

Associations among Estimated Glomerular Filtration Rate, Proteinuria, and Adverse Cardiovascular Outcomes

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Summary

Background and objectives Most studies of chronic kidney disease (CKD) and outcomes focus on mortality and ESRD, with limited data on other adverse outcomes. This study examined the associations among proteinuria, eGFR, and adverse cardiovascular (CV) events.

Design, setting, participants, & measurements This was a population-based longitudinal study with patients identified from province-wide laboratory data from Alberta, Canada, between 2002 and 2007. Selected for this study from a total of 1,526,437 patients were 920,985 (60.3%) patients with at least one urine dipstick measurement and 102,701 patients (6.7%) with at least one albumin-creatinine ratio (ACR) measurement. Time to hospitalization was considered for one of four indications: congestive heart failure (CHF), coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), peripheral vascular disease (PVD), and stroke/transient ischemic attacks [TIAs] (cerebrovascular accident [CVA]/TIA).

Results After a median follow-up of 35 months, in fully adjusted models and compared with patients with estimated GFR (eGFR) of 45 to 59 ml/min per 1.73 m² and no proteinuria, patients with heavy proteinuria by dipstick and eGFR \geq 60 ml/min per 1.73 m² had higher rates of CABG/PCI and CVA/TIA. Similar results were obtained in patients with proteinuria measured by ACR.

Conclusions Risks of major CV events at a given level of eGFR increased with higher levels of proteinuria. The findings extend current data on risk of mortality and ESRD. Measurement of proteinuria is of incremental prognostic benefit at every level of eGFR. The data support use of proteinuria measurement with eGFR for definition and risk stratification in CKD.

Clin J Am Soc Nephrol 6: 1418–1426, 2011. doi: 10.2215/CJN.09741110

Introduction

The increasing prevalence of chronic kidney disease (CKD) and its associated cardiovascular (CV) morbidity and mortality are putting a considerable burden on healthcare systems around the world (1–4). Even a mild reduction in estimated glomerular filtration rate (eGFR) is associated with adverse clinical outcomes (5,6), as is increased urinary protein excretion. Among subjects with normal kidney function, proteinuria is associated in a continuous fashion with an increased risk of these outcomes, which is further amplified in the setting of reduced eGFR (7–10).

Multiple studies have demonstrated an association between eGFR or increased urine protein excretion and adverse CKD outcomes in subjects at a high CV risk (11–16) and in the general population (4–9,17–21). However, these studies typically used a single measure of CKD (proteinuria or eGFR) and many focused on mortality or renal outcomes. Of studies

that do consider CV outcomes, many have used a composite CV disease outcome rather than considering the components individually (18). We recently described the relationship between lower eGFR and proteinuria in hospitalization for acute myocardial infarction and all-cause mortality (4). Data describing how proteinuria and eGFR can be used together to predict other adverse outcomes such as hospitalization for heart failure, peripheral vascular disease (PVD), cerebrovascular events, cerebrovascular events, and coronary revascularization are limited. This information would be potentially useful to inform ongoing discussions about how best to stratify the risk of adverse outcomes among people with CKD (22).

We used a large population-based cohort of patients receiving care in a universal healthcare system to investigate the incremental prognostic value of proteinuria for these CV outcomes as compared with eGFR alone.

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Study Population and Methods

Design, Setting, Population, and Data Sources

We did a population-based cohort study of all adults ≥ 18 years of age who had at least one outpatient serum creatinine measurement performed as a result of usual clinical care in the province of Alberta, Canada, during the study period (May 1, 2002 to December 31, 2006 for seven of the nine geographically based provincial health regions, and between July 1, 2003 and January 1, 2005 and December 31, 2006, respectively, for the other two regions) (23). Patients were excluded if they were treated with dialysis or a kidney transplant at baseline (23). To be eligible for inclusion, patients also had to have had at least one outpatient measure of proteinuria, as described below.

