ORIGINAL RESEARCH

Albuminuria, Reduced Kidney Function, and the Risk of ST- and non–ST-segment–elevation myocardial infarction

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***Background*—**Chronic kidney disease is a recognized independent risk factor for cardiovascular disease, but whether the risks of ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment–elevation myocardial infarction (NSTEMI) differ in the chronic kidney disease population is unknown.

***Methods and Results*—**Using administrative data from Ontario, Canada, we examined patients ≥66 years of age with an outpatient estimated glomerular filtration rate (eGFR) and albuminuria measure for incident myocardial infarction from 2002 to 2015. Adjusted Fine and Gray subdistribution hazard models accounting for the competing risk of death were used. In 248 438 patients with 1.2 million person-years of follow-up, STEMI, NSTEMI, and death occurred in 1436 (0.58%), 4431 (1.78%), and 30 015 (12.08%) patients, respectively. The highest level of albumin-to-creatinine ratio (>30 mg/mmol) was associated with a 2-fold higher adjusted risk of both STEMI and NSTEMI among patients with eGFR≥60 mL/(min·1.73 m^2) compared to albumin-to-creatinine ratio <3 mg/mmol. The lowest level of eGFR (<30 mL/[min·1.73 m^2]) was not associated with higher STEMI risk but with a 4-fold higher risk of NSTEMI compared to those with eGFR≥60 mL/(min·1.73 m^2). The lowest eGFR (<30 mL/[min·1.73 m^2]) and highest albumin-to-creatinine ratio (>30 mg/mmol) were associated with a greater than 4-fold higher risk of both STEMI and NSTEMI (subdistribution hazard models [95% confidence interval] 4.53 [3.30-6.21] and 4.42 [3.67-5.32], respectively) compared to albumin-to-creatinine ratio <3 mg/mmol and eGFR≥60 mL/(min·1.73 m^2).

***Conclusions*—**Elevations in albuminuria are associated with a higher risk of both NSTEMI and STEMI, regardless of kidney function, whereas reduced kidney function alone is associated with a higher NSTEMI risk. **(*J Am Heart Assoc*. 2018;7:e009995. DOI: 10.1161/JAHA.118.009995.)**

Key Words: chronic kidney disease • competing risks • epidemiology • myocardial infarction • non–ST-segment–elevation acute coronary syndrome • ST-segment–elevation myocardial infarction

Chronic kidney disease (CKD), defined by declines in the estimated glomerular filtration rate (eGFR) and/or the presence of albuminuria (measured by the albumin-to-creatinine ratio [ACR]), is highly prevalent (12% to 14%) in developed nations and is anticipated to rise over the coming decades.[1-3] Among patients with CKD, cardiovascular disease is the leading cause of death with the adjusted 2-year mortality of patients with acute myocardial infarction (MI) approaching 20%.[4-6]

The CKD population is heterogeneous in that a substantial proportion of patients present with isolated albuminuria, isolated reductions in kidney function, or both.[1] The differential combinations of reductions in eGFR and/or elevations in ACR alter multiple physiological processes and may lead

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Clinical Perspective

What Is New?

- This large, epidemiological study demonstrates that elevations in albuminuria were associated with a higher risk of both non–ST-elevation myocardial infarction (MI) and ST-elevation MI, regardless of kidney function, whereas reduced kidney function alone is associated with a higher non–ST-elevation MI risk.

What Are the Clinical Implications?

- Because patients with chronic kidney disease are at a very high risk of MI, preceding knowledge of a patient's estimated glomerular filtration rate and albuminuria may aid in predicting the risk of an ST-elevation MI versus a non–ST-elevation MI.

individuals to different MI types. Previous studies suggest that elevations in ACR lead to a prothrombotic state, predisposing individuals to ST-segment–elevation myocardial infarction (STEMI), whereas declines in eGFR predispose individuals to vascular calcification and non–ST-segment–elevation myocardial infarction (NSTEMI).

