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 m^2 and no proteinuria, patients with heavy proteinuria by dipstick and eGFR $\geq$ 60 ml/min per 1.73 m^2 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.

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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.

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 ≥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 ≥ 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 ≥$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			Proteinuria Measured by ACR		
	≥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

[a]Among patients with proteinuria measured by dipstick.

[b]Data 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 m^2) 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 m^2 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 m^2 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 m^2 and nephritic-range proteinuria *versus* eGFR 45 to 59.9 ml/min per 1.73 m^2 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	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	584,00	8013	820,571
	Adjusted rate	0.22	0.33	0.26	0.23	1.3	1.6	1.9	1.4	0.22	0.52	0.83	0.25	0.58	0.86	1.4	0.61
	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	1.4 to 1.7	1.6 to 2.3	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	0.58 to 0.64
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	0.26	0.29	0.39	0.27	1.4	1.4	1.7	1.4	0.32	0.49	0.94	0.34	0.68	0.88	1.3	0.7
	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	0.28	0.33	0.37	0.29	1.3	1.4	1.7	1.3	0.44	0.53	1.00	0.44	0.73	1.08	1.5	0.82
	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	0.24	0.41	0.66	0.36	0.9	0.9	2.2	1.2	0.64	0.83	0.86	0.61	0.83	1.01	1.5	0.9
	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	Overall	Normal ACR	Mild ACR	Heavy ACR	Overall	Normal ACR	Mild ACR	Heavy ACR	Overall	Normal ACR	Mild ACR	Heavy ACR	Overall
≥60	Events (*n*)	131	49	12	192	1096	365	98	1559	281	238	110	629	405	187	63	655
	People in cell (*n*)	64, 146	14, 597	2805	81, 548	64, 146	14, 597	2805	81, 548	64, 146	14, 597	2805	81, 548	64, 146	14, 597	2805	81, 548
	Adjusted rate	0.5	0.6	0.8	0.5	5.0	6.1	8.2	5.3	1.1	2.6	5.5	1.5	1.8	2.7	4.7	2.1
	95% CI	0.4 to 0.6	0.4 to 0.8	0.4 to 1.4	0.4 to 0.6	4.7 to 5.4	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	1.9 to 2.3
45 to 59.9	Events (*n*)	62	26	12	100	278	117	56	451	174	186	88	448	149	105	48	302
	People in cell (*n*)	10, 316	3520	1126	14, 962	10, 316	3520	1126	14, 962	10, 316	3520	1126	14, 962	10, 316	3520	1126	14, 962
	Adjusted rate	0.7	0.7	1.0	0.7	5.6	6.0	9.0	5.9	1.6	3.6	5.8	2.2	1.9	3.2	5.1	2.4
	95% CI	0.5 to 0.9	0.4 to 1.1	0.6 to 1.9	0.5 to 0.9	4.9 to 6.4	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	2.1 to 2.7
30 to 44.9	Events (*n*)	25	23	7	55	86	57	35	178	105	128	97	330	76	50	33	159
	People in cell (*n*)	2474	1624	837	4935	2474	1624	837	4935	2474	1624	837	4935	2474	1624	837	4935
	Adjusted rate	0.8	1.0	0.7	0.8	6.7	6.4	7.5	6.5	2.4	4.1	6.9	3.1	2.9	2.8	4.1	2.8
	95% CI	0.5 to 1.2	0.6 to 1.7	0.3 to 1.5	0.6 to 1.2	5.4 to 8.4	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	2.3 to 3.4
15 to 29.9	Events (*n*)	3	8	9	20	9	8	13	30	37	62	49	148	9	16	16	41
	People in cell (*n*)	344	476	436	1256	344	476	436	1256	344	476	436	1256	344	476	436	1256
	Adjusted rate	0.6	1.4	2.4	1.4	5.6	3.6	6.1	4.8	4.8	6.5	6.2	4.6	2.5	3.3	3.9	2.9
	95% CI	0.2 to 2.0	0.7 to 3.1	1.2 to 4.9	0.8 to 2.3	2.9 to 10.8	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, $P = 0.01$; PCI or CABG, $P = 0.01$; CHF, $P < 0.001$; and 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.

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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.