Assessment of Kidney Function, Proteinuria, and Albuminuria

The eGFR for each patient was estimated using the four-variable Modifications of Diet in Renal Disease (MDRD) study equation (24). Although data on race were not available, misclassification of eGFR was expected to be minimal because $< 1\%$ of the Alberta population is black (24). 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. For patients with more than one measurement of serum creatinine, the date of the last measurement in the 6-month period was used as the index date. Index eGFR was categorized as ≥ 60 , 45 to 59.9, 30 to 44.9 and 15 to 29.9 ml/min per 1.73 m^2 . Because of inaccuracies in assessment of kidney function using the MDRD study equation at higher levels of kidney function, and to permit comparisons with similar studies, we categorized patients with higher levels of function into one category (eGFR ≥ 60 ml/min per 1.73 m^2).

Assessment of proteinuria was by use of urine dipstick and albumin-creatinine ratio (ACR) on the basis of outpatient random spot urine measurements. Dipstick proteinuria was assessed using a standard urinalysis procedure (Chemstrip 10 UA, Roche Diagnostics US or similar). In the primary analysis we included all patients with at least one urine dipstick measurement and defined proteinuria as normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick $\geq 2+$) (25). In sensitivity analyses, we considered an alternate definition of proteinuria that was based on ACR and defined as normal (ACR < 30 mg/g), mild (ACR 30 to 300 mg/g), or heavy (ACR > 300 mg/g) (25). For dipstick proteinuria and ACR, we performed additional analyses that subdivided the heavy proteinuria category into heavy (dipstick 2+; ACR 300 to 2000 mg/g) and nephrotic (dipstick $\geq 3+$; ACR > 2000 mg/g) categories.

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 as an ordinal variable according to these three categories, with the median of all respective measurements selected for each patient with multiple measurements, whereas the median of ACR measurements in continuous variables were categorized into ordinal variables for analysis.

Sociodemographic and Clinical Variables

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 $> 85\%$ of the Alberta population is Caucasian (26). Socioeconomic status was categorized as high income (annual adjusted taxable family income $\geq \$39,250$ Canadian dollars [CAD]), low income (annual adjusted taxable family income $< \$39,250$ CAD), and low income with subsidy (receiving social assistance) on the basis of government records (27,28). Diabetes mellitus and hypertension were identified from hospital discharge records and physician claims on the basis of validated algorithms (29,30). Other comorbid conditions were identified using validated *International Classification of Disease (ICD), Ninth Revision, Clinical Modification* and *ICD, Tenth Revision* coding algorithms applied to physician claims and hospitalization data (31). The presence of one or more diagnostic codes in any position up to 3 years before cohort entry was used for identification of comorbidities.

Evaluation of Study Outcomes

We considered time to first hospitalization for one of four indications, with each patient only allowed to contribute to one event (the first outcome for each patient): (1) congestive heart failure (CHF), (2) coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), (3) PVD, and (4) stroke/transient ischemic attacks (cerebrovascular accident [CVA]/TIA) defined using algorithms from medical claims data and ICD Tenth Revision codes (Supplemental Material). Participants were followed from their index date until study end (March 31, 2007).

Statistical Analyses

Poisson regression was used to evaluate the associations among proteinuria, eGFR, 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. For each outcome of interest, the first hospitalization episode was used in the analysis.

We calculated crude (unadjusted) and fully adjusted rates of first hospitalization for each of the outcomes (PVD, CABG/PCI, CHF, and CVA/TIA) by level of GFR and proteinuria. We separately considered urine dipstick and ACR to classify proteinuria. We did statistical adjustment for the sociodemographic variables and comorbidities listed in Table 1 and the two-way interactions of proteinuria and eGFR.