An understanding of the individual and combined contributions of albuminuria and kidney function may aid in accurately determining MI risk. This increased understanding can help clinicians to target appropriate primary preventative therapies for their patients with CKD. Early STEMI identification is of particular importance because the institution and success of reperfusion strategies are time dependent. However, CKD patients with a STEMI are nearly 2-fold more likely to present with atypical features, leading to possible delays in treatments. As a result, the determination of STEMI risk based on eGFR and ACR levels may heighten suspicion and aid in identification of high-risk individuals at a population level. It is well established that albuminuria and eGFR are associated with incident NSTEMI and MI-induced mortality[7-9]; however, considerably less is known regarding the relationship between STEMI and CKD. It remains unclear whether simple, readily available measures of kidney function are similarly predictive of STEMI events. Thus, we set out to determine the association of MI type according to levels of albuminuria and eGFR. We hypothesized that the risk and types (STEMI and NSTEMI) of MI would differ by levels of kidney function.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Setting

We conducted a retrospective cohort study of individuals with an outpatient serum creatinine laboratory measurement and a random urine ACR between April 1, 2002 and March 31, 2013. Our cohort was followed for up to 3 years after the serum creatinine measurement. We used administrative databases held at the Institute for Clinical Evaluative Sciences (ICES) to obtain patient characteristics, laboratory, medication, and outcome data on residents of Ontario, Canada.[10] These data sets were linked using unique encoded identifiers and analyzed at ICES. This study used individual-level deterministic linkage across multiple databases to create our data set. Individuals were deidentified for analytic purposes, so informed consent was waived. The linkage rate for each of these databases was >96%. This study was approved by an institutional review committee at Sunnybrook Health Sciences Centre. The reporting of this study follows the RECORD (Reporting of Studies Conducted Using Observational Routinely Collected Health Data) guidelines for observational studies (Table S1).[11]

Participants

Patients were included in the study if they had a urine ACR measurement and an eGFR measurement within 12 months before the eGFR measurement. The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR.[12] The date of the urine ACR measurement was counted as the index date for study inclusion. Outpatient eGFR measures have previously been validated.[13] Serum creatinine values were corrected for isotope-dilution mass spectrometry harmonization.

Individuals were excluded on the basis of the following criteria: (1) missing age, sex, ICES key number data, or non-Ontario residents (data cleaning); (2) evidence of death on or before the index date; (3) age <66; (4) kidney transplant recipients; (5) evidence of chronic dialysis before index date; (6) history of MI, coronary artery bypass graft surgery, or percutaneous coronary intervention. Patients with age ≤66 were excluded; drug and medication information is captured in Ontario, Canada.

Exposures, Comorbidities, and Outcomes

At baseline, eGFR and ACR were used to categorize kidney function based on the KDIGO (Kidney Disease Improving Global Outcomes) guidelines.[14] Outcomes were examined by combinations of ACR (<3, 3-30, >30 mg/mmol) and eGFR (>60, 45-59, 30-44, <30 mL/[min·1.73 m^2]) level as previous studies reported differential clinical risk based on the 2 combinations. KDIGO eGFR categories 15 to 29 and <15 were collapsed because of the small sample size.

Demographic variables were ascertained at index, including age, sex, income, place of residence, and clinical variables. Income was determined using the neighborhood-level income based on an individual patient's postal code for his or her primary residence. Comorbidities were ascertained in the 5 years before the index date (angina, valve replacement, hypertension, diabetes mellitus, dyslipidemia, stroke or transient ischemic attack, and venous thromboembolism). Healthcare resource utilization was ascertained in the 1 year preceding the index date, including visits to hospitals, emergency departments, nephrologists, and cardiologists. We used the Adjusted Clinical Group scoring system to score comorbidity using The Johns Hopkins ACG System (version 10). The Adjusted Clinical Group is a population/patient case-mix adjustment system that provides a relative measure of the individual's expected consumption of health services.[15] *International Classification of Diseases* Revision *9* (*ICD-9*) and *9-CM* (*ICD-9-CM*) codes are categorized into 32 groups, called ambulatory diagnostic groups, on the basis of clinical similarity, chronicity, likelihood of requiring specialty care, and disability. We also used resource utilization bands to ascertain resources utilization based on their overall disease burden. Medication prescription information was obtained up to 120 days before the index date.[16]

The primary study outcomes were STEMI hospitalization (*ICD-10-CA* codes I21.0-3, R94.30, any diagnosis type) or NSTEMI hospitalization (*ICD-10* codes I21.4, R94.31, any diagnosis type). STEMI and NSTEMI *ICD-10* diagnostic codes have been validated with agreements of 85.2% and 100.0%, respectively, in those ≥65 years of age.[17] If there were multiple eligible outcome events, we recorded only the first. We also examined all-cause mortality defined using the death indicator in the Registered Persons Database.[10] To account for the differences at baseline, we adjusted for demographics (age, sex, income quintile, long-term care status), year of index, comorbid illness (angina, valve replacement, hypertension, diabetes mellitus, dyslipidemia, stroke or transient ischemic attack, atrial fibrillation or flutter, venous thromboembolism), healthcare utilization (number of visits to the hospital, emergency department, a nephrologist, a cardiologist, ambulatory diagnostic groups, and resource utilization bands), and medication usage (β-blockers, antihypertensive agents, statins, antiplatelets, anticoagulants) in our models.

