome comprised end-stage renal disease or doubling of serum creatinine level. Although the current NKF KDOQI staging system also considers persons with abnormal renal imaging to have stage 1 or stage 2 CKD, this information was not available in the internal or external validation data sets. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

patients who were pregnant or menstruating (**Appendix Figure 1**).

We used the NHANES 1999 to 2006 data set to determine the number of persons who would meet criteria for each of our new CKD risk categories, as well as for each stage of the current NKF KDOQI system. We included 17 401 NHANES 1999 to 2006 participants with complete information on serum creatinine level and ACR.

Classification Thresholds and Outcomes

We categorized the index eGFR for each patient as 90 or greater, 60 to 89.9, 45 to 59.9, 30 to 44.9, or 15 to 29.9 mL/min per 1.73 m^2. We classified proteinuria among patients as normal (ACR <30 mg/g or urine dipstick negative), mild (ACR 30 to 300 mg/g or urine dipstick trace or 1+), or heavy (ACR >300 mg/g or urine dipstick ≥2+) (21).

Our 2 outcomes were all-cause mortality and a composite of ESRD (defined as registration for long-term dialysis or renal transplantation [22]) or doubling of serum creatinine level at the end of follow-up. Information on the renal outcome was available from the AKDN database for both the derivation and internal validation cohorts. Information on mortality was obtained from the Alberta Bureau of Vital Statistics for the internal validation sample and from death certificates matched to the National Death Index as described elsewhere (23) for the NHANES III external validation cohort. Patients who experienced the composite renal outcome and then died were considered to have experienced both outcomes, with the date for each event used to calculate follow-up time. Patients who first experienced a doubling of serum creatinine level and then developed ESRD were considered to have experienced the composite renal outcome, with the date of the doubling of serum creatinine level (the first event) used to calculate follow-up time.

In the AKDN data set, all outcomes were assessed from the date of the baseline eGFR measurement until study end (31 March 2007). Patients in NHANES III were followed for mortality outcomes through 31 December 2000.

Statistical Analysis

Derivation Data Set

We analyzed patients in the AKDN with ACR measurements (102 701 patients) separately from those for whom dipstick results were available (920 985 patients). One half of the patients in each of ACR and dipstick cohorts were randomly and uniquely assigned to the derivation group (51 345 and 460 362 patients, respectively) or the internal validation group (51 356 and 460 623 patients).

In the ACR derivation data set, we used Poisson regression to calculate rates of the composite renal outcome per 1000 person-years for each of 12 groups defined by the 4 eGFR and 3 proteinuria strata (**Appendix Figure 2**, available at www.annals.org). These groups were ranked from lowest to highest according to the rate of the composite renal outcome and then for all-cause mortality. We also performed this analysis and ranking for both outcomes in the dipstick cohort. The resulting 4 rank-ordered lists were very similar; these results were used to inform the combination of the groups into 5 CKD risk categories, ranging from 0 (no CKD) to 4 (most severe CKD). Categories were formed by combining groups with similar rates of adverse outcomes.

Validation Data Set

We validated the new CKD risk categories by using the AKDN (internal) and NHANES III (external) data sets (**Appendix Figure 1**). We used Poisson regression to determine the rate of the clinical outcomes in each current system CKD stage and each alternate system risk category in the validation cohorts, with output expressed per 1000 person-years. Reclassification tables were created by cross-tabulating outcomes from both the current and alternate systems (24). The consistency of these findings was also

Table 1. **Patient Characteristics***

Characteristic	AKDN Database				External Validation Cohort (NHANES III)
	ACR		Dipstick Test		ACR (n = 14 358)
	Derivation (n = 51 345)	Validation (n = 51 356)	Derivation (n = 460 362)	Validation (n = 460 623)	
Demographic and clinical					
Age, *y*†	57.0 (15.0)	57.0 (15.0)	48.7 (16.7)	48.7 (16.7)	44.9 ± 0.5
Women, %	45	45	56	56	49
Mean BMI (±SE), *kg/m²*	–	–	–	–	26.6 ± 0.1
Current smoker, %	–	–	–	–	28.9
Race or ethnicity, %					
Non-Hispanic white	–	–	–	–	76.7
Non-Hispanic black	–	–	–	–	10.3
Mexican American	–	–	–	–	5.1
Other	–	–	–	–	7.9
Socioeconomic status, %‡					
Low	27	27	19	19	32
Low with subsidy	3	3	2	2	–
Diabetes, %	54	54	7	7	6
Hypertension, %	50	50	22	22	24
Cerebrovascular disease, %	4	4	2	2	2
Peripheral vascular disease, %	3	3	1	1	–
Congestive heart failure, %	5	5	2	2	2
Mean total cholesterol level (±SE)					
mmol/L	–	–	–	–	5.29 ± 0.02
mg/dL	–	–	–	–	204.4 ± 0.8
Mean HDL cholesterol level (±SE)					
mmol/L	–	–	–	–	1.31 ± 0.01
mg/dL	–	–	–	–	50.4 ± 0.4
eGFR, %					
>60 mL/min per 1.73 m²	79	79	89	89	95
45–59.9 mL/min per 1.73 m²	15	15	9	9	4
30–44.9 mL/min per 1.73 m²	5	5	2	2	1
15–29.9 mL/min per 1.73 m²	1	1	0.4	0.4	0.2
ACR, %					
<30	75	75	–	–	92
30–300	20	20	–	–	7
>300	5	5	–	–	1
Dipstick test results, %					
Negative for protein	–	–	91	91	–
Trace or 1+ for protein	–	–	8	8	–
≥2+ for protein	–	–	1	1	–
Follow-up and outcome					
Median follow-up (IQR), *mo*	38 (24, 48)	38 (24, 48)	35 (21, 45)	35 (21, 45)	104 (85, 123)
Deaths, *n (%)*	2600 (5.1)	2726 (5.3)	13896 (3.0)	14063 (3.1)	2115 (14.7)
ESRD or doubling of serum creatinine level, *n (%)*§	515 (1.0)	511 (1.0)	1420 (0.3)	1359 (0.3)	–
ESRD, *n (%)*	187 (0.4)	192 (0.4)	389 (0.1)	382 (0.1)	–
Doubling of serum creatinine level, *n (%)*§	455 (1.1)	457 (1.1)	1284 (0.4)	1230 (0.4)	–

ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; BMI = body mass index; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HDL = high-density lipoprotein; IQR = interquartile range; NHANES III = Third National Health and Nutrition Examination Survey.
* Totals do not always add to 100% because of rounding.
† Reported as mean (SD) or mean (±SE).
‡ For AKDN patients, "low socioeconomic status" was defined as an annual family income <$39 250 Canadian, and "low with subsidy" as receiving social assistance, on the basis of government of Alberta health care insurance records. For NHANES patients, "low socioeconomic status" was defined as an annual household income <$20 000.
§ Denominators for calculating numbers and percentages for doubling of serum creatinine level: ACR derivation cohort, 43 191; ACR validation cohort, 43 099; dipstick test derivation cohort, 310 150; and dipstick test validation cohort, 310 169. Not all patients had the required >1 serum creatinine measurement at the end of follow-up to perform this calculation.