The primary analysis was based on the cohort of participants who had data for proteinuria available from dipstick urinalysis. In sensitivity analyses, we repeated statistical models for the subset of participants who had data for proteinuria on the basis of urinary ACRs. 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

Table 1. Demographic and clinical characteristics of participants by level of kidney function or proteinuria

Characteristics	Primary Analysis (n = 920,985)						Sensitivity Analysis (n = 102,701)					
	eGFR (ml/min per 1.73 m ²) ^a						Proteinuria Measured by Dipstick					
	≥60	45 to 59.9	30 to 44.9	15 to 29.9	None	Mild	Heavy	None	Mild	Heavy		
n	820,571	79,845	16,713	3856	836,550	71,557	12,878	77,280	20,217	5204		
Age ^b	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	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		
PVD	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												
low	16	38	60	60	18	25	33	24	34	36		
low with subsidy	2	2	2	3	2	4	4	3	3	5		

Data expressed as percentage. Totals do not always add to 100% because of rounding. Socioeconomic status was categorized as high (annual adjusted taxable family income ≥\$39,250 CAD), low (annual adjusted taxable family income <\$39,250 CAD), and low with subsidy (receiving social assistance) on the basis of Alberta government records. COPD, chronic obstructive pulmonary disease; Diabetes-C, diabetes with end-organ damage; Diabetes-NC, diabetes without end-organ damage; eGFR, estimated GFR; PVD, peripheral vascular disease; CHF, congestive heart failure; ACR, albumin-creatinine ratio

^aAmong patients with proteinuria measured by dipstick.

^bData expressed as mean (SD).

trend in dipstick proteinuria was defined by values of 1, 2, and 3 for normal, mild, and heavy proteinuria, respectively. We also repeated analyses for all outcomes stratifying on the presence/absence of diabetes and hypertension. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC) and STATA version 10.1 (STATA Corporation, College Station, TX). A *P* value of < 0.05 was used to indicate statistical significance. The institutional review boards of the Universities of Calgary and Alberta approved the study and granted waiver of patient consent.

Results

General Characteristics

A total of 1,530,447 patients had at least one outpatient serum creatinine measurement during the study period. We excluded all patients (*n* = 3728) with ESRD (on renal replacement therapy or eGFR < 15 ml/min per 1.73 m²) and 282 patients who died or reached end of follow-up on their index date. Of the remaining 1,526,437 patients, 920,985 (60.3%) had at least one urine dipstick measurement and 102,701 (6.7%) had at least one ACR measurement. Characteristics of the patients by level of eGFR and proteinuria are shown in Table 1.

A total of 102,701 patients had at least one urinary ACR measurement performed. Patients in this subset were older (57.0 ± 15.0 years *versus* 48.0 ± 16.6 years) and more likely to be male (54.5% *versus* 43.4%) or diabetic (54.1% *versus* 3.4%) than those without such measurements (all *P* < 0.001; χ^2 test and *t* test for categorical and continuous variables, respectively). A higher proportion of patients in this subset had mild (19.7% *versus* 7.3%) or heavy proteinuria (5.1% *versus* 1.1%) than in those without measurements of urinary ACR (both *P* < 0.001; χ^2 test).

Follow-Up and Outcomes

During a median follow-up of 35 months (interquartile range: 22 to 44 months), 1891 of patients (0.2%) were hospitalized at least once for PVD, 7309 (0.8%) for CABG/PCI, 4265 (0.5%) for CHF, and 4692 (0.5%) for a cerebrovascular event (CVA/TIA).

Likelihood of Clinical Outcomes by Level of eGFR and Proteinuria

Within each stratum of eGFR, there was substantial variability in risk, with patients who had heavier proteinuria by dipstick having markedly increased adjusted rates of all of the adverse outcomes. Of note, the adjusted rate of hospitalization for CHF, PVD, and CVA/TIA increased with lower eGFR and heavier proteinuria. In contrast, the rate of revascularization procedures (CABG/PCI) increased with heavier proteinuria, but it tended to decline with lower eGFR (Table 2).