Statistical Methods

Baseline characteristics were estimated across categories of ACR, and differences were calculated using chi-squared (categorical) and Kruskal-Wallis (continuous) tests and are reported as *P*-values. Significance was defined as $P<0.05$. Continuous data are presented as medians (25th, 75th percentiles), and categorical data as frequencies (percentages). We calculated the incidence rates (defined as the number of events per 100 000 person-years of follow-up) of STEMI and NSTEMI by eGFR and ACR categories. We examined the association of ACR and eGFR categories on the first event of STEMI or NSTEMI using the Fine-Gray model to account for the competing event of death.[18] This method allows the handling of multiple potential outcomes and is especially useful in CKD studies, where death is a common competing outcome.[19] We utilized the subdistribution hazard ratio (sHR) which is a regression model for the cumulative incidence function. To examine if eGFR and ACR categories were effect modifiers on the association of STEMI and NSTEMI, additional models incorporating interaction terms were created (eGFR×ACR).[19] All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Population Demographics and Baseline Characteristics

In total, 3 798 652 patients had outpatient laboratory measurement records of serum creatinine and ACR, of whom 248 438 patients were included in the analytic cohort (Figure 1). Roughly one quarter of the study cohort had reduced kidney function (eGFR <60 mL/[min·1.73 m^2]) and elevated albuminuria (≥3 mg/mmol), by 24% and 27%, respectively. The median (25th, 75th percentiles) age was 72±6 years across the entire cohort and was significantly different ($P<0.001$) among ACR categories (Table 1). The majority of the cohort were male (55.0%), but the percentage of women increased with increasing ACR. The proportion of individuals with all comorbidities including angina, hypertension, diabetes mellitus, and dyslipidemia increased across increasing ACR categories. This was also true for filled medication prescriptions for β-blockers, antihypertensive agents, statins, antiplatelet agents, and anticoagulants.

STEMI and NSTEMI Events in Follow-Up

A total of 1436 (0.58%) STEMI and 4431 (1.78%) NSTEMI hospitalizations were observed over 1.1 million total person-years of follow-up. Table 2 and Figures 2 and 3 show the number of events and incidence rates per 100 000 person-years stratified by ACR and eGFR risk categories. Stepwise increases in the incidence rates of STEMI and NSTEMI were observed with higher ACR and lower eGFR categories. The incidence rate of NSTEMI was higher compared to STEMI across all risk categories. Within ACR risk categories, the incidence rates of STEMI and NSTEMI were higher with lower eGFR categories, with the exception of those with an ACR

