



Online article and related content
current as of February 3, 2010.

Relation Between Kidney Function, Proteinuria, and Adverse Outcomes

Brenda R. Hemmelgarn; Braden J. Manns; Anita Lloyd; et al.

JAMA. 2010;303(5):423-429 (doi:10.1001/jama.2010.39)

<http://jama.ama-assn.org/cgi/content/full/303/5/423>

Supplementary material

eTables and eFigures

<http://jama.ama-assn.org/cgi/content/full/303/5/423/DC1>

Correction

[Contact me if this article is corrected.](#)

Citations

[Contact me when this article is cited.](#)

Topic collections

Cardiovascular System; Renal Diseases; Renal Diseases, Other; Prognosis/
Outcomes; Cardiovascular Disease/ Myocardial Infarction

[Contact me when new articles are published in these topic areas.](#)

Related Articles published in
the same issue

Proteinuria

Janet M. Torpy et al. *JAMA*. 2010;303(5):470.

Subscribe

<http://jama.com/subscribe>

Permissions

permissions@ama-assn.org

<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts

<http://jamaarchives.com/alerts>

Reprints/E-prints

reprints@ama-assn.org

Relation Between Kidney Function, Proteinuria, and Adverse Outcomes

Brenda R. Hemmelgarn, MD, PhD

Braden J. Manns, MD, MSc

Anita Lloyd, MSc

Matthew T. James, MD

Scott Klarenbach, MD, MSc

Robert R. Quinn, MD, PhD

Natasha Wiebe, MMath, PStat

Marcello Tonelli, MD, SM

for the Alberta Kidney Disease Network

CURRENT GUIDELINES CLASSIFY chronic kidney disease (CKD) into 5 stages, based chiefly on estimated glomerular filtration rate (eGFR) (eTable 1, available at <http://www.jama.com>).¹ Adoption of the scheme has facilitated large-scale estimates of CKD prevalence, led to multiple studies examining the relation between CKD severity and clinical outcomes, and permitted a global effort to educate physicians and the public about the implications of CKD.² Despite these benefits, the guidelines have been criticized because they do not incorporate information about the presence and severity of proteinuria, an important marker of CKD that is associated with adverse outcomes.³⁻⁵

As many as 26 million Americans have CKD, of whom almost 50% (10.1 million) have stage 1 or stage 2 CKD—in which eGFR is normal or nearly normal and CKD is defined by abnormal urinalysis or renal imaging studies.⁶ However, only 25% of Americans with proteinuria have overtly reduced eGFR (<60 mL/min/1.73 m²), and a similar proportion of those with low eGFR have proteinuria.⁷ Therefore, low eGFR and proteinuria do not always coexist, suggesting that eGFR and pro-

See also Patient Page.

Context The current staging system for chronic kidney disease is based primarily on estimated glomerular filtration rate (eGFR) with lower eGFR associated with higher risk of adverse outcomes. Although proteinuria is also associated with adverse outcomes, it is not used to refine risk estimates of adverse events in this current system.

Objective To determine the association between reduced GFR, proteinuria, and adverse clinical outcomes.

Design, Setting, and Participants Community-based cohort study with participants identified from a province-wide laboratory registry that includes eGFR and proteinuria measurements from Alberta, Canada, between 2002 and 2007. There were 920 985 adults who had at least 1 outpatient serum creatinine measurement and who did not require renal replacement treatment at baseline. Proteinuria was assessed by urine dipstick or albumin-creatinine ratio (ACR).

Main Outcome Measures All-cause mortality, myocardial infarction, and progression to kidney failure.

Results The majority of individuals (89.1%) had an eGFR of 60 mL/min/1.73 m² or greater. Over median follow-up of 35 months (range, 0-59 months), 27 959 participants (3.0%) died. The fully adjusted rate of all-cause mortality was higher in study participants with lower eGFRs or heavier proteinuria. Adjusted mortality rates were more than 2-fold higher among individuals with heavy proteinuria measured by urine dipstick and eGFR of 60 mL/min/1.73 m² or greater, as compared with those with eGFR of 45 to 59.9 mL/min/1.73 m² and normal protein excretion (rate, 7.2 [95% CI, 6.6-7.8] vs 2.9 [95% CI, 2.7-3.0] per 1000 person-years, respectively; rate ratio, 2.5 [95% CI, 2.3-2.7]). Similar results were observed when proteinuria was measured by ACR (15.9 [95% CI, 14.0-18.1] and 7.0 [95% CI, 6.4-7.6] per 1000 person-years for heavy and absent proteinuria, respectively; rate ratio, 2.3 [95% CI, 2.0-2.6]) and for the outcomes of hospitalization with acute myocardial infarction, end-stage renal disease, and doubling of serum creatinine level.

Conclusion The risks of mortality, myocardial infarction, and progression to kidney failure associated with a given level of eGFR are independently increased in patients with higher levels of proteinuria.

JAMA. 2010;303(5):423-429

www.jama.com

teinuria could be used together to identify individuals at high risk.