Sensitivity Analyses

Results were consistent when analyses were restricted to the subset of 102,701 patients who had urinary ACR measurements performed (Table 3). Specifically, rate increased progressively at levels of eGFR below 60 ml/min per 1.73 m² and with mild or heavy proteinuria within all eGFR strata for all study outcomes except for revascularization

procedures (CABG/PCI) in the fully adjusted analysis (Table 3). Results were similar when stratified on diabetes or on hypertension (separately).

Results were also consistent when the heavy proteinuria category was subdivided to separately present results for dipstick cohort patients with the heaviest proteinuria (dipstick ≥ 3+). Compared with those without significant proteinuria, patients with heaviest proteinuria (dipstick ≥ 3+) had markedly elevated rates of all four CV outcomes. In fact, rates of CABG/PCI, CHF, and CVA/TIA were all substantially higher among those with eGFR ≥ 60 and the heaviest proteinuria (dipstick ≥ 3+) than in those with eGFR 45 to 59.9 ml/min per 1.73 m² but no proteinuria (adjusted relative rates for dipstick cohort 1.4 [95% confidence interval {CI} 1.0 to 2.0], 3.8 [95% CI 2.9 to 5.1], and 3.8 [95% CI 2.8 to 5.1], respectively), although the increased risk of PVD was not statistically significant (1.4 [95% CI 0.7 to 3.0]). Results were similar when ACR > 2000 mg/g was used to define nephritic-range proteinuria in the ACR cohort (adjusted relative rates for eGFR ≥ 60 ml/min per 1.73 m² and nephritic-range proteinuria *versus* eGFR 45 to 59.9 ml/min per 1.73 m² but no proteinuria in ACR cohort: CABG/PCI 1.8 [95% CI 1.0 to 3.0], CHF 5.2 [95% CI 3.3 to 8.3], and CVA/TIA 3.2 [95% CI 1.7 to 6.2], respectively).

We performed three other sensitivity analyses, all of which confirmed that the rate of adverse outcomes increased at higher levels of proteinuria. First, we repeated analyses among the subgroup of participants who had only a single measurement of proteinuria. Second, analyses were repeated after excluding subjects with a prior history of the outcome of interest. Third, analyses were repeated after excluding subjects who were hospitalized for any reason within 3 months preceding the index date (all *P* for trend < 0.001).

Discussion

Our study examined the joint association among eGFR, proteinuria, and a range of clinically relevant CV events. We showed that proteinuria was independently associated with several different CV events at all levels of eGFR, and that considering information on proteinuria provided additional prognostic information for people with higher and lower levels of eGFR. These results were consistent for all four clinical outcomes studied, including hospitalization for PVD, coronary revascularization, heart failure, or cerebrovascular events. Thus, the presence or absence of proteinuria in all stages of CKD is potentially useful for refining estimates of risk that are based on eGFR alone. The rate of hospitalization for CHF, PVD, and CVA/TIA increased with lower eGFR and heavier proteinuria. In contrast, although the rate of revascularization procedures (CABG/PCI) increased with heavier proteinuria, it was lower among those with lower eGFR, perhaps because of concern about compromising renal function as a consequence of coronary revascularization.

Many prior studies have found an association between adverse clinical outcomes and kidney dysfunction (4–9,17–20), and several have shown an association between increased urinary protein excretion and the risk of death or CV events (9,17,32,33). Despite this, data on how proteinuria and eGFR can be used together to predict the risk of