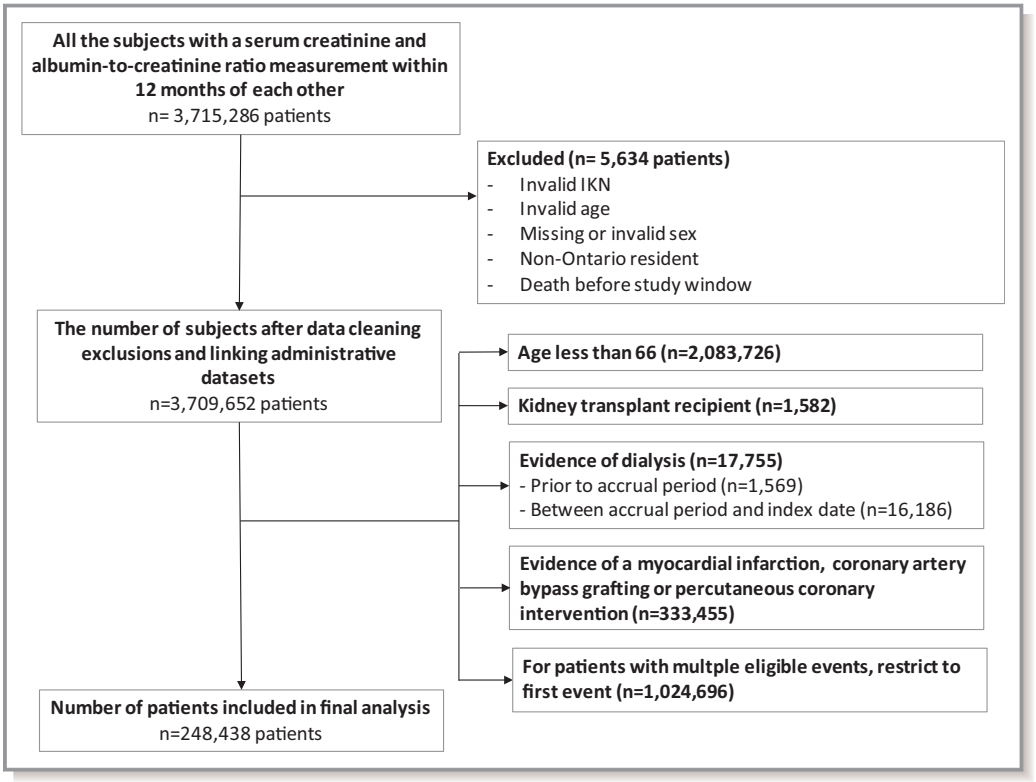

Figure 1. Cohort creation flowchart.

<3 mg/mmol. Within eGFR risk categories, the incidence rates of STEMI and NSTEMI were higher with higher ACR categories, with the exception of those with an eGFR of 45 to 59 mL/(min·1.73 m^2).

Compared with individuals with an ACR <3 mg/mmol and an eGFR ≥60 mL/(min·1.73 m^2), there was an overall trend toward higher relative risks of STEMI and NSTEMI with a higher ACR and a lower eGFR (Table 3). Measures of kidney function were significant effect modifiers for both STEMI and NSTEMI (STEMI eGFR×ACR interaction *P* value 0.01, NSTEMI eGFR×ACR interaction *P*<0.0001). For individuals with an ACR >30 mg/mmol with an eGFR ≥60 mL/(min·1.73 m^2), the adjusted risks of STEMI and NSTEMI were 2- and 2.5-fold higher, respectively, than those in individuals with a low ACR (<3 mg/mmol) with a normal eGFR (STEMI sHR 1.96, 95% confidence interval 1.45-2.66; NSTEMI sHR 2.46, 95% confidence interval 2.08-2.91). Individuals with the lowest eGFR (<30 mL/[min·1.73 m^2]) and the lowest ACR (<3 mg/mmol) had similar STEMI risks to those with a normal eGFR and the lowest ACR. However, individuals with the lowest eGFR and the lowest ACR had a nearly 4-fold higher risk of NSTEMI compared with those having a normal eGFR and lowest ACR. For the combination of lowest eGFR (<30 mL/[min·1.73 m^2]) and highest ACR (>30 mg/mmol), the adjusted risks of STEMI and NSTEMI were 4-fold higher than those in people with an ACR <3 mg/mmol and eGFR <30 mL/(min·1.73 m^2) (STEMI sHR 4.53, 95% confidence interval 3.30-6.21; NSTEMI sHR 4.42, 95% confidence interval 3.67-5.32).

Discussion

In this large population-based study, we found that CKD was independently associated with an increased risk of both STEMI and NSTEMI. An isolated elevation in albuminuria significantly increased the risk of both STEMI and NSTEMI, whereas an isolated decrease in eGFR only increased the risk of NSTEMI. The combination of low kidney function and elevated albuminuria was associated with a greater than 4-fold higher risk of both MI types. Elevations in albuminuria demonstrated a more consistent higher risk of STEMI and may be a valuable and readily available test to improve risk prediction.

Our findings focused on individuals over the age of 66, a cohort traditionally defined as the age of retirement in the US Social Security Act.[20] Our study cohort is highly relevant as the American population is aging, with the proportion of people over the age of 65 predicted to increase from 12% in the year 2000 to 20% by the year 2030.[21] Furthermore, based on Medicare claims data, the prevalence of CKD is high among those of advanced age compared with younger individuals at 10% and 1.5%, respectively.[21,22] This greater burden of CKD among those with advanced age coincides