Table 2. **Rates of Mortality and Adverse Renal Outcomes for the Current NKF KDOQI CKD Staging System and Alternate CKD Risk Categories, by Stage or Risk Category**

Cohort and Stage or Risk Category	Rate of Composite Renal Outcome (95% CI), per 1000 Patient-Years		Rate of All-Cause Mortality (95% CI), per 1000 Patient-Years	
	NKF KDOQI System	Alternate System	NKF KDOQI System	Alternate System
AKDN ACR (*n* = 51 356)				
0 (no CKD)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	8.9 (8.3–9.5)	8.9 (8.3–9.5)
1	4.6 (3.2–6.6)	2.3 (1.9–2.8)	15.3 (12.5–18.8)	19.7 (18.3–21.1)
2	4.7 (3.8–5.7)	4.6 (3.4–6.2)	24.7 (22.6–27.1)	46.2 (42.1–50.8)
3	6.9 (6.0–7.8)	12.7 (10.3–15.7)	36.0 (34.0–38.2)	53.1 (47.9–58.8)
4	71.2 (59.2–85.8)	58.3 (51.2–66.5)	117.9 (102.6–135.5)	86.1 (77.5–95.6)
AKDN dipstick (*n* = 460 623)				
0 (no CKD)	0.4 (0.3–0.4)	0.4 (0.3–0.4)	6.0 (5.9–6.2)	6.0 (5.9–6.2)
1	1.9 (1.4–2.5)	1.4 (1.2–1.5)	20.0 (18.3–21.8)	20.7 (20.0–21.3)
2	2.2 (1.9–2.6)	4.4 (3.7–5.2)	22.4 (21.3–23.6)	61.2 (58.5–64.1)
3	3.5 (3.2–3.8)	10.7 (9.3–12.4)	35.3 (34.4–36.3)	69.3 (65.5–73.4)
4	63.7 (56.7–71.5)	57.0 (51.8–62.8)	154.7 (143.9–166.2)	126.5 (118.7–134.7)
NHANES III (*n* = 14 358)				
0 (no CKD)	–	–	6.0 (5.0–7.0)	6.0 (5.0–7.0)
1	–	–	15.1 (9.8–20.4)	24.4 (21.3–27.5)
2	–	–	34.2 (27.7–40.7)	73.2 (56.7–89.7)
3	–	–	46.8 (39.9–53.7)	73.1 (55.7–90.5)
4	–	–	112.7 (61.7–163.7)	92.0 (64.4–119.6)

ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; CKD = chronic kidney disease; NHANES III = Third National Health and Nutrition Survey; NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

assessed by using reclassification tables prepared by subgroups stratified by patient age (≥60 and <60 years), sex, and diabetes status.

We estimated the number of U.S. adults with CKD under both the current and the alternate systems, adjusting the proportion of U.S. adults with albuminuria for anticipated persistence (presence on repeated testing) as described elsewhere (3).

Analyses were performed with Stata MP, version 11 (StataCorp, College Station, Texas), for the derivation and internal validation data sets and with SUDAAN, version 9.1 (Research Triangle Institute, Research Triangle Park, North Carolina), for the external validation data set (to account for this study's complex sampling design). Sampling weights were applied for all NHANES III and NHANES 1999 to 2006 analyses to account for unequal probabilities of selection, oversampling, and nonresponse. The institutional review boards of the University of Calgary and University of Alberta approved this study.

Role of the Funding Source

This study was funded by the Alberta Heritage Foundation for Medical Research. The funding organization played no role in the design, conduct, or analysis of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Table 1 shows characteristics of study patients. Clinical characteristics, duration of follow-up, and incidence of clinical outcomes were similar in both the internal derivation and validation cohorts. Some characteristics, such as age, prevalence of diabetes, and hypertension, varied considerably between the ACR and dipstick test cohorts. Age and most clinical characteristics of the external validation cohort were more similar to the AKDN dipstick test cohort than to the AKDN ACR cohort.

We grouped patients into 5 risk categories (**Figure 1**) on the basis of rates of outcomes in strata defined by eGFR and proteinuria in the AKDN derivation data sets (**Appendix Figure 2**). **Table 2** shows the rates of the composite renal outcome and all-cause mortality among patients in the validation cohorts at each stage of the current system and each risk category in the alternate system. Event rates increased with increasing risk category in the alternate system. In contrast, increases in event rates were less evident at the higher stages of the current system. However, neither classification system showed graded increases in mortality with more severe CKD in the external validation analysis (**Table 2**). In the internal validation analyses, event rates also increased with higher risk categories in subgroups stratified by age (<60 vs. ≥60 years), diabetes status, and sex (Tables 1 to 12 in the **Supplement,** available at www.annals.org). However, stage 1 event rates in the current system exceeded those for higher stages in age-stratified analyses for renal and mortality outcomes (Tables 1, 2, 7, and 8 in the **Supplement**).