We studied a large cohort of individuals receiving routine clinical care in a single Canadian province, in which all residents are covered by government-sponsored health insurance. We examined the association between reduced eGFR, proteinuria, and adverse clinical outcomes, including all-cause mortality, myocardial infarction, and progression to kidney failure. We hypothesized that patients with both reduced eGFR and proteinuria would be at higher risk of these outcomes than participants with one or neither characteristic.

METHODS

The study population included all adults 18 years and older with at least 1 outpatient serum creatinine measurement in

Author Affiliations: Departments of Medicine (Drs Hemmelgarn, Manns, James, and Quinn) and Community Health Sciences (Drs Hemmelgarn, Manns, and James), University of Calgary, Calgary, Alberta, Canada; Departments of Medicine (Mss Lloyd and Wiebe and Drs Klarenbach and Tonelli) and Public Health Sciences (Drs Klarenbach and Tonelli), University of Alberta, Edmonton, Alberta; and Division of Nephrology, Foothills Medical Centre, Calgary, Alberta (Drs Hemmelgarn, Manns, James, and Quinn).

A list of the Alberta Kidney Disease Network members appears at <http://www.AKDN.info>.

Corresponding Author: Brenda R. Hemmelgarn, MD, PhD, Division of Nephrology, Foothills Medical Centre, 1403 29th St NW, Calgary, AB T2N 2T9, Canada (brenda.hemmelgarn@albertahealthservices.ca).

the province of Alberta, Canada, between May 1, 2002, and December 31, 2006, for 7 of the 9 geographically based provincial health regions, and between July 1, 2003, and January 1, 2005, and December 31, 2006, respectively, for the other 2 regions. Patients were excluded if they were treated with dialysis or a kidney transplant at baseline or if the baseline estimate of kidney function was clinically implausible (serum creatinine <0.28 mg/dL [multiply by 88.4 to get $\mu\text{mol/L}$]). To be eligible for inclusion, patients also had to have had at least 1 outpatient measure of proteinuria as described in this section. This study was facilitated by a previously described⁸ provincial laboratory repository: the Alberta Kidney Disease Network (AKDN).

Measurement of Kidney Function, Proteinuria, and Albuminuria

The eGFR for each patient was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.⁹ Although data on race were not available, misclassification of eGFR was expected to be minimal because less than 1% of the Alberta population is black.¹⁰ Baseline kidney function (index eGFR) was estimated using all outpatient serum creatinine measurements taken within a 6-month period of the first creatinine measurement, with the index eGFR defined as the mean of the measurements in this 6-month period. The date of the last serum creatinine measurement in the 6-month period was used as the index date for individuals with more than a single measurement.⁸ Index eGFR was categorized as 60 mL/min/1.73 m² or greater, 45 to 59.9 mL/min/1.73 m², 30 to 44.9 mL/min/1.73 m², and 15 to 29.9 mL/min/1.73 m². Because of inaccuracies in assessment of kidney function using the MDRD Study equation at higher levels of kidney function, and to permit comparisons with related studies,¹¹ we categorized individuals with higher levels of function into 1 category (eGFR ≥ 60 mL/min/1.73 m²).

Proteinuria was captured by urine dipstick as well as albumin-creatinine ratio (ACR) based on outpatient ran-

dom spot urine measurements. In the primary analysis, we included all patients with at least 1 urine dipstick measurement and defined proteinuria as normal (urine dipstick reading negative), mild (urine dipstick reading trace or 1+), or heavy (urine dipstick reading $\geq 2+$).¹² In sensitivity analyses, we considered an alternate definition of proteinuria based on ACR, defined as normal (ACR <30 mg/g), mild (ACR 30-300 mg/g), or heavy (ACR >300 mg/g).¹²

All outpatient urine dipstick and ACR measurements in the 6-month periods before and after the index eGFR were used to establish baseline proteinuria and albuminuria. Analyses used proteinuria or albuminuria as an ordinal variable according to these 3 categories, with the median of all respective measurements selected for each patient with multiple measurements.

Covariates

Demographic data were determined from the administrative data files of the provincial health ministry (Alberta Health and Wellness). Aboriginal race/ethnicity was determined from First Nations status in the registry file; it was not possible to identify other race/ethnic groups, although more than 85% of the Alberta population is white.¹⁰ Socioeconomic status was categorized as high income (annual adjusted taxable family income \geq CaD \$39 250 [US \$37 695]), low income (annual adjusted taxable family income $<$ CaD \$39 250), and low income with subsidy (receiving social assistance) based on government records.¹³ Diabetes mellitus and hypertension were identified from hospital discharge records and physician claims based on validated algorithms.^{14,15} Other comorbid conditions were identified using validated *International Classification of Diseases, Ninth Revision, Clinical Modification*, and *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*, coding algorithms applied to physician claims and hospitalization data.¹⁶ The presence of 1 or more diagnostic code in any position up to

3 years prior to cohort entry was used for identification of comorbidities.

Ascertainment of Outcomes

Patients were followed up from their index date until study end (March 31, 2007). The primary outcome of interest was all-cause mortality, as identified from the Alberta Health and Wellness Registry file. Secondary outcomes were first hospitalization for acute myocardial infarction¹⁷; occurrence of end-stage renal disease, defined as the date of registration for chronic dialysis or renal transplantation¹⁸; and the occurrence of an outpatient serum creatinine measurement that was twice as high as the first creatinine measurement during the study period (corresponding to a 50% decline in kidney function), assessed at the end of follow-up.