Table 2. Adjusted rates of clinical outcomes per 1000 person-years by level of eGFR and proteinuria measured by dipstick

eGFR (ml/min per 1.73 m ²)	Outcome	PVD			PCI or CABG			CHF			CVA/TIA						
		Normal Proteinuria	Mild Proteinuria	Heavy Proteinuria	Overall	Normal Proteinuria	Mild Proteinuria	Heavy Proteinuria	Overall	Normal Proteinuria	Mild Proteinuria	Heavy Proteinuria	Overall				
≥60	Events (n)	973	159	21	1153	4745	587	131	5463	1253	404	136	1793	2313	374	105	2792
	People in cell (n)	754,158	58,400	8013	820,571	754,158	58,400	8013	820,571	754,158	58,400	8013	820,571	754,158	58,400	8013	820,571
	Adjusted rate 95% CI	0.21 to 0.25	0.27 to 0.39	0.17 to 0.41	0.21 to 0.25	1.3 to 1.4	1.6 to 1.7	1.6 to 2.3	1.3 to 1.4	1.3 to 1.4	0.20 to 0.24	0.46 to 0.59	0.69 to 1.00	0.23 to 0.27	0.55 to 0.62	0.77 to 0.96	1.2 to 1.8
45 to 59.9	Events (n)	366	77	25	468	1116	191	67	1374	841	266	130	1237	933	211	75	1219
	People in cell (n)	68,768	8783	2294	79,845	68,768	8783	2294	79,845	68,768	8783	2294	79,845	68,768	8783	2294	79,845
	Adjusted rate 95% CI	0.23 to 0.31	0.23 to 0.38	0.26 to 0.59	0.23 to 0.31	1.3 to 1.5	1.2 to 1.6	1.3 to 2.2	1.3 to 1.5	0.29 to 0.36	0.42 to 0.58	0.78 to 1.15	0.30 to 0.37	0.62 to 0.74	0.76 to 1.04	1.1 to 1.7	0.64 to 0.76
30 to 44.9	Events (n)	132	50	22	204	254	88	52	394	507	202	152	861	331	139	77	547
	People in cell (n)	11,823	3296	1594	16,713	11,823	3296	1594	16,713	11,823	3296	1594	16,713	11,823	3296	1594	16,713
	Adjusted rate 95% CI	0.22 to 0.34	0.25 to 0.45	0.24 to 0.58	0.24 to 0.35	1.1 to 1.4	1.1 to 1.7	1.3 to 2.2	1.2 to 1.5	0.39 to 0.51	0.45 to 0.63	0.83 to 1.21	0.39 to 0.50	0.64 to 0.83	0.89 to 1.31	1.2 to 1.9	0.72 to 0.92
15 to 29.9	Events (n)	21	21	24	66	27	16	35	78	180	109	85	374	60	37	37	134
	People in cell (n)	1801	1078	977	3856	1801	1078	977	3856	1801	1078	977	3856	1801	1078	977	3856
	Adjusted rate 95% CI	0.15 to 0.38	0.26 to 0.64	0.43 to 1.02	0.26 to 0.48	0.6 to 1.3	0.5 to 1.4	1.6 to 3.2	0.9 to 1.5	0.53 to 0.77	0.66 to 1.03	0.67 to 1.10	0.52 to 0.71	0.63 to 1.08	0.72 to 1.42	1.0 to 2.1	0.74 to 1.10

Adjusted for age; gender; diabetes; hypertension; socioeconomic status; and history of cancer, cerebrovascular disease, CHF, chronic 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, PVD, renal disease, or rheumatic disease. In this analysis, dipstick urinalysis was used to classify participants with respect to proteinuria as normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick ≥2+). Adjusted rate is given per 1000 patient-years. *n* = 920,985. The tests for linear trend across proteinuria categories were all significant at the *P* < 0.001 level. Tests for trend across eGFR categories were PVD, *P* = 0.01; PCI or CABG, *P* = 0.81; CHF, *P* < 0.001; and CVA/TIA, *P* < 0.001. CI, confidence interval; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Table 3. Adjusted rates of clinical outcomes per 1000 person-years in strata defined by eGFR and urinary ACR