Reclassification With Alternate Staging System

Most patients did not have CKD and were classified as stage 0 in both systems (**Appendix Tables 1** and **2**, avail-

Table 3. **Reclassification Accuracy of the Alternate Classification System for the Composite Renal Outcomes of End-Stage Renal Disease or Doubling of Serum Creatinine Level, by Subgroup***

AKDN Cohort and Subgroup	Patients (Events/No Events), *n*	Reclassification Accuracy					
		Events, *n (% with events)*			No Events, *n (% without events)*		
		Incorrect	Correct	Net	Incorrect	Correct	Net
ACR							
Total population	51 356 (511/50 845)	118 (23.1)	178 (34.8)	60 (11.7)	2174 (4.3)	13 591 (26.7)	11 417 (22.5)
Age <60 y	29 325 (177/29 148)	22 (12.4)	77 (43.5)	55 (31.1)	1070 (3.7)	4578 (15.7)	3508 (12.0)
Age ≥60 y	22 031 (334/21 697)	96 (28.7)	101 (30.2)	5 (1.5)	1104 (5.1)	9013 (41.5)	7909 (36.5)
No diabetes	23 599 (107/23 492)	26 (24.3)	21 (19.6)	−5 (−4.7)	554 (2.4)	5428 (23.1)	4874 (20.7)
Diabetes	27 757 (404/27 353)	92 (22.8)	157 (38.9)	65 (16.1)	1620 (5.9)	8163 (29.8)	6543 (23.9)
Men	28 009 (288/27 721)	54 (18.8)	104 (36.1)	50 (17.4)	1327 (4.8)	6557 (23.7)	5230 (18.9)
Women	23 347 (223/23 124)	64 (28.7)	74 (33.2)	10 (4.5)	847 (3.7)	7034 (30.4)	6187 (26.8)
Referral at stage 2†	51 356 (511/50 845)	70 (13.7)	11 (2.2)	−59 (−11.5)	350 (0.7)	10 472 (20.6)	10 122 (19.9)
Referral at stage 3‡	51 356 (511/50 845)	71 (13.9)	58 (11.4)	−13 (−2.5)	1344 (2.6)	8078 (15.9)	6734 (13.2)
Dipstick test							
Total population	460 623 (1359/459 264)	409 (30.1)	254 (18.7)	−155 (−11.4)	5732 (1.2)	65 697 (14.3)	59 965 (13.1)
Age <60 y	346 983 (427/346 556)	62 (14.5)	110 (25.8)	48 (11.2)	3383 (1.0)	28 261 (8.2)	24 878 (7.2)
Age ≥60 y	113 640 (932/112 708)	347 (37.2)	144 (15.5)	−203 (−21.8)	2349 (2.1)	37 436 (33.2)	35 087 (31.1)
No diabetes	427 901 (826/427 075)	261 (31.6)	105 (12.7)	−156 (−18.9)	4103 (1.0)	56 758 (13.3)	52 655 (12.3)
Diabetes	32 722 (533/32 189)	148 (27.8)	149 (28)	1 (0.2)	1629 (5.1)	8939 (27.8)	7310 (22.7)
Men	203 828 (714/203 114)	195 (27.3)	155 (21.7)	−40 (−5.6)	3223 (1.6)	25 906 (12.8)	22 683 (11.2)
Women	256 795 (645/256 150)	214 (33.2)	99 (15.3)	−115 (−17.8)	2509 (1.0)	39 791 (15.5)	37 282 (14.6)
Referral at stage 2†	460 623 (1359/459 264)	225 (16.6)	19 (1.4)	−206 (−15.2)	1206 (0.3)	54 627 (11.9)	53 421 (11.6)
Referral at stage 3‡	460 623 (1359/459 264)	275 (20.2)	78 (5.7)	−197 (−14.5)	3946 (0.9)	44 533 (9.7)	40 587 (8.8)

ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network.
* For sample calculations for reclassification or referral, see the **Appendix**, available at www.annals.org.
† Reclassification is defined as movement from referral to nonreferral (stage 2, 3, or 4 in the old system to risk category 1 in the new system) or vice versa.
‡ Reclassification is defined as movement from referral to nonreferral (stage 3 or 4 in the old system to risk category 1 or 2 in the new system) or vice versa.

able at www.annals.org). Most of the remaining patients were reclassified to a lower risk category with the alternate system, but reclassification accuracy differed between patients who did or did not go on to develop the renal outcome, as well as on the basis of proteinuria measure. Using ACR as a measure of proteinuria, higher proportions of both samples (with and without the outcome) were classified correctly; however, the alternate system was more accurate for patients who did not versus those who did develop the renal outcome (for example, net correct classification by using ACR was 22.5% and 11.7%, respectively) (**Table 3** and the **Appendix**, available at www.annals.org). Findings differed by subgroup; reclassification with the alternate system was more accurate for younger patients (age <60 years) and men who went on to develop the renal outcome; older patients (age ≥60 years) and women who did not go on to develop renal events; and patients with diabetes.

Reclassification was generally less accurate with dipstick testing than with ACR and was especially inaccurate for patients who went on to develop the renal outcome (11.4% more of whom were incorrectly classified). Substantially fewer patients experienced the renal outcome in the overall study population, so the absolute number of patients who experienced the composite renal outcome and were incorrectly reclassified was much smaller in all analyses than the number of patients who did not experience the event and were correctly reclassified.

Reclassification in the alternate system was generally less accurate for mortality than for the renal outcome. Although correct reclassifications outnumbered incorrect reclassifications for patients who survived, the alternate system consistently and incorrectly reclassified more patients who died to a lower category in all 3 validation cohorts (**Table 4**, **Appendix**, and **Appendix Table 2**). The same generally held true for subgroups stratified by age, diabetes status, and sex.

Implications of the Alternate System for Health Services

Under the assumption that persons classified as current system stages or alternate system risk categories 3 and 4 would be referred for specialist care (and that those in lower categories would not), the alternate system would lead to more missed than correct referrals among patients who developed the renal outcome, but would improve referral accuracy among those who did not (**Table 3**). Dipstick testing was also less accurate than ACR, which could lead to more missed referrals among patients who developed the renal outcome and lesser improvement in referral accuracy among those who did not. Again, because substantially fewer patients experienced the renal outcome than did not, the number of patients without events who would avoid unnecessary referrals under the alternate system was much larger than the number of those who would experience a composite renal event and would not be re-

Table 4. **Reclassification Accuracy of the Alternate Classification System for All-Cause Mortality, by Subgroup***