Statistical Analyses

Poisson regression was used to evaluate the association between the renal risk factors and each of the outcomes of interest, with output expressed as the rate per 1000 person-years. If the Poisson assumption that variance equals the mean was not met, a negative binomial model was used. We first calculated age-adjusted rates for each of the outcomes (all-cause mortality, hospitalization for myocardial infarction, end-stage renal disease, and doubling of serum creatinine) by level of eGFR and proteinuria, considering urine dipstick reading and ACR separately to classify proteinuria. We then calculated fully adjusted event rates for each of the outcomes, adjusting for the sociodemographic variables and comorbidities listed in TABLE 1. Two-way interactions between eGFR and proteinuria were assessed for all 4 clinical outcomes.

The primary analysis was based on the cohort of participants who had data for proteinuria available from dipstick urinalysis. This analysis had greater than 99% statistical power (for $\alpha = .05$) to detect a 10% increase in the likelihood of death among (1) individuals with eGFR of 60 mL/min/1.73 m² or greater compared with those with eGFR of 15 to 29.9 mL/min/1.73 m² and (2) individuals with

heavy proteinuria compared with those with no proteinuria. In sensitivity analyses, we repeated statistical models for the subset of participants who had data for proteinuria based on urinary ACRs. We repeated analyses examining the relation between proteinuria and adverse outcomes in 2 subgroups of clinical interest: those with eGFR 45 to 59.9 mL/min/1.73 m² (who account for the large majority of people with CKD) and those with “mildly reduced eGFR” as defined by current guidelines (eGFR 60-89.9 mL/min/1.73 m²).

We performed sensitivity analyses in strata defined by participant age (≥65 and <65 years). In all analyses, we performed tests for linear trend across categories of proteinuria and eGFR. The variables used to calculate the tests for trend in eGFR and ACR were defined by the median values of these parameters in each category. The variable used to calculate the test for trend in dipstick-measured proteinuria was defined by values of 1, 2, and 3 for normal, mild, and heavy proteinuria, respectively.²⁰ Finally, we repeated the analysis using

eGFR and ACR as continuous variables, with ACR log-transformed because of its skewed distribution. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) and Stata version 10.1 (StataCorp, College Station, Texas). A P value of <.05 was used to indicate statistical significance without adjustment for multiple comparisons. The institutional review boards of the University of Calgary and University of Alberta approved the study and granted waiver of patient consent.

Table 1. Demographic and Clinical Characteristics of Participants by Level of Kidney Function or Proteinuria^a

	Primary Analysis, % (N = 920 985)							Sensitivity Analysis, % (n = 102 701)		
	eGFR, mL/min/1.73 m ^{2b}				Proteinuria Measured by Dipstick			Proteinuria Measured by ACR		
	≥60 (n = 820 571)	45-59.9 (n = 79 845)	30-44.9 (n = 16 713)	15-29.9 (n = 3856)	None (n = 836 550)	Mild (n = 71 557)	Heavy (n = 12 878)	None (n = 77 280)	Mild (n = 20 217)	Heavy (n = 5204)
Age, mean (SD), y	46.4 (15.4)	65.8 (14.0)	75.1 (12.2)	74.7 (13.9)	48.4 (16.3)	50.8 (19.7)	55.4 (20.3)	55.8 (14.7)	60.5 (15.5)	60.1 (15.8)
Female sex	55	64	65	61	56	52	44	46	45	40
Aboriginal	2	1	1	2	2	4	4	3	4	6
Diabetes	6	13	25	36	6	14	31	49	67	74
Hypertension	18	49	76	82	21	32	50	46	60	69
Cerebrovascular disease	2	6	12	15	2	4	8	3	6	8
Peripheral vascular disease	1	4	9	14	1	3	6	2	5	8
CHF	1	7	20	33	2	5	11	4	8	14
Cancer	4	8	13	16	4	7	10	5	7	7
COPD	13	18	25	30	13	18	21	15	19	22
Dementia	1	3	8	11	1	3	4	1	2	2
Diabetes-C	0	1	5	11	0	1	6	2	6	14
Diabetes-NC	3	7	15	26	3	7	18	21	32	43
AIDS/HIV	0	0	0	0	0	0	0	0	0	0
Metastatic solid tumor	0	1	2	3	0	1	2	0	1	1
Myocardial infarction	1	5	12	18	2	4	8	4	7	10
Mild liver disease	1	1	2	2	1	2	2	1	2	2
Moderate/severe liver disease	0	0	0	1	0	0	0	0	0	0
Paralysis	0	1	1	2	0	1	1	0	1	1
Peptic ulcer disease	2	3	5	7	2	3	4	3	3	4
Renal disease	0	3	18	52	1	3	14	2	5	16
Rheumatic disease	1	2	4	5	1	2	3	1	2	2
Socioeconomic status ^c										
Low	16	38	60	60	18	25	33	24	34	36
Low with subsidy	2	2	2	3	2	4	4	3	3	5

Abbreviations: ACR, albumin-creatinine ratio; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; diabetes-C, diabetes with end organ damage; diabetes-NC, diabetes without end organ damage; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

^aTotals do not always add to 100 because of rounding.