References

1. James MT, Hemmelgarn BR, Tonelli M: Early recognition and prevention of chronic kidney disease. *Lancet* 375: 1296–1309, 2010
2. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Chronic kidney disease as a global public health problem: Approaches and initiatives—A position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 72: 247–259, 2007
3. Meguid El Nahas A, Bello AK: Chronic kidney disease: The global challenge. *Lancet* 365: 331–340, 2005
4. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M: Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 303: 423–429, 2010
5. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 375: 2073–2081, 2010
6. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: Chronic kidney disease and mortality risk: A systematic review. *J Am Soc Nephrol* 17: 2034–2047, 2006
7. Grimm RH Jr, Svendsen KH, Kasiske B, Keane WF, Wahi MM: Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Kidney Int Suppl* 63: S10–S14, 1997
8. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108: 2154–2169, 2003
9. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS: Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110: 32–35, 2004
10. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE; PREVEND Study Group: Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Int Med* 249: 519–526, 2001
11. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN: Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 120: 1577–1584, 2009
12. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S, Investigators HS: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421–426, 2001
13. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629–636, 2001
14. Rahman M, Pressel S, Davis B, Nwachuku C, Wright J, Whelton P, Barzilay J, Batuman V, Eckfeldt J, Farber M, Franklin S, Henriquez M, Kopyt N, Louis G, Saklayen M, Stanford C, Walworth C, Ward H, Wiegmann T: Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. *Ann Intern Med* 144: 172–180, 2006
15. Solomon SD, Lin J, Solomon CG, Jablonski KA, Rice MM, Steffes M, Domanski M, Hsia J, Gersh BJ, Arnold JM, Rouleau J, Braunwald E, Pfeffer MA: Prevention of events with ACEII: Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. *Circulation* 116: 2687–2693, 2007
16. Yokoyama H, Oishi M, Kawai K, Sone H; Japan Diabetes Clinical Data Management Study Group: Reduced GFR and microalbuminuria are independently associated with prevalent cardiovascular disease in type 2 diabetes: JDDM study 16. *Diabetic Medicine* 25: 1426–1432, 2008
17. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106: 1777–1782, 2002
18. 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* 351: 1296–1305, 2004
19. Clausen P, Jensen JS, Jensen G, Borch-Johnsen K, Feldt-Rasmussen B: Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation* 103: 1869–1874, 2001
20. Kasiske BL: The kidney in cardiovascular disease. *Ann Intern Med* 134: 707–709, 2001
21. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT, Group PS: Cardiovascular and renal outcome in subjects with K/DOQI stage 1–3 chronic kidney disease: The importance of urinary albumin excretion. *Nephrol Dial Transplant* 23: 3851–3858, 2008
22. KDIGO reaches consensus on CKD staging. Available at: http://www.kdigo.org/news_KDIGO_Consensus_on_CKD_Staging.php. Accessed March 15, 2010
23. Hemmelgarn BR, Clement F, Manns BJ, Klarenbach S, James MT, Ravani P, Pannu N, Ahmed SB, MacRae J, Scott-Douglas N, Jindal K, Quinn R, Culleton BF, Wiebe N, Krause R, Thorlacius L, Tonelli M: Overview of the Alberta Kidney Disease Network. *BMC Nephrol* 10: 30, 2009
24. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
25. Lamb EJ, MacKenzie F, Stevens PE: How should proteinuria be detected and measured? *Ann Clin Biochem* 46: 205–217, 2009
26. Ethnocultural portrait of Canada highlight tables, 2006 Census. Available at: http://www12.statcan.ca/english/census06/data/highlights/ethnic/index. Accessed June 15, 2009
27. Alberta Health and Wellness. Alberta health care insurance plan/premiums and rates. Available at: http://wwwhealthalbertaca/AHCIP/premium-subsidyhtml. Accessed May 2, 2008
28. Sin DD, Svenson LW, Cowie RL, Man SF: Can universal access to health care eliminate health inequities between children of poor and nonpoor families? A case study of childhood asthma in Alberta. *Chest* 124: 51–56, 2003
29. Hux JE, Ivis F, Flintoft V, Bica A: Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 25: 512–516, 2002
30. Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, Hill MD, Ghali WA, McAlister FA: Validation of a case definition to define hypertension using administrative data. *Hypertension* 54: 1423–1428, 2009
31. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding

algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 43: 1130–1139, 2005
32. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: A prospective study. *Am J Med* 109: 1–8, 2000
33. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P: Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE study. *Ann Intern Med* 139: 901–906, 2003
34. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. *J Am Soc Nephrol* 15: 1307–1315, 2004
35. Knight EL, Rimm EB, Pai JK, Rexrode KM, Cannuscio CC, Manson JE, Stampfer MJ, Curhan GC: Kidney dysfunction, inflammation, and coronary events: A prospective study. *J Am Soc Nephrol* 15: 1897–1903, 2004
36. Stuveling EM, Hillege HL, Bakker SJ, Asselbergs FW, de Jong PE, Gans RO, de Zeeuw D: C-reactive protein and microalbuminuria differ in their associations with various domains of vascular disease. *Atherosclerosis* 172: 107–114, 2004
37. Gansevoort RT, Verhave JC, Hillege HL, Burgerhof JG, Bakker SJ, de Zeeuw D, de Jong PE; for the PREVEND Study Group: The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidney Int Suppl* April: S28–S35, 2005
38. Bangstad HJ, Try K, Dahl-Jorgensen K, Hanssen KF: New semiquantitative dipstick test for microalbuminuria. *Diabetes Care* 14: 1094–1097, 1991
39. Cook NR, Ridker PM: Advances in measuring the effect of individual predictors of cardiovascular risk: The role of reclassification measures. *Ann Intern Med* 150: 795–802, 2009
40. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS: Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Stat Med* 27: 157–172; discussion 207–212, 2008

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