eGFR (ml/min per 1.73 m ²)	Outcome	PVD			PCI or CABG			CHF			CVA/TIA			
		Normal ACR	Mild ACR	Heavy ACR	Normal ACR	Mild ACR	Heavy ACR	Normal ACR	Mild ACR	Heavy ACR	Normal ACR	Mild ACR	Heavy ACR	
≥60	Events (n)	131	49	12	365	98	1559	281	238	110	629	405	187	63
	People in cell (n)	64,146	14,597	2805	14,597	2805	81,548	64,146	14,597	2805	81,548	64,146	14,597	2805
	Adjusted rate	0.5	0.6	0.8	6.1	8.2	5.3	1.1	2.6	5.5	1.5	1.8	2.7	4.7
45 to 59.9	95% CI	0.4 to 0.6	0.4 to 0.8	0.4 to 1.4	5.5 to 6.8	6.7 to 10.0	5.0 to 5.6	0.9 to 1.2	2.2 to 3.0	4.4 to 6.7	1.4 to 1.7	1.6 to 2.0	2.3 to 3.2	3.6 to 6.1
	Events (n)	62	26	12	117	56	451	174	186	88	448	149	105	48
	People in cell (n)	10,316	3520	1126	10,316	1126	14,962	10,316	3520	1126	14,962	10,316	3520	1126
30 to 44.9	Adjusted rate	0.7	0.7	1.0	6.0	9.0	5.9	1.6	3.6	5.8	2.2	1.9	3.2	5.1
	95% CI	0.5 to 0.9	0.4 to 1.1	0.6 to 1.9	4.9 to 7.2	6.9 to 11.8	5.3 to 6.5	1.3 to 1.9	3.0 to 4.4	4.6 to 7.3	1.9 to 2.6	1.6 to 2.3	2.6 to 4.0	3.7 to 6.9
	Events (n)	25	23	7	57	35	178	105	128	97	330	76	50	33
15 to 29.9	People in cell (n)	2474	1624	837	1624	837	4935	2474	1624	837	4935	2474	1624	837
	Adjusted rate	0.8	1.0	0.7	6.4	7.5	6.5	2.4	4.1	6.9	3.1	2.9	2.8	4.1
	95% CI	0.5 to 1.2	0.6 to 1.7	0.3 to 1.5	4.8 to 8.4	5.4 to 10.7	5.6 to 7.8	2.0 to 3.1	3.3 to 5.0	5.5 to 8.8	2.6 to 3.6	2.2 to 3.7	2.0 to 3.8	2.8 to 5.9
Overall	Events (n)	3	8	9	8	13	30	37	62	49	148	9	16	41
	People in cell (n)	344	476	436	476	436	1256	344	476	436	1256	344	476	436
	Adjusted rate	0.6	1.4	2.4	3.6	6.1	4.8	4.8	6.5	6.2	4.6	2.5	3.3	3.9
95% CI	0.2 to 2.0	0.7 to 3.1	1.2 to 4.9	1.8 to 7.2	3.5 to 10.7	3.3 to 7.0	3.4 to 6.8	4.8 to 8.7	4.5 to 8.6	3.7 to 5.7	1.2 to 4.8	1.9 to 5.5	2.3 to 6.7	2.0 to 4.1

Adjusted for age; gender; diabetes; hypertension; socioeconomic status; and history of cancer, cerebrovascular disease, CHF, chronic 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, PVD, renal disease, or rheumatic disease. In this analysis, only urinary ACR was used to classify participants with respect to proteinuria: normal (ACR < 30 mg/g), mild (ACR 30 to 300 mg/g), or heavy (ACR > 300 mg/g). n = 102,701. The tests for linear trend across proteinuria categories were all significant at the P < 0.001 level except for PVD (P = 0.15). Tests for trend across eGFR categories were PVD, P = 0.01; CHF, P = 0.01; PCI or CABG, P = 0.01; CVA/TIA, P < 0.007.