^bAmong patients with proteinuria measured by dipstick.

^cSocioeconomic status was categorized as high (annual adjusted taxable family income ≥CaD \$39 250 [US \$37 695]), low (annual adjusted taxable family income <CaD \$39 250), and low with subsidy (receiving social assistance) based on Government of Alberta health care insurance records.¹⁹

RESULTS

A total of 1 530 447 participants had at least 1 outpatient serum creatinine measurement during the study period. We excluded 2345 people with end-stage renal disease prior to cohort entry and 1383 with index eGFR of less than 15 mL/min/1.73 m². An additional 282 individuals were excluded because they either died or reached end of follow-up on their index date. Of the 1 526 437 participants, 920 985 (60.3%) had at least 1 urine dipstick measurement and 102 701 (6.7%) had at least 1 ACR measurement. Characteristics of the participants by level of eGFR and proteinuria are shown in Table 1. The majority of individuals (89.1%) in the primary analysis with proteinuria measured by urine dipstick had an eGFR of 60 mL/min/1.73 m² or greater.

A total of 102 701 participants had at least 1 urinary ACR measurement performed; individuals in this subset were older (mean [SD] age, 57.0 [15.0]

years vs 48.0 [16.6] years) and more likely to be male (54.5% vs 43.4%) or diabetic (54.1% vs 3.4%) and had a higher mean (SD) Charlson score (0.94 [1.6] vs 0.43 [1.1]) than those without such measurements (all *P* < .001; χ^2 test and *t* test for categorical and continuous variables, respectively). A higher proportion of participants in this subset had mild (19.7% vs 7.3%) or heavy proteinuria (5.1% vs 1.1%) than in those without measurements of urinary ACR (both *P* < .001, χ^2 test).

Age-Adjusted Likelihood of Clinical Outcomes by Level of eGFR and Proteinuria

During median follow-up of 35 months (range, 0-59 months), 27 959 participants (3.0%) died, 5772 (0.6%) were hospitalized for myocardial infarction, 771 (0.08%) initiated renal replacement therapy, and 2514 (0.4%) experienced a doubling of serum creatinine. The age-adjusted rates of these

outcomes were all increased at lower levels of eGFR and at heavier proteinuria (eTable 2 and eTable 3).

Adjusted Likelihood of Clinical Outcomes by Level of eGFR and Proteinuria

Within each stratum of eGFR, there was substantial variability in risk with participants who had heavier proteinuria having markedly increased adjusted rates of all 4 adverse outcomes (TABLE 2; eFigure 1, available at <http://www.jama.com>). The adjusted mortality risk was more than 2-fold higher among individuals with heavy proteinuria and eGFR of 60 mL/min/1.73 m² or greater as compared with those with eGFR of 45 to 59.9 mL/min/1.73 m² and normal protein excretion (rate ratio, 2.5; 95% confidence interval [CI], 2.3-2.7). Significant interactions between eGFR and proteinuria were observed for death, initiation of renal replacement, and doubling of serum creatinine—

Table 2. Adjusted Rates Per 1000 Person-Years of Clinical Outcomes by Level of eGFR and Proteinuria Measured by Dipstick^a