Table 1. Baseline Characteristics Stratified by Albumin-to-Creatinine Ratio

	Total	Albumin-to-Creatinine Ratio (mg/mmol)			*P* Value
		<3	3 to 30	≥30	
Total, N (%)	248 438	183 522 (74)	53 407 (21)	11 509 (5)	
Age, median (25th, 75th percentiles)	72 (67, 78)	71 (67, 77)	74 (68, 80)	73 (68, 80)	<0.001
Male, N (%)	136 669 (55.0)	103 122 (56.2)	28 226 (52.9)	5321 (46.2)	<0.001
Income quintile, N (%)					
1	48 585 (19.6)	34 419 (18.8)	11 497 (21.5)	2669 (23.2)	<0.001
2	55 150 (22.2)	40 129 (21.9)	12 202 (22.8)	2819 (24.5)	
3	49 990 (20.1)	37 113 (20.2)	10 607 (19.9)	2270 (19.7)	
4	48 108 (19.4)	36 208 (19.7)	9911 (18.6)	1989 (17.3)	
5	45 995 (18.5)	35 238 (19.2)	9035 (16.9)	1722 (15.0)	
Residential status, rural, N (%)	22 608 (9.1)	17 159 (9.3)	4574 (8.6)	875 (7.6)	<0.001
Long-term care resident, N (%)	2497 (1.0)	1281 (0.0)	942 (0.0)	274 (0.0)	<0.001
Estimated glomerular filtration rate, N (%)					
≥60 mL/(min·1.73 m^2)	181 303 (73.0)	142 447 (77.6)	34 085 (63.8)	4771 (41.5)	<0.001
45 to 59 mL/(min·1.73 m^2)	41 247 (16.6)	28 423 (15.5)	10 331 (19.3)	2493 (21.7)	
30 to 44 mL/(min·1.73 m^2)	19 099 (7.7)	10 412 (5.7)	6394 (12.0)	2293 (19.9)	
<30 mL/(min·1.73 m^2)	6789 (2.7)	2240 (1.2)	2597 (4.9)	1952 (17.0)	
Comorbidities					
Angina, N (%)	2248 (0.9%)	1471 (0.8)	625 (1.2)	152 (1.3)	<0.001
Heart valve replacement, N (%)	560 (0.2%)	371 (0.2)	160 (0.3)	29 (0.3)	<0.001
Hypertension, N (%)	192 316 (77.4%)	139 174 (75.8)	43 279 (81.0)	9863 (85.7)	<0.001
Diabetes mellitus, N (%)	128 212 (51.6%)	88 678 (48.3)	31 722 (59.4)	7812 (67.9)	<0.001
Dyslipidemia, N (%)	6057 (2.4%)	3892 (2.1)	1664 (3.10)	501 (4.4)	<0.001
Atrial fibrillation/flutter, N (%)	8023 (3.2)	4480 (2.4)	2821 (5.3)	722 (6.3)	<0.001
Stroke/transient ischemic attack, N (%)	4402 (1.8)	2727 (1.5)	1304 (2.4)	371 (3.2)	<0.001
Venous thromboembolism, N (%)	4180 (1.7)	2899 (1.6)	1031 (1.9)	250 (2.2)	<0.001
Health care utilization					
Hospitalizations, median (25th, 75th percentiles)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	<0.001
Emergency department visits, median (25th, 75th percentiles)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 1)	<0.001
Nephrologist visits, N (%)					
0	231 969 (93.4)	175 806 (95.8)	47 747 (89.4)	8416 (73.1)	<0.001
1 to 3	14 546 (5.9)	7100 (3.9)	4991 (9.3)	2455 (21.3)	
>3	1923 (0.8)	616 (0.3)	669 (1.3)	638 (5.5)	
Cardiologist visits, N (%)					
0	216 181 (87.0)	161 417 (88.0)	45 265 (84.8)	9499 (82.5)	<0.001
1 to 3	27 975 (11.3)	19 452 (10.6)	6885 (12.9)	1638 (14.2)	
>3	4282 (1.7)	2653 (1.4)	1257 (2.4)	372 (3.2)	
Adjusted diagnostic groups, N (%)					
0 to 4	56 323 (22.7)	42 509 (23.0)	11 612 (22.0)	2202 (19.0)	<0.001
5 to 9	122 712 (49.4)	92 277 (50.0)	25 188 (47.0)	5247 (46.0)	
10 to 14	60 043 (24.2)	42 729 (23.0)	14 003 (26)	3311 (29.0)	