CV events are relatively sparse. Most prior studies have been done in populations with known CV disease or CV disease risk factors, evaluated the link between kidney function and mortality rather than CV events, have not reported data on eGFR and proteinuria, or have reported the independent risk of one measure (eGFR or proteinuria) while controlling for the other. Still other studies have considered a composite of multiple CV disease outcomes rather than the individual components (18), which is potentially problematic because common events such as hospitalization for CHF could have obscured the nature of true associations with less common events such as CVA/TIA or PVD and may not distinguish between adverse events and hospitalization for a potentially beneficial intervention.

For example, a pooled analysis of four large, community-based studies—the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, and the Framingham Offspring Study (34)—did not find eGFR alone to be independently associated with coronary events and stroke (perhaps because of insufficient statistical power and relatively younger population than our own cohort), although eGFR was associated with the primary composite endpoint of CV events and mortality (34).

Similarly, a recent meta-analysis of 14 studies comprising 105,872 subjects found that low eGFR and increasing levels of albuminuria were independently associated with all-cause and CV mortality, but it did not report on the risk of individual CV outcomes (5). The large sample size of the study presented here allowed us to extend these findings to other clinically relevant outcomes, including CVA/TIA, coronary revascularization, heart failure, and PVD.

It is not fully clear how concomitant proteinuria and low eGFR mediate increased CV risk, but several possibilities exist. First, proteinuria and low kidney function often coexist with other CV risk factors (2,3). Although we adjusted for several potential CV risk factors, we cannot exclude the possibility of residual confounding. Second, rather than being causally linked to CV disease themselves, proteinuria and low eGFR may be markers of endothelial dysfunction, inflammation, severity of vascular disease, and subclinical atherosclerosis (19,34–36). Finally, CKD patients with proteinuria and low eGFR may have worse CV outcomes than those with either parameter alone.

Our study has several strengths, including its large size, community-based design, rigorous statistical methods, and information on four clinically relevant CV outcomes. In addition, we had access to data on two widely used measurements of urinary protein excretion (dipstick proteinuria and ACR), which increases the generalizability of our findings. Our study also has limitations that should be considered when interpreting results. First, this was an observational study of a predominantly Caucasian population. Whether our results apply to other countries or settings will require additional study. Moreover, we cannot exclude the possibility of false-positive/negative outcomes given the known imprecision associated with single urine specimens (37). However, results were similar when ACR was used, and ACR has been shown to reliably reflect albuminuria in population-based studies (37,38). Furthermore, we included multiple measures of urine protein over

a 6-month period before and after the index date to increase precision, and although we have excluded proteinuria measurements associated with hospitalizations, we cannot eliminate the possibility of the confounding among several measurements, comorbidities, and worst outcomes in this study. However, when analyses were restricted to the subset with a single baseline measurement the results were similar. Specifically, the risk of all four adverse outcomes remained significantly higher in those with greater baseline proteinuria.

Although we did not calibrate the GFR assay against the reference laboratory assay used to develop the MDRD equation, this is unlikely to have affected our conclusion that the presence and severity of proteinuria substantially modify the risk associated with a given level of eGFR. Additionally, we restricted our analysis for GFR to the MDRD equation because it is more established and the most widely used equation, although use of other equations is now increasingly being advocated. Other potential limitations include the reported inaccuracies of using diagnostic codes to define diseases and outcomes and our use of a large window period for ascertainment of baseline comorbidities. Moreover, we were limited by the absence of information on the use of medications to treat diabetes or hypertension because only those aged >65 years have publicly funded drug coverage in Alberta. We were therefore unable to adjust for the use of these medications in the analysis.

Furthermore, the optimal method on how best to assess and quantify improvement in risk prediction for CV disease is still controversial. It has been advocated that the use of the receiver-operating characteristic curve should be the main criterion, but others have argued in favor of other measures such as the use of Net Reclassification Improvement and Integrated Discrimination Improvement (39,40). Although we did not perform such analyses in this study, this may be a fruitful potential avenue for future research.