Cohort and Subgroup	Patients (Events/No Events), *n*	Reclassification Accuracy					
		Events, *n (% with events)*			No Events, *n (% without events)*		
		Incorrect	Correct	Net	Incorrect	Correct	Net
AKDN ACR							
Total population	51 356 (2726/48 630)	1157 (42.4)	341 (12.5)	−816 (−29.9)	2011 (4.1)	12 552 (25.8)	10 541 (21.7)
Age <60 y	29 325 (438/28 887)	112 (25.6)	58 (13.2)	−54 (−12.3)	1089 (3.8)	4488 (15.5)	3399 (11.8)
Age ≥60 y	22 031 (2288/19 743)	1045 (45.7)	283 (12.4)	−762 (−33.3)	922 (4.7)	8064 (40.8)	7142 (36.2)
No diabetes	23 599 (798/22 801)	339 (42.5)	54 (6.8)	−285 (−35.7)	521 (2.3)	5115 (22.4)	4594 (20.1)
Diabetes	27 757 (1928/25 829)	818 (42.4)	287 (14.9)	−531 (−27.5)	1490 (5.8)	7437 (28.8)	5947 (23.0)
Men	28 009 (1662/26 347)	653 (39.3)	223 (13.4)	−430 (−25.9)	1208 (4.6)	5958 (22.6)	4750 (18.0)
Women	23 347 (1064/22 283)	504 (47.4)	118 (11.1)	−386 (−36.3)	803 (3.6)	6594 (29.6)	5791 (26.0)
Referral at stage 2†	51 356 (2726/48 630)	679 (24.9)	26 (1.0)	−653 (−24.0)	335 (0.7)	9863 (20.3)	9528 (19.6)
Referral at stage 3‡	51 356 (2726/48 630)	763 (28.0)	147 (5.4)	−616 (−22.6)	1255 (2.6)	7386 (15.2)	6131 (12.6)
AKDN dipstick test							
Total population	460 623 (14 063/446 560)	5626 (40.0)	886 (6.3)	−4740 (−33.7)	3243 (0.7)	60 480 (13.5)	57 237 (12.8)
Age <60 y	346 983 (2529/344 454)	416 (16.4)	113 (4.5)	−303 (−12)	3380 (1.0)	27 907 (8.1)	24 527 (7.1)
Age ≥60 y	113 640 (11 534/102 106)	5210 (45.2)	773 (6.7)	−4437 (−38.5)	1720 (1.7)	32 573 (31.9)	30 853 (30.2)
No diabetes	427 901 (10 932/416 969)	4255 (38.9)	532 (4.9)	−3723 (−34.1)	3676 (0.9)	52 764 (12.7)	49 088 (11.8)
Diabetes	32 722 (3131/29 591)	1371 (43.8)	354 (11.3)	−1017 (−32.5)	1424 (4.8)	7716 (26.1)	6292 (21.3)
Men	203 828 (7376/196 452)	2537 (34.4)	532 (7.2)	−2005 (−27.2)	2846 (1.4)	23 564 (12.0)	20 718 (10.5)
Women	256 795 (6687/250 108)	3089 (46.2)	354 (5.3)	−2735 (−40.9)	2254 (0.9)	36 916 (14.8)	34 662 (13.9)
Referral at stage 2†	460 623 (14 063/446 560)	3440 (24.5)	83 (0.6)	−3357 (−23.9)	284 (0.1)	51 412 (11.5)	51 128 (11.4)
Referral at stage 3‡	460 623 (14 063/446 560)	4132 (29.4)	367 (2.6)	−3765 (−26.8)	2799 (0.6)	40 676 (9.1)	37 877 (8.5)
NHANES III§							
Total population‡	177 181 000	4 725 000 (28.4)	839 000 (5.0)	−3 886 000 (−23.4)	976 000 (0.6)	9 168 000 (5.7)	8 192 000 (5.1)
Age <60 y	137 079 000	226 000 (5.3)	195 000 (4.6)	−31 000 (−0.7)	667 000 (0.5)	3 339 000 (2.6)	2 672 000 (2.1)
Age ≥60 y	40 101 000	4 499 000 (36.2)	644 000 (5.2)	3 855 000 (−31.0)	309 000 (1.1)	5 782 000 (20.9)	5 473 000 (19.8)
No diabetes	166 327 000	3 559 000 (26.0)	471 000 (3.4)	−3 088 000 (−22.6)	631 000 (0.4)	7 586 000 (5.0)	6 955 000 (4.6)
Diabetes	10 853 000	1 166 000 (39.3)	368 000 (12.4)	−798 000 (−26.9)	345 000 (4.4)	1 582 000 (20.1)	1 237 000 (15.7)
Men	84 363 000	2 076 000 (24.6)	513 000 (6.1)	−1 563 000 (−18.5)	522 000 (0.7)	3 262 000 (4.3)	2 740 000 (3.6)
Women	92 817 000	2 649 000 (32.3)	325 000 (4.0)	−2 324 000 (−28.3)	455 000 (0.5)	5 906 000 (7.0)	5 451 000 (6.5)
Referral at stage 2†	177 181 000	3 162 000 (19.0)	157 000 (0.9)	−3 005 000 (−18.1)	367 000 (0.2)	7 990 000 (5.0)	7 632 000 (4.8)
Referral at stage 3‡	177 181 000	3 069 000 (18.4)	519 000 (3.1)	−2 550 000 (−15.3)	735 000 (0.5)	5 256 000 (3.3)	4 521 000 (2.8)

ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; NHANES III = Third National Health and Nutrition Examination Survey.
* For sample calculations for reclassification or referral, see the **Appendix**, available at www.annals.org.
† Reclassification is defined as movement from referral to nonreferral (stage 2, 3, or 4 in the old system to risk category 1 in the new system) or vice versa.
‡ Reclassification is defined as movement from referral to nonreferral (stage 3 or 4 in the old system to risk category 1 or 2 in the new system) or vice versa.
§ Numbers of events and no events are not presented for the NHANES III data because of the complex survey sample design.

ferred. Results were similar for an assumed referral threshold of stage or risk category 2 (**Table 3**).

Our results were qualitatively similar in analyses of mortality. The alternate system would potentially reduce unnecessary referrals among patients who survived but would lead to more missed than correct referrals among patients who died, regardless of whether the referral threshold was set at stage 2 or 3.

Finally, compared with the current system, fewer U.S. adults were classified with more advanced CKD under the alternate system (**Table 5**).

DISCUSSION

A staging system for CKD should classify persons on the basis of their renal prognosis (25), especially if such classification influences subsequent management, such as specialist referral or specific therapies for patients with more advanced disease. Although the current NKF KDOQI system for classification of CKD was a notable achievement, it has been criticized for not meeting these criteria (26), and others (27–31) have since proposed adding information about proteinuria to eGFR to better classify risk among patients with CKD.