Continued

Table 1. Continued

	Total	Albumin-to-Creatinine Ratio (mg/mmol)			*P* Value
		<3	3 to 30	≥30	
15 to 19	9052 (3.6)	5827 (3.0)	2519 (5.0)	706 (6.0)	
20+	308 (0.1)	180 (0.0)	85 (0.0)	43 (0.0)	
Resource utilization bands, N (%)					
0	594 (0.2)	442 (0.0)	126 (0.0)	26 (0.0)	<0.001
1 (low)	1408 (0.6)	1114 (1.0)	253 (1.0)	41 (0.0)	
2	13 459 (5.4)	10 254 (6.0)	2723 (5.0)	482 (4.0)	
3	135 585 (54.6)	103 872 (57.0)	26 650 (50.0)	5063 (44.0)	
4	61 060 (24.6)	44 308 (24.0)	13 693 (26.0)	3059 (27.0)	
5 (high)	36 332 (14.6)	23 532 (13.0)	9962 (19.0)	2838 (25.0)	
Medications					
β-Blockers, N (%)	58 662 (23.6)	39 297 (21.4)	15 379 (28.8)	3986 (34.6)	<0.001
Antihypertensive agents, N (%)	141 912 (57.1)	98 128 (53.5)	35 072 (65.7)	8712 (75.7)	<0.001
Statins, N (%)	115 629 (46.5)	83 626 (45.6)	25 859 (48.4)	6144 (53.4)	<0.001
Antiplatelet agents, N (%)	20 557 (8.3)	13 386 (7.3)	5692 (10.7)	1479 (12.9)	<0.001
Anticoagulants, N (%)	14 195 (5.7)	8302 (4.5)	4756 (8.9)	1137 (9.9)	<0.001

with a high prevalence of traditional risk factors such as diabetes mellitus and hypertension.

Previous studies have clearly demonstrated a higher risk of MI and cardiovascular mortality with low eGFR and/or albuminuria.[7,8,23-25] Hallan et al, examining data from the HUNT II Norwegian health study, found a 6.7-fold higher adjusted cardiovascular mortality risk for individuals with an eGFR <45 mL/(min·1.73 m^2) and high ACR compared to an eGFR >75 mL/(min·1.73 m^2) and a normal ACR.[7] In 920 985 individuals in Alberta, Canada, Hemmelgarn et al reported a stepwise increase in the adjusted MI rate with an increase in ACR, a decrease in eGFR, or a combination of both.[8,26] However, data on MI type, specifically the relationship between STEMI and kidney disease, are limited. A report by the National Cardiovascular Data ACTION Registry identifies MI type by eGFR categories but lacks information on

Table 2. STEMI and NSTEMI Events and Incidence Rate Per 100 000 Person-Years in 5-Year Follow-Up, Stratified by Albumin-to-Creatinine Ratio and eGFR Risk Categories

	Albumin-to-Creatinine Ratio (mg/mmol)					
	<3		3 to 30		>30	
eGFR (mL/[min·1.73 m^2])	N (%)	IR (95% CI)	N (%)	IR (95% CI)	N (%)	IR (95% CI)
STEMI						
≥60	637 (0.4)	0.97 (0.89, 1.05)	228 (0.7)	1.50 (1.31, 1.70)	45 (0.9)	2.18 (1.59, 2.92)
45 to 59	151 (0.5)	1.16 (0.99, 1.37)	89 (0.9)	1.98 (1.59, 2.43)	18 (0.7)	1.71 (1.01, 2.70)
30 to 44	86 (0.8)	1.87 (1.50, 2.31)	53 (0.8)	2.00 (1.50, 2.62)	38 (1.7)	4.16 (2.94, 5.71)
<30	15 (0.7)	1.65 (0.92, 2.72)	28 (1.1)	2.92 (1.94, 4.22)	48 (2.5)	7.00 (5.16, 9.28)
NSTEMI						
≥60	1534 (1.1)	2.33 (2.21, 2.45)	760 (2.2)	4.99 (4.64, 5.36)	151 (3.2)	7.34 (6.21, 8.60)
45 to 59	518 (1.8)	3.99 (3.66, 4.35)	296 (2.9)	6.58 (5.85, 7.37)	119 (4.8)	11.33 (9.38, 13.56)
30 to 44	305 (2.9)	6.65 (5.92, 7.44)	221 (3.5)	8.38 (7.31, 9.56)	131 (5.7)	14.37 (12.01, 17.05)
<30	93 (4.2)	10.27 (8.29, 12.58)	150 (5.8)	15.74 (13.32, 18.47)	153 (7.8)	22.47 (19.05, 26.33)

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; IR, incidence rate; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction.