	Proteinuria											
	All-Cause Mortality ^b			Myocardial Infarction ^b			End-stage Renal Disease ^b			Doubling of Serum Creatinine ^c		
	Normal	Mild	Heavy	Normal	Mild	Heavy	Normal	Mild	Heavy	Normal	Mild	Heavy
eGFR ≥60^d												
Events, No.	12 157	3191	722	3171	474	103	62	11	35	739	223	146
Patients, No.	754 158	58 400	8013	754 158	58 400	8013	754 158	58 400	8013	487 335	39 835	5867
Rate (95% CI)	2.7 (2.6-2.8)	5.8 (5.5-6.0)	7.2 (6.6-7.8)	0.9 (0.9-1.0)	1.3 (1.2-1.5)	1.6 (1.3-2.0)	0.03 (0.02-0.03)	0.05 (0.03-0.09)	1.0 (0.7-1.4)	0.6 (0.5-0.6)	1.6 (1.4-1.9)	5.9 (5.0-7.0)
eGFR 45-59.9^d												
Events, No.	4513	1598	514	1011	200	73	27	19	39	269	106	144
Patients, No.	68 768	8783	2294	68 768	8783	2294	68 768	8783	2294	58 562	7635	2011
Rate (95% CI)	2.9 (2.7-3.0)	5.2 (4.9-5.5)	7.2 (6.5-7.8)	1.2 (1.1-1.2)	1.3 (1.1-1.5)	1.8 (1.4-2.3)	0.2 (0.1-0.2)	0.7 (0.5-1.2)	4.3 (3.1-6.1)	0.9 (0.8-1.0)	2.1 (1.7-2.5)	10.0 (8.3-11.9)
eGFR 30-44.9^d												
Events, No.	2162	1059	511	359	116	73	36	40	103	178	133	177
Patients, No.	11 823	3296	1594	11 823	3296	1594	11 823	3296	1594	10 926	3004	1462
Rate (95% CI)	4.0 (3.7-4.2)	5.8 (5.4-6.2)	7.5 (6.8-8.2)	1.4 (1.3-1.6)	1.5 (1.2-1.8)	2.1 (1.6-2.7)	1.3 (0.9-1.8)	4.2 (3.0-6.0)	16.1 (12.5-20.7)	2.0 (1.7-2.4)	4.7 (3.9-5.7)	12.8 (10.7-15.3)
eGFR 15-29.9^d												
Events, No.	644	481	407	84	49	59	61	81	257	73	94	232
Patients, No.	1801	1078	977	1801	1078	977	1801	1078	977	1685	997	912
Rate (95% CI)	6.7 (6.2-7.3)	9.1 (8.2-10.0)	10.4 (9.3-11.6)	2.1 (1.6-2.6)	2.2 (1.6-2.9)	3.3 (2.5-4.3)	12.7 (9.3-17.3)	25.2 (18.9-33.4)	65.9 (52.3-82.9)	4.5 (3.5-5.9)	10.5 (8.3-13.3)	24.7 (20.7-29.6)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.
^aAdjusted for age; sex; diabetes; hypertension; socioeconomic status; and history of cancer, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, dementia, diabetes with end organ damage, diabetes without chronic complication, AIDS/HIV, metastatic solid tumor, myocardial infarction, mild liver disease, moderate or severe liver disease, paralysis, peptic ulcer disease, peripheral vascular disease, renal disease, and rheumatic disease. In this analysis, dipstick urinalysis was used to classify participants with respect to proteinuria: normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick ≥2+).
^bn=920 985 for all-cause mortality, myocardial infarction, and end-stage renal disease.
^cn=620 231 for doubling of serum creatinine at end of follow-up.
^dUnit of measure for eGFR is mL/min/1.73 m². The tests for linear trend across eGFR categories and across proteinuria categories were all significant at the *P* < .001 level.

such that the additional risk of heavier proteinuria was reduced at lower eGFR (all *P* for interaction statistically significant at $<.001$)—but not for myocardial infarction (*P* for interaction, .08). However, the difference in risk associated with moderate or heavy proteinuria (as compared with those without proteinuria) appeared clinically relevant within every eGFR stratum and for all 4 clinical outcomes.

Sensitivity Analyses

Results were consistent when analyses were restricted to the subset of 102 701 participants who had urinary ACR measurements performed (TABLE 3; eFigure 2). Specifically, risk increased progressively at levels of eGFR below 60 mL/min/1.73 m² and with mild or heavy proteinuria within all eGFR strata—for all 4 clinical outcomes (adjusted rate ratio for mortality, 2.3 [95% CI, 2.0-2.6] for individuals with heavy proteinuria and eGFR of 60 mL/min/1.73 m² or greater as compared with those with

eGFR of 45 to 59.9 mL/min/1.73 m² and normal protein excretion). Next we repeated analyses using a more conservative definition of heavy proteinuria (ACR >2000 mg/g). Compared with those without significant proteinuria, participants with ACRs greater than 2000 mg/g had markedly elevated rates of adverse outcomes. For example, among participants with eGFRs of 45 to 59.9 mL/min/1.73 m², those with heavy proteinuria by this definition had adjusted rates of 21.5 (95% CI, 15.5-29.9), 11.2 (95% CI, 6.4-19.8), and 27.9 (95% CI, 17.6-44.2) per 1000 person-years, respectively, for mortality, myocardial infarction, and initiation of renal placement therapy, as compared with rates of 7.0 (95% CI, 6.3-7.6), 3.7 (95% CI, 3.2-4.3), and 0.3 (95% CI, 0.2-0.6), respectively, for those without proteinuria.

Because current guidelines for the classification of CKD describe eGFR between 60 and 90 mL/min/1.73 m² as “mildly reduced,” we examined the prognostic value of proteinuria within

this category specifically. Among the 597 870 participants, a graded increase in the adjusted rate of all-cause mortality was seen with rates of 2.2 (95% CI, 2.1-2.3), 4.3 (95% CI, 4.1-4.6), and 5.1 (95% CI, 4.7-5.6) per 1000 person-years among participants with no, mild, or heavy proteinuria, respectively (*P* for trend $<.001$). Similar findings were seen for the outcomes of myocardial infarction (rates, 1.0 [95% CI, 0.9-1.0], 1.4 [95% CI, 1.2-1.5], and 1.6 [95% CI, 1.2-1.9]; *P* for trend $<.001$), initiation of renal replacement therapy (rates, 0.02 [95% CI, 0.02-0.03], 0.04 [95% CI, 0.02-0.09], and 0.8 [95% CI, 0.5-1.3]; *P* for trend $<.001$), or doubling of serum creatinine (rates, 0.3 [95% CI, 0.3-0.4], 0.9 [95% CI, 0.7-1.1], and 2.8 [95% CI, 2.2-3.6]; *P* for trend $<.001$).