We developed an alternate risk classification system that uses eGFR and proteinuria measures to categorize the risk for clinically relevant loss of kidney function or death

Table 5. **Estimated Classification of U.S. Adults Under the Current NKF KDOQI System and the Alternate System of CKD Risk Categories, by Stage**

Stage or Risk Category	Classification Under NKF KDOQI System (95% CI), *n**	Classification Under Alternate System (95% CI), *n**
0 (no CKD)	176.5 (174.7–178.4)	176.5 (174.8–178.2)
1	3.7 (3.3–4.1)	18.5 (17.3–19.7)
2	6.5 (6.0–7.1)	4.1 (3.6–4.6)
3	15.6 (14.3–17.0)	2.5 (2.2–2.9)
4	0.7 (0.5–0.9)	1.4 (1.2–1.7)

CKD = chronic kidney disease; NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative.
* In millions of U.S. adults. Data are estimated from NHANES (National Health and Nutrition Examination Survey) 1999 to 2006. The proportion of Americans with proteinuria was adjusted for anticipated persistence (presence on repeated testing) as described elsewhere (3). Sampling weights were calibrated on the basis of the proportion of patients missing data by 10-year age group, sex, and race or ethnicity. Adjusting the sampling weights corrects for differences in missing data across age, sex, and race or ethnicity strata but assumes that data within strata are missing randomly. **Figure 1** contains definitions of the stages and categories.

among patients with CKD, and we report several findings. First, the rate of the composite renal outcome increased with increasing risk categories in the alternate system, both in the overall study population and in subgroups stratified by age, sex, and diabetes—which is partly attributable to the way in which we developed the alternate system. In contrast, the rate of the renal outcome was similar in stages 1 and 2 in the current system, and rates were higher in stage 1 than in stage 2 in analyses stratified by age. To the extent that higher stages of disease should be associated with greater risk for adverse outcomes, this may suggest that the alternate system is preferable.

Second, the alternate system classifies fewer persons as having more advanced CKD; the projected number of U.S. adults assigned to risk categories 3 and 4 of the alternate system would be 3.9 million, compared with 16.3 million assigned to stages 3 and 4 of the current system.

Third, among reclassified patients, the alternate system seemed more accurate for (more likely to correctly reclassify) those who did not go on to develop the renal outcome than those who did. Under the assumption that patients might be referred to a nephrologist in CKD stage or risk category 2 or 3, our findings suggest that some patients who develop renal events might be denied appropriate care under the alternate system as a result of this misclassification. However, the absolute number of patients who went on to develop renal events and who were incorrectly reclassified to a lower risk category or below the referral risk category threshold was small, and it was outnumbered in each of our analyses by those who did not go on to develop adverse renal outcomes and were correctly classified to a lower risk category or below the referral risk category threshold. Use of the alternate system for staging patients or populations will therefore partly depend on opinions about acceptable tradeoffs between increased health system efficiency (fewer referrals) and potentially missed cases of progressive CKD. Also, many patients who are incorrectly reclassified to a lower risk category on the basis of a single serum creatinine and proteinuria measurement could be identified and properly reclassified in follow-up testing. Other considerations, such as the psychological effect of labeling persons with more or less advanced disease, may also inform perspectives about the use of the alternate system, but these would require further study (26).

Fourth, reclassification using the alternate system seemed to be more accurate when proteinuria was measured with ACR than with dipstick testing, for patients with and those without events. This may suggest that the choice of proteinuria measure in the alternate system might be based on judgments about how best to balance accuracy (which is better with ACR) with availability (which is better with the less expensive and more accessible urine dipstick test). However, this finding should be interpreted cautiously because of the many differences in population characteristics between the ACR and dipstick cohorts and it requires confirmation in future analyses adjusted for those differences.

Fifth, the reclassification accuracy of the alternate system differed by age, sex, and diabetes status. Accuracy was higher among patients younger than 60 years who went on to develop the renal outcome and among patients 60 years or older who did not. Our interpretation is that the alternate system usefully distinguishes the presence of heavy proteinuria with preserved eGFR (which is relatively more common in younger adults and associated with a worse renal prognosis) from reduced eGFR but no proteinuria (which is more common in older adults and associated with a relatively good renal prognosis). Reclassification accuracy was higher in men than in women among those who developed the renal outcome; however, accuracy in men was lower among those who did not. The explanation for this finding is unclear. Correct reclassification was also more common for patients with diabetes than those without diabetes, both in those who experienced events and those who did not, although the differences in accuracy were minimal among patients in either subgroup who went on to develop events.

Finally, reclassification accuracy was worse overall for mortality than for the combined renal outcome, mostly because the alternate system incorrectly classified patients who went on to die as being in a lower risk category. The importance of this finding depends on perspectives about the purpose of a CKD staging or risk classification system. Although we judged these analyses to be valuable because CKD is strongly associated with excess mortality (32, 33), we do not believe that weaker performance for mortality should preclude use of the alternate system. Adverse renal outcomes are more closely related than mortality to measures of renal function, and a CKD staging or risk classification system that accurately predicts adverse renal outcomes might not be expected to accurately predict mortality.

The KDIGO working group for practice guidelines on the classification of CKD will soon commence its revisions to the existing staging system. Although the consensus is that using information on both eGFR and proteinuria would be an improvement on the current system in terms of risk stratification, limited data describe the potential implications of such a change (9). Our study informs this process by demonstrating the potential implications of such revision, although the optimal approach to using proteinuria and eGFR in combination is not yet known.

Our study has limitations. We developed and sought to validate the new risk categories in a North American sample, but given the global audience for the proposed KDIGO guidelines, additional studies will be needed to confirm that our findings are generalizable to other populations and countries. Second, current recommendations for specialist referral among patients with CKD include criteria other than eGFR, which suggests that we may have overestimated the extent to which the new risk categories

might reduce the burden on health services. Finally, the follow-up in our study was relatively short for assessing progression to kidney failure and mortality, especially for persons with higher baseline eGFRs.

In conclusion, a risk classification system based on eGFR and proteinuria that incorporates prognostic information about renal outcomes and mortality identified fewer patients as having advanced CKD than the current, widely used staging system. The accuracy of the alternate system differed between patients who did and did not go on to develop adverse renal events and mortality and in subgroups stratified by age and diabetes, but accuracy was clearly higher when proteinuria was assessed by using ACR than by using dipstick testing. The alternate system could reduce unnecessary referrals for care, at the cost of not referring or delaying referral for some patients who go on to develop ESRD or die. These findings suggest that the current CKD staging system could be revised to include information on proteinuria; however, the optimal method for doing so requires further study, and the wisdom of using such a system in practice will require deliberations about the relative costs and benefits to patients. Nevertheless, our method for developing this risk classification system is an improvement over consensus-based processes because it uses information about relevant clinical outcomes. Our methods could serve as a useful example for future disease classification systems.