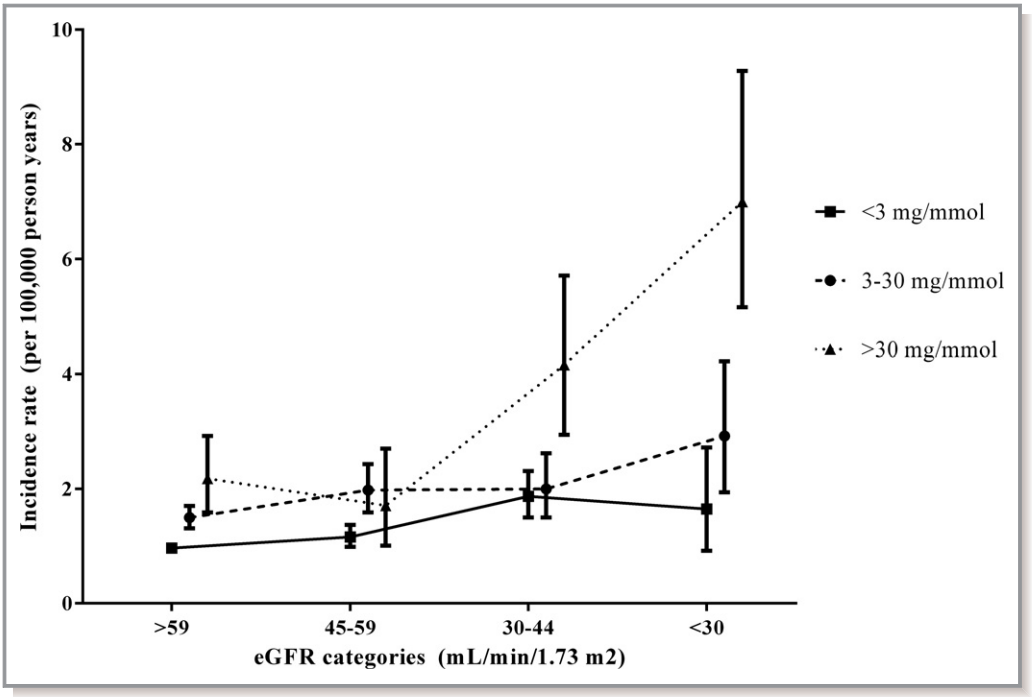

Figure 2. Incidence rate per 100 000 person-years of STEMI by levels of eGFR and ACR. ACR indicates albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; STEMI, ST-segment–elevation myocardial infarction.

albuminuria.[9] Akerblom et al reported an association of an alternative kidney filtration marker (cystatin C) and acute coronary syndrome that did not differ by MI type.[27] However, the study lacked albuminuria data and examined patients with a relatively high median eGFR. Our study clearly identifies the differing risk profile in MI type by a higher ACR, a lower eGFR,

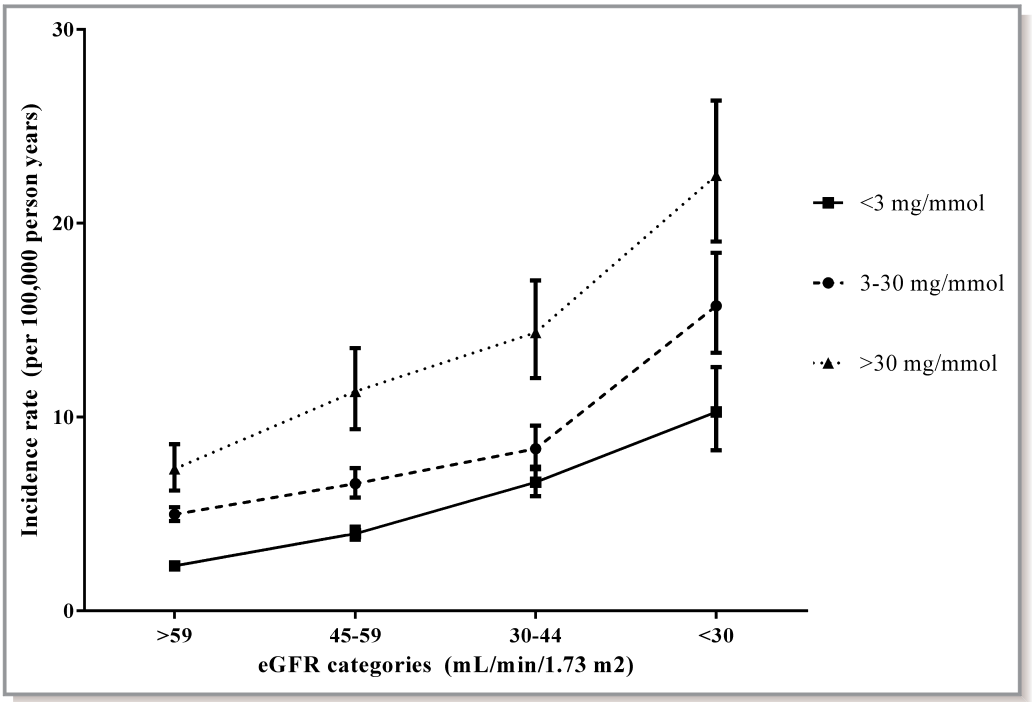

Figure 3. Incidence rate per 100 000 person-years of non–ST-elevation myocardial infarction by levels of estimated glomerular filtration rate and albumin-to-creatinine ratio. eGFR indicates estimated glomerular filtration rate; NSTEMI, non–ST-segment–elevation myocardial infarction.