Because there has been controversy about whether the prognostic implications of CKD vary in younger and older populations, we repeated analyses stratifying on age. All findings were similar among participants who were 65 years

Table 3. Adjusted Rates Per 1000 Person-Years of Clinical Outcomes by Level of eGFR and Proteinuria Measured by Albumin-Creatinine Ratio^a

	Proteinuria											
	All-Cause Mortality ^b			Myocardial Infarction ^b			End-stage Renal Disease ^b			Doubling of Serum Creatinine ^c		
	Normal	Mild	Heavy	Normal	Mild	Heavy	Normal	Mild	Heavy	Normal	Mild	Heavy
eGFR ≥60^d												
Events, No.	1611	809	268	619	249	77	13	5	30	137	104	111
Patients, No.	64 146	14 597	2805	64 146	14 597	2805	64 146	14 597	2805	51 249	12 672	2539
Rate (95% CI)	6.3 (6.0-6.7)	9.9 (9.2-10.8)	15.9 (14.0-18.1)	3.0 (2.8-3.3)	4.2 (3.7-4.8)	6.4 (5.1-8.1)	0.06 (0.03-0.10)	0.09 (0.04-0.23)	2.45 (1.70-3.59)	1.0 (0.9-1.2)	2.8 (2.3-3.4)	13.4 (11.0-16.4)
eGFR 45-59.9^d												
Events, No.	643	490	206	211	138	52	9	9	4	49	58	110
Patients, No.	10 316	3520	1126	10 316	3520	1126	10 316	3520	1126	9547	3298	1067
Rate (95% CI)	7.0 (6.4-7.6)	11.9 (10.7-13.2)	18.0 (15.6-20.9)	3.7 (3.2-4.3)	5.9 (4.9-7.2)	7.3 (5.5-9.7)	0.3 (0.17-0.64)	0.9 (0.49-1.82)	8.3 (5.9-11.9)	1.6 (1.2-2.1)	4.8 (3.6-6.2)	25.0 (20.2-30.5)
eGFR 30-44.9^d												
Events, No.	336	339	213	91	80	49	10	21	7	37	42	120
Patients, No.	2474	1624	837	2474	1624	837	2474	1624	837	2360	1549	800
Rate (95% CI)	10.0 (8.9-11.3)	14.1 (12.4-15.9)	18.9 (16.2-21.9)	5.3 (4.3-6.6)	6.7 (5.2-8.6)	8.4 (6.2-11.3)	1.7 (0.8-3.2)	4.8 (3.1-7.5)	27.3 (20.9-35.8)	4.1 (2.9-5.7)	6.6 (4.8-9.1)	33.4 (27.1-41.2)
eGFR 15-29.9^d												
Events, No.	91	166	154	13	28	27	8	35	128	9	27	108
Patients, No.	344	476	436	344	476	436	344	476	436	333	452	422
Rate (95% CI)	16.3 (13.0-20.5)	22.0 (18.5-26.0)	24.6 (20.5-29.6)	5.1 (2.9-9.0)	8.6 (5.7-12.8)	9.7 (6.4-14.6)	9.0 (4.4-18.5)	27.6 (18.7-40.4)	97.3 (75-127)	6.2 (3.2-12.0)	13.8 (9.2-20.7)	51.8 (40.8-66.5)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.
^aAdjusted for age; sex; diabetes; hypertension; socioeconomic status; and history of cancer, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, dementia, diabetes with end organ damage, diabetes without chronic complication, AIDS/HIV, metastatic solid tumor, myocardial infarction, mild liver disease, moderate or severe liver disease, paralysis, peptic ulcer disease, peripheral vascular disease, renal disease, and rheumatic disease. In this analysis, only urinary albumin-creatinine ratio (ACR) was used to classify participants with respect to proteinuria: normal (ACR <30 mg/g), mild (ACR 30-300 mg/g), or heavy (ACR >300 mg/g).
^bn=102 701 for all-cause mortality, myocardial infarction, and end-stage renal disease.
^cn=86 288 for doubling of serum creatinine at end of follow-up.
^dUnit of measure for eGFR is mL/min/1.73 m². The tests for linear trend across eGFR categories and across proteinuria categories were all significant at the *P* < .001 level.

and older as compared with those who were younger. Specifically, the risk of all 4 clinical outcomes increased significantly in both age strata with declining eGFR (all *P* for trend <.001), as well as with heavier proteinuria (all *P* for trend <.001).

Finally, results with eGFR and ACR as continuous variables were consistent with categorical analyses. The increase in adjusted rate per 10-mL/min/1.73 m² decrease in eGFR was most pronounced for the outcome end-stage renal disease, followed by doubling of serum creatinine, myocardial infarction, and all-cause mortality (increase in rates, 2.17 [95% CI, 2.02-2.34], 1.15 [95% CI, 1.10-1.19], 1.09 [95% CI, 1.05-1.12], and 1.04 [95% CI, 1.03-1.06], respectively). Similar findings were seen per 10-fold increase in ACR with an increase in adjusted rates of 1.92 (95% CI, 1.81-2.04), 1.76 (95% CI, 1.70-1.82), 1.18 (95% CI, 1.14-1.21), and 1.22 (95% CI, 1.21-1.24), respectively, for initiation of renal replacement therapy, doubling of serum creatinine, myocardial infarction, and all-cause mortality.