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Note: Drs. Tonelli, Muntner, and Hemmelgarn participated in the 2010 Kidney Disease: Improving Global Outcomes Controversies Conference, which brought investigators from around the world together to discuss how the current NKF KDOQI CKD staging system might be refined.

Grant Support: By an interdisciplinary research team grant from the Alberta Heritage Foundation for Medical Research (AHFMR), career salary awards from the AHFMR (Drs. Hemmelgarn, Tonelli, and Klarenbach), New Investigator Awards from the Canadian Institutes of Health Research (Drs. Hemmelgarn, Tonelli, and Manns), a joint initiative between Alberta Health and Wellness and the Universities of Alberta and Calgary (Drs. Hemmelgarn, Klarenbach, Manns, and Tonelli), and a Shire Biochem—KRESCENT Joint Fellowship and an AHFMR research Award (Dr. James).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-0837.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Code for AKDN data is available from Dr. Tonelli (e-mail, mtonelli-admin@med.ualberta.ca). Code for NHANES III data is not available. *Data set:* AKDN data are not available. NHANES III data are available at www.cdc.gov/nchs/nhanes.htm.

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Appendix: Sample Calculations

Combined Renal Outcome Reclassification

In the ACR validation cohort (51 356 patients), 34.8% of patients who had a renal event were correctly reclassified to a higher stage by the alternative system compared with the current system (for example, from NKF KDOQI stage 1 to stage 2) (**Table 3**). This percentage is calculated by dividing the number of patients who had a renal event and were reclassified to a higher stage by the total number of renal events ([178 ÷ 511] × 100 = 34.8%).

Similarly, in the ACR validation cohort (51 356 patients), 26.7% of patients who did not have a renal event were correctly reclassified to a lower stage by the alternative system compared with the current system (for example, from NKF KDOQI stage 3 to stage 2). This percentage is calculated by dividing the number of patients who did not have a renal event and were reclassified to a lower stage by the total number of patients who did not have a renal event ([13 591 ÷ 50 845] × 100 = 26.7%).

Referral

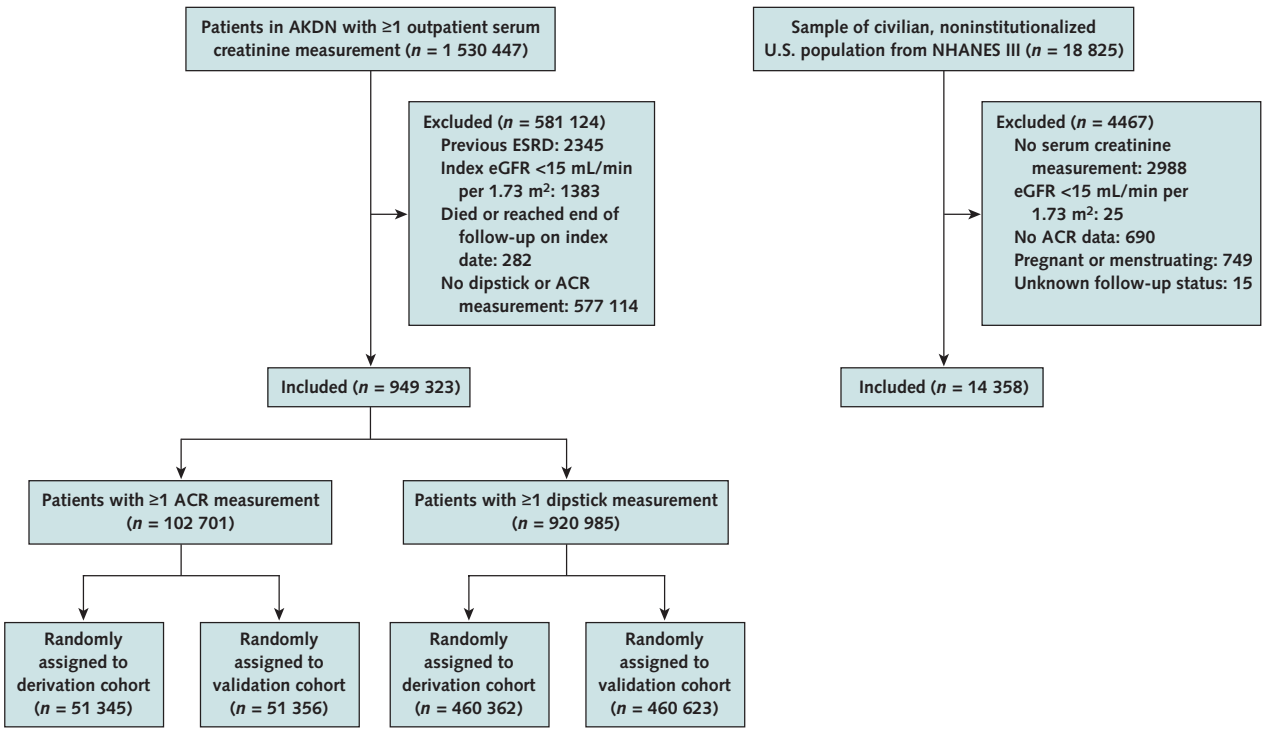
Assuming that persons classified as having stage 3 chronic kidney disease by either system would be referred, then in the ACR validation cohort (51 356 patients), 58 patients had a renal event and correctly moved from nonreferral in the current system to referral in the alternate system (**Table 3**). The corresponding percentage for this movement is calculated by dividing this number by the total number of renal events in the ACR cohort ([58 ÷ 511] × 100 = 11.4%).

Mortality

In the ACR validation cohort (51 356 patients), 12.5% of patients who died were correctly reclassified to a higher stage by the alternative system compared with the current system (for example, from NKF KDOQI stage 1 to stage 2). This percentage is calculated by dividing the number of patients who died and were reclassified to a higher stage by the total number of deaths ([341 ÷ 2726] × 100 = 12.5%).