Table 3. Adjusted Hazard Ratios of STEMI and NSTEMI Stratified by Albumin-to-Creatinine Ratio and eGFR Risk Categories

	Albumin-to-Creatinine Ratio (mg/mmol)		
	<3	3 to 30	>30
eGFR (mL/[min·1.73 m^2])	HR (95% CI)	HR (95% CI)	HR (95% CI)
STEMI			
≥60	Referent	1.40 (1.20-1.63)	1.96 (1.45-2.66)
45 to 59	1.07 (0.89-1.28)	1.57 (1.24-1.97)	1.37 (0.85-2.19)
30 to 44	1.55 (1.22-1.97)	1.43 (1.07-1.92)	2.99 (2.13-4.19)
<30	1.17 (0.69-1.98)	1.88 (1.26-2.79)	4.53 (3.30-6.21)
NSTEMI			
≥60	Referent	1.78 (1.63-1.94)	2.46 (2.08-2.91)
45 to 59	1.33 (1.20-1.48)	1.80 (1.58-2.04)	3.12 (2.58-3.78)
30 to 44	1.83 (1.61-2.09)	1.93 (1.66-2.24)	3.40 (2.82-4.10)
<30	2.12 (1.78-2.76)	3.09 (2.57-3.70)	4.42 (3.67-5.32)

Models adjusted for age, sex, income quintile, residential status, long-term care residence, year of index, hypertension, dyslipidemia, diabetes mellitus, obesity, angina, heart valve replacement, atrial fibrillation or flutter, stroke or transient ischemic attack, venous thromboembolism, hospitalizations, emergency department visits, nephrology visits, cardiology visits, adjusted clinical groups and resource utilization bands, and β-blocker, antihypertensive, statin, antiplatelet, and oral anticoagulant prescription, as defined in baseline characteristics. STEMI: eGFR×ACR interaction P=0.01. NSTEMI: eGFR×ACR interaction P<0.0001. ACR indicates albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, STEMI, ST-segment–elevation myocardial infarction.

and their combination. The elevated risk of STEMI was evident and related to higher albuminuria excretion with no increase in risk with an isolated lower eGFR level.

Mechanistically, the presence of albuminuria or a low eGFR seem to exhibit different effects on vasculature. Coronary artery calcification has been associated with adverse cardiovascular events, and studies have shown that lower levels of eGFR are associated with a greater propensity for vascular calcification.[28,29] The presence of nontraditional risk factors in CKD such as abnormal mineral metabolism, predominantly hyperphosphatemia and hypercalcemia, likely facilitates progression of vascular calcification and subsequent NSTEMI.[6,30] This was illustrated by the nearly 4-fold higher risk of NSTEMI with low levels of eGFR in the absence of albuminuria observed in our study. Conversely, albuminuria has been demonstrated to be an independent risk factor for arterial thromboembolism.[31,32] In 1989, the Steno Hypothesis proposed that proteinuria reflects a generalized dysfunction in vascular endothelium.[33] Since then, studies have shown that factors associating proteinuria with increased cardiovascular risk include vascular endothelial growth factor, inflammation, and thrombotic factors. The pathogenesis of proteinuria related to vascular endothelial growth factor is not clear, but endothelial dysfunction is a potential cause because it is important in the maintenance of endothelial function and endothelial repair after injury.[34,35] Yilmaz et al showed that proteinuria is associated with asymmetric dimethylarginine, an inflammatory biomarker that inhibits nitric oxide production, which results in endothelial dysfunction and atherosclerosis.[36] High-sensitivity C-reactive protein is associated with both a higher global cardiometabolic risk[37] and increasing levels of proteinuria.[38,39] Finally, von Willebrand factor, soluble vascular cell adhesion molecule, fibrinogen, and tissue plasminogen activator are elevated with higher levels of urinary albumin excretion.[40] Last, elevations in albuminuria may arise from 2 distinct but interrelated processes because it is a marker of endothelial dysfunction and/or elevated blood