COMMENT

In this large, community-based cohort of all adults undergoing laboratory testing in a single Canadian province, we demonstrated that prognosis associated with a given level of eGFR varies substantially based on the presence and severity of proteinuria. In fact, patients with heavy proteinuria but without overtly abnormal eGFR appeared to have worse clinical outcomes than those with moderately reduced eGFR but without proteinuria. Results were consistent for 2 different measures of proteinuria; consistent for several clinically relevant outcomes, including all-cause mortality, myocardial infarction, and the need for renal replacement; and robust to multivariable adjustment and a variety of sensitivity analyses.

These findings are important because current guidelines for the classification and staging of CKD are based on eGFR without explicit consideration of the severity of concomitant proteinuria.¹ In addition, computerized re-

porting of eGFR (generally without consideration of proteinuria) is increasingly used to assist physicians in identifying patients at high risk of adverse outcomes—or those who might benefit from specialist care.²¹ Although our findings do not directly address which patients would benefit from referral to a nephrologist, they do suggest that risk stratification performed in terms of eGFR alone is relatively insensitive to clinically relevant gradients in risk.

Staging systems for the classification of disease are often used to group affected persons into categories that are associated with similar prognoses, generally in a fashion that assigns people with worse prognoses to more advanced stages.²² Although the introduction of the NKF-K/DOQI (National Kidney Foundation/Dialysis Outcomes Quality Initiative) scheme for classification of CKD represented a major advance for researchers and clinicians, our findings suggest that this scheme does not meet these 2 criteria. For example, the age-adjusted rates of all-cause mortality and kidney failure appear to vary up to 4- and 50-fold (depending on the severity of proteinuria) within a given stage as defined by the current scheme. Similarly, a patient with an eGFR of 80 mL/min/1.73 m² and 3+ proteinuria on dipstick reading (or ACR of 400 mg/g) would be assigned to stage 1 CKD under the current system—even though his or her age-adjusted risks of death and the need for renal replacement therapy would be approximately 2 and 10 times higher, respectively, than an otherwise similar patient with an eGFR of 50 mL/min/1.73 m² but no evidence of proteinuria (stage 3 disease).

This latter finding is particularly striking given the high prevalence of stage 3 CKD (defined by eGFRs of 30-59.9 mL/min/1.73 m² with or without proteinuria) in our study, which accounts for the large majority of North American individuals with CKD.⁶ An additional finding of our analysis is that the risk is heterogeneous within this stage, even when it is defined by eGFR alone. As previously reported, the risk

of all-cause mortality in our study was markedly higher among participants with eGFRs of 30 to 44.9 mL/min/1.73 m² than among those with eGFRs of 45 to 59.9 mL/min/1.73 m².¹¹ Our data extend this finding to other adverse outcomes, including myocardial infarction and progression to kidney failure. The heterogeneity of risk among the large number of people currently classified as having stage 3 CKD (even when stratified by proteinuria) suggest that consideration should be given to subdividing this stage as done in our analysis, as well as by proteinuria. Focusing clinical attention on people at highest risk (as defined by the intersection of eGFR and proteinuria) may prove to be a more cost-effective approach to preventing the complications of CKD, although further work is required to confirm this hypothesis.

Although other equations²³ and serum markers²⁴ are available for estimating GFR, we used the MDRD Study equation because it is the most widely used at present. Current practice in Western countries emphasizes the use of ACR rather than dipstick urinalysis in the assessment of CKD.¹ Although dipstick urinalysis has less favorable diagnostic properties than ACR for the assessment of proteinuria,²⁵ it is also considerably less expensive. Our results suggest that dipstick urinalysis adds considerable prognostic information to that associated with eGFR alone—and the magnitude of excess risk observed with heavy proteinuria appeared similar whether assessed by dipstick or by ACR. Because the majority of people with CKD worldwide live in low- or middle-income nations,²⁶ our data support the further study of dipstick urinalysis as a valid alternative to ACR for risk stratification in resource-limited settings.

Our study has limitations due to its observational nature. First, the cohort was limited to individuals who had an outpatient serum creatinine measurement and a measure of urinary protein performed as part of routine care—and therefore does not include individuals who did not use medical

services. However, since we studied nearly 1 million individuals, and considering the universal nature of health care coverage in Alberta, this limitation is unlikely to invalidate our finding that proteinuria adds substantial prognostic value to that associated with eGFR alone. Second, proteinuria and albuminuria may have been misclassified because of the known variability of these measurements based on a single measurement.¹² However, we attempted to reduce this misclassification by using all urine measurements in a 6-month period before and after the index eGFR. In addition, results were robust to use of 2 different measures of proteinuria and were consistent for multiple clinically relevant outcomes.

Third, we assessed the incidence of doubling of serum creatinine during follow-up, which may have included some participants with acute renal failure as well as those with progression of CKD. However, since we excluded inpatient measurements of serum creatinine, and given that the prevalence of acute renal failure in the community is less than 1%,²⁷ this likely accounted for the minority of such events—although this degree of kidney function loss is clinically relevant whether due to acute or chronic disease.²⁸ Fourth, the follow-up in our study was relatively short to assess progression to kidney failure, especially for people with higher levels of baseline eGFR, although this is unlikely to have threatened the validity of our conclusions. Finally, we did not have information on characteristics such as use of alcohol, tobacco, and antihypertensive medications, which may have resulted in residual confounding. However, given the magnitude of the effect sizes observed in our study, it is unlikely that further adjustment for these covariates would negate the observed associations.