Similarly, in the ACR validation cohort (51 356 patients), 25.8% of patients who did not die were correctly reclassified to a lower stage by the alternative system compared with the current system (for example, from NKF KDOQI stage 3 to stage 2) (**Table 4**). This percentage is calculated by dividing the number of patients who did not die and were reclassified to a lower stage by the total number of patients who did not die ([12 552 ÷ 48 630] × 100 = 25.8%).

Appendix Figure 1. **Study flow diagram.**



ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; NHANES III = Third National Health and Nutrition Examination Survey.

Appendix Figure 2. **Rates of the composite renal outcome and all-cause mortality, per 1000 patient-years, in the AKDN ACR derivation cohort.**

Rates (Rank), per 1000 Patient-Years

eGFR, *mL/min per 1.73 m²*	Proteinuria		
	Normal	Mild	Heavy
≥60	0.8 (1)	2.3 (3)	13.4 (7)
45–59.9	1.4 (2)	6.3 (5)	34.3 (10)
30–44.9	5.6 (4)	11.8 (6)	55.5 (11)
15–29.9	14.1 (8)	32.0 (9)	165.6 (12)

How Ranks Fit in the Categories

	Proteinuria	
Normal	Mild	Heavy
Category 0 (1)	Category 1 (2, 3)	Category 3 (6, 7, 8)
Category 1 (2, 3)	Category 2 (4, 5)	Category 4 (9, 10, 11, 12)
Category 2 (4, 5)	Category 3 (6, 7, 8)	Category 4 (9, 10, 11, 12)
Category 3 (6, 7, 8)	Category 4 (9, 10, 11, 12)	Category 4 (9, 10, 11, 12)

AKDN ACR Derivation Cohort (*n* = 51 345)

NKF KDOQI System

Composite Renal Outcome			All-Cause Mortality		
Stage	Patients, %	Rate (95% CI)	Stage	Patients, %	Rate (95% CI)
Stage 0	0.2	0.8 (0.6–1.0)	Stage 0	2.4	8.4 (7.8–9.0)
Stage 1	1.2	4.4 (3.1–6.4)	Stage 1	4.2	15.9 (13.1–19.3)
Stage 2	1.2	4 (3.2–5.0)	Stage 2	6.6	22 (19.9–24.2)
Stage 3	2.4	7.4 (6.5–8.4)	Stage 3	11	34.3 (32.3–36.4)
Stage 4	16.6	65.9 (54.5–79.8)	Stage 4	33.5	124 (108–141)

Alternate System

Composite Renal Outcome			All-Cause Mortality		
Stage	Patients, %	Rate (95% CI)	Stage	Patients, %	Rate (95% CI)
Stage 0	0.2	0.8 (0.6–1.0)	Stage 0	2.4	8.4 (7.8–9.0)
Stage 1	0.6	1.9 (1.5–2.4)	Stage 1	5.7	18.6 (17.3–20.0)
Stage 2	1.9	6 (4.6–7.8)	Stage 2	13.1	41.1 (37.3–45.4)
Stage 3	3.8	12.9 (10.5–15.8)	Stage 3	14	47.4 (42.5–52.7)
Stage 4	15.3	56 (49.2–63.8)	Stage 4	26.5	92.5 (83.8–102)

AKDN Dipstick Derivation Cohort (*n* = 460 362)

NKF KDOQI System

Composite Renal Outcome			All-Cause Mortality		
Stage	Patients, %	Rate (95% CI)	Stage	Patients, %	Rate (95% CI)
Stage 0	0.1	0.4 (0.3–0.4)	Stage 0	1.6	5.8 (5.7–6.0)
Stage 1	0.4	1.6 (1.2–2.2)	Stage 1	4.6	18.6 (17.0–20.4)
Stage 2	0.6	2.2 (1.8–2.5)	Stage 2	6.4	22.4 (21.3–23.6)
Stage 3	1.2	3.8 (3.5–4.2)	Stage 3	10.8	35.4 (24.5–36.4)
Stage 4	15.2	66.7 (59.5–74.8)	Stage 4	41	167.6 (156–180)

Alternate System

Composite Renal Outcome			All-Cause Mortality		
Stage	Patients, %	Rate (95% CI)	Stage	Patients, %	Rate (95% CI)
Stage 0	0.1	0.4 (0.3–0.4)	Stage 0	1.6	5.8 (5.7–6.0)
Stage 1	0.4	1.3 (1.2–1.5)	Stage 1	6.1	20.7 (20.0–21.3)
Stage 2	1.6	5.4 (4.6–6.3)	Stage 2	18.3	61.7 (58.9–64.5)
Stage 3	3.3	12.5 (11.0–14.3)	Stage 3	18.8	71.2 (67.4–75.3)
Stage 4	13.7	56 (50.8–61.8)	Stage 4	32.3	126.2 (118–135)

Rates of the 12 categories are ranked from lowest to highest risk. ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; eGFR = estimated glomerular filtration rate; NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Appendix Table 1. **Rate of the Composite Renal Outcome, per 1000 Patient-Years, in the 2 AKDN Internal Validation Cohorts***

NKF KDOQI CKD Stage	Alternate System CKD Risk Categories					Total
	0 (No CKD)	1	2	3	4	
AKDN ACR cohort						
0 (no CKD)						
Events, *n*	68					68
No events, *n*	31 962					31 962
Rate	0.7					0.7
Alternate system classification, %†	100.0					–
Total patients, %‡	–					62.4
1						
Events, *n*		17		11		28
No events, *n*		1953		350		2303
Rate		3.3		11.9		4.6
Alternate system classification, %†		84.5		15.5		–
Total patients, %‡		–		–		4.5
2						
Events, *n*		42		47		89
No events, *n*		5351		994		6345
Rate		2.6		15.4		4.7
Alternate system classification, %†		83.8		16.2		–
Total patients, %‡		–		–		12.5
3						
Events, *n*		28	43	24	120	215
No events, *n*		5121	2957	814	830	9722
Rate		1.7	4.6	9.9	43.1	6.9
Alternate system classification, %†		51.8	30.2	8.4	9.6	–
Total patients, %‡		–	–	–	–	19.4
4						
Events, *n*				5	106	111
No events, *n*				162	351	513
Rate				10.6	97.4	71.2
Alternate system classification, %†				26.8	73.2	–
Total patients, %‡				–	–	1.2
Total						
Events, *n*	68	87	43	87	226	511
No events, *n*	31 962	12 425	2957	2320	1181	50 845
Rate	0.7	2.3	4.6	12.7	58.3	3.4
Alternate system classification, %§	62.4	24.4	5.8	4.7	2.7	–
AKDN dipstick cohort						
0 (no CKD)						
Events, *n*	375					375
No events, *n*	376 699					376 699
Rate	0.37					0.37
Alternate system classification, %†	100.0					–
Total patients, %‡	–					81.9
1						
Events, *n*		27		19		46
No events, *n*		8771		1206		9977
Rate		1.3		6.4		1.9
Alternate system classification, %†		87.8		12.2		–
Total patients, %‡		–		–		2.2
2						
Events, *n*		85		59		144
No events, *n*		20 322		2740		23 062
Rate		1.5		7.9		2.2
Alternate system classification, %†		87.9		12.1		–
Total patients, %‡		–		–		5.0
3						
Events, *n*		140	135	56	176	507
No events, *n*		34 305	10 228	1560	1786	47 879
Rate		1.3	4.4	12.8	34.7	3.5
Alternate system classification, %†		71.2	21.4	3.3	4.1	–
Total patients, %‡		–	–	–	–	10.5
4						
Events, *n*				49	238	287
No events, *n*				842	805	1647
Rate				21.2	108.5	63.7