In conclusion, we found that the presence and severity of proteinuria is strongly associated with higher risk of major CV outcomes at higher and lower levels of eGFR. Taken together, our data suggest that proteinuria and eGFR should be used for risk stratification of people with CKD.

Acknowledgments

This work was supported by an interdisciplinary team grant from the Alberta Heritage Foundation for Medical Research (AHFMR). Drs. Hemmelgarn, Tonelli, and Klarenbach were supported by career salary awards from AHFMR. Dr. Tonelli was also supported by a Government of Canada Research Chair in the optimal care of chronic kidney disease. Drs. Hemmelgarn, Klarenbach, Manns, and Tonelli were all supported by a joint initiative between Alberta Health and Wellness and the Universities of Alberta and Calgary. Dr. James was supported by a Shire Biochem-KRESCENT Joint Fellowship and an AHFMR research award. Dr. Bello was supported by the Division of Nephrology, Department of Medicine, University of Alberta. The funding organizations played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript. 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.

Disclosures

Drs. Tonelli 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 National Kidney Foundation–Kidney Disease Outcomes Quality Initiative CKD staging system might be refined, including the potential role of proteinuria.

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Received: November 1, 2010 **Accepted:** February 3, 2011

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Albuminuria and Cardiovascular Risk: Time for a New Direction?," on pages 1235–1237

Supplemental information for this article is available online at www.cjasn.org.

Supplemental Material: ICD-9 and ICD-10 Codes

1. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781.
2. Lee DS, Donovan L, Austin PC, Gong Y, Liu PP, Rouleau JL, Tu JV. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Medical Care*. 2005;43(2):182-188.
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Supplemental Table 1: Cerebrovascular accident/transient ischemic attack (CVA/TIA)

ICD-9-CM Codes	ICD-9-CM Description	ICD-10-CA Codes	ICD-10-CA Description
362.3	Retinal vascular occlusion	H34.1	Central retina artery occlusion
433	Occlusion and stenosis of precerebral arteries	I63	Cerebral infarction
434	Occlusion of cerebral arteries	I64	Stroke, not specified as hemorrhage or infarction
436	Acute, but ill-defined cerebrovascular disease		
431	Intracerebral hemorrhage	I61	Intracerebral hemorrhage
430	Subarachnoid hemorrhage	I60	Subarachnoid hemorrhage
435	Transient cerebral ischemia	G45	Transient cerebral ischemic attacks and related syndromes

Supplemental Table 2: Congestive Heart Failure (CHF)

ICD-9-CM Codes	ICD-9-CM Description	ICD-10-CA Codes	ICD-10-CA Description
428	Heart failure	I50	Heart failure

Supplemental Table 3: Percutaneous coronary intervention (PCI)

ICD-10-CA/CCI Codes	ICD-10-CA/CCI Description
1.IJ.50	Dilation, coronary arteries
1.IJ.57.GQ	Percutaneous transluminal approach
1.IL.35	Pharmacotherapy (local), vessels of heart

Supplemental Table 4: Coronary artery bypass graft surgery (CABG)

ICD-10-CA/CCI Codes	ICD-10-CA/CCI Description
1.IJ.76	Bypass, coronary arteries

Supplemental Table 5: Peripheral vascular disease (PVD)

ICD-10-CA Codes	ICD-10-CA Description
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
I73.1	Thromboangiitis obliterans (Buerger's disease)
I73.8	Other specified peripheral vascular diseases
I73.9	Peripheral vascular disease, unspecified
I77.1	Stricture of artery
I79.0	Aneurysm of aorta in diseases classified elsewhere
I79.2	Peripheral angiopathy in diseases classified elsewhere
K55.1	Chronic vascular disorders of intestine
K55.8	Other vascular disorders of intestine
K55.9	Vascular disorder of intestine, unspecified
Z95.8	Presence of other cardiac and vascular implants and grafts
Z95.9	Presence of cardiac and vascular implant and graft, unspecified