In conclusion, we found that the risks of death, myocardial infarction, and progression to kidney failure at a given level of eGFR were independently increased in individuals with higher levels of proteinuria. These findings suggest that future revisions of the classification

system for CKD should incorporate information from proteinuria.

Author Contributions: Dr Hemmelgarn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hemmelgarn, Klarenbach, Wiebe, Tonelli.

Acquisition of data: Hemmelgarn, James, Quinn.

Analysis and interpretation of data: Hemmelgarn, Manns, Lloyd, James, Klarenbach, Quinn, Wiebe, Tonelli.

Drafting of the manuscript: Hemmelgarn, Tonelli.

Critical revision of the manuscript for important intellectual content: Hemmelgarn, Manns, Lloyd, James, Klarenbach, Quinn, Wiebe, Tonelli.

Statistical analysis: Hemmelgarn, Lloyd, James, Quinn, Wiebe, Tonelli.

Obtained funding: Hemmelgarn, Manns, Tonelli.

Administrative, technical, or material support: Hemmelgarn, James, Quinn.

Study supervision: Hemmelgarn, Wiebe, Tonelli.

Financial Disclosures: None reported.

Funding/Support: Drs Hemmelgarn, Tonelli, and Klarenbach were supported by awards from the Alberta Heritage Foundation for Medical Research (AHFMR). Drs Hemmelgarn, Manns, and Tonelli were also supported by awards from the Canadian Institutes of Health Research. Drs Hemmelgarn, Manns, Klarenbach, and Tonelli were supported by a joint initiative between Alberta Health and Wellness and the Universities of Alberta and Calgary. Dr James was supported by a KRESCENT and AHFMR Fellowship. This work was supported by a grant from the AHFMR Interdisciplinary Team Grants Program to Drs Hemmelgarn, Manns, and Tonelli.

Role of the Sponsor: The funding organizations had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Online-Only Material: eTables 1, 2, and 3 and eFigures 1 and 2 are available at <http://www.jama.com>.

REFERENCES

1. K/DOQI clinical practice guidelines for chronic kidney disease. *Am J Kidney Dis*. 2002;39(2 suppl 1):S1-S266.
2. Hsu CY, Chertow GM. Chronic renal confusion. *Am J Kidney Dis*. 2000;36(2):415-418.
3. Hillege HL, Fidler V, Diercks GF, et al; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation*. 2002;106(14):1777-1782.
4. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation*. 2004;110(1):32-35.
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril. *Ann Intern Med*. 2001;134(8):629-636.
6. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.
7. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening. *Kidney Int*. 2002;61(6):2165-2175.
8. Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. *BMC Nephrol*. 2009;10:30.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine. *Ann Intern Med*. 1999;130(6):461-470.
10. Ethnocultural portrait of Canada highlight tables, 2006 census. Statistics Canada. <http://www12.statcan.ca/english/census06/data/highlights/ethnic/index.cfm?Lang=E>. Accessed June 15, 2009.
11. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.
12. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? *Ann Clin Biochem*. 2009;46(pt 3):205-217.
13. Sin DD, Svenson LW, Cowie RL, Man SF. Can universal access to health care eliminate health inequities between children of poor and nonpoor families? *Chest*. 2003;124(1):51-56.
14. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario. *Diabetes Care*. 2002;25(3):512-516.
15. Quan H, Khan N, Hemmelgarn BR, et al; Hypertension Outcome and Surveillance Team of the Canadian Hypertension Education Programs. Validation of a case definition to define hypertension using administrative data. *Hypertension*. 2009;54(6):1423-1428.
16. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
17. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144(2):290-296.
18. Manns BJ, Mortis GP, Taub KJ, McLaughlin K, Donaldson C, Ghali WA. The Southern Alberta Renal Program database. *Clin Invest Med*. 2001;24(4):164-170.
19. Premium assistance program: premium subsidy. Alberta Health and Wellness. <http://www.health.alberta.ca/AHCIP/premium-subsidy.html>. Accessed May 2, 2008.
20. Altman D. *Practical Statistics for Medical Research (Statistics Texts)*. New York, NY: Chapman & Hall/CRC; 1990.
21. 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.
22. Chen ML, Hsu CY. Should the K/DOQI definition of chronic kidney disease be changed? *Am J Kidney Dis*. 2003;42(4):623-625.
23. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
24. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med*. 2005;352(20):2049-2060.
25. Ciavarella A, Silletti A, Forlani G, et al. A screening test for microalbuminuria in type 1 (insulin-dependent) diabetes. *Diabetes Res Clin Pract*. 1989;7(4):307-312.
26. Hossain MP, Goyder EC, Rigby JE, El Nahas M. CKD and poverty. *Am J Kidney Dis*. 2009;53(1):166-174.
27. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults. *BMJ*. 1993;306(6876):481-483.
28. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury. *Am J Kidney Dis*. 2009;53(6):961-973.