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Appendix Table 1—Continued

NKF KDOQI CKD Stage	Alternate System CKD Risk Categories					Total
	0 (No CKD)	1	2	3	4	
Alternate system classification, %†				46.1	53.9	–
Total patients, %‡				–	–	0.4
Total						
Events, *n*	375	252	135	183	414	1359
No events, *n*	376 699	63 398	10 228	6348	2591	459 264
Rate	0.37	1.4	4.4	10.7	57.0	1.1
Alternate system classification, %§	81.9	13.8	2.3	1.4	0.7	–

ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; CKD = chronic kidney disease; NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

* Patients were classified according to both the NKF KDOQI and alternate systems, and the observed composite renal outcome rates were cross-tabulated by stage or risk category in each system. Shaded boxes indicate groups of patients who would be reclassified under the alternate system compared with the NKF KDOQI system. Stage 2 of the NKF KDOQI system and risk category 2 of the alternate system do not overlap.

† Indicates the percentage of all patients at the given NKF KDOQI stage assigned to each alternate system risk category.

‡ Indicates the total percentage of the sample at the given NKF KDOQI stage.

§ Indicates the total percentage of the sample at each alternate system risk category.

Appendix Table 2. **All-Cause Mortality Rate, per 1000 Patient-Years, in the 2 AKDN Internal Validation Cohorts***

NKF KDOQI CKD Stage	Alternate System CKD Risk Categories					Total
	0 (no CKD)	1	2	3	4	
AKDN ACR cohort						
0 (no CKD)						
Events, *n*	828					828
No events, *n*	31 202					31 202
Rate	8.9					8.9
Alternate system classification, %†	100.0					–
Total patients, %‡	–					62.4
1						
Events, *n*		68		26		94
No events, *n*		1902		335		2237
Rate		13.1		28.1		15.3
Alternate system classification, %†		84.5		15.5		–
Total patients, %‡		–		–		4.5
2						
Events, *n*		351		121		472
No events, *n*		5042		920		5962
Rate		21.9		39.4		24.7
Alternate system classification, %†		83.82		16.18		–
Total patients, %‡		–		–		12.5
3						
Events, *n*		328	435	176	194	1133
No events, *n*		4821	2565	662	756	8804
Rate		19.6	46.2	72.6	68.1	36.0
Alternate system classification, %†		51.8	30.2	8.4	9.6	–
Total patients, %‡		–	–	–	–	19.4
4						
Events, *n*				43	156	199
No events, *n*				124	301	425
Rate				90.9	128.5	117.9
Alternate system classification, %†				26.8	73.2	–
Total patients, %‡				–	–	1.2
Total						
Events, *n*	828	747	435	366	350	2726
No events, *n*	31 202	11 765	2565	2041	1057	48 630
Rate	8.9	19.7	46.2	53.1	86.1	18.0
Alternate system classification, %§	62.4	24.4	5.8	4.7	2.7	–
AKDN dipstick cohort						
0 (no CKD)						
Events, *n*	6177					6177
No events, *n*	370 897					370 897
Rate	6.0					6.0
Alternate system classification, %†	100.0					–
Total patients, %‡	–					81.9
1						
Events, *n*		407		83		490
No events, *n*		8391		1142		9533
Rate		18.9		28.0		20.0
Alternate system classification, %†		87.8		12.2		–
Total patients, %‡		–		–		2.2
2						
Events, *n*		1194		284		1478
No events, *n*		19 213		2515		21 728
Rate		20.4		38.0		22.4
Alternate system classification, %†		87.9		12.1		–
Total patients, %‡		–		–		5.0
3						
Events, *n*		2246	1886	523	519	5174
No events, *n*		32 199	8477	1093	444	43 212
Rate		21.2	61.2	119.2	100.7	35.3
Alternate system classification, %†		71.2	21.4	3.3	4.1	–
Total patients, %‡		–	–	–	–	10.5
4						
Events, *n*				300	444	744
No events, *n*				591	599	1190
Rate				127.8	180.3	154.7

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Appendix Table 2—**Continued**

NKF KDOQI CKD Stage	Alternate System CKD Risk Categories					Total
	0 (no CKD)	1	2	3	4	
Alternate system classification, %†				46.1	53.9	–
Total patients, %‡				–	–	0.4
Total						
Events, *n*	6177	3847	1886	1190	963	14 063
No events, *n*	370 897	59 803	8477	5341	2042	446 560
Rate	6.0	20.7	61.2	69.3	126.5	11.1
Alternate system classification, %§	81.9	13.8	2.3	1.4	0.7	–

ACR = albumin–creatinine ratio; AKDN = Alberta Kidney Disease Network; CKD = chronic kidney disease; NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

* Patients were classified according to both the NKF KDOQI and alternate systems, and the observed mortality rates were cross-tabulated by stage or risk category in each system. Shaded boxes indicate groups of patients who would be reclassified under the alternate system compared with the NKF KDOQI system. Stage 2 of the NKF KDOQI system and risk category 2 of the alternate system do not overlap.

† Indicates the percentage of all patients at the given NKF KDOQI stage assigned to each alternate system risk category.

‡ Indicates the total percentage of the sample at the given NKF KDOQI stage.

§ Indicates the total percentage of the sample at each alternate system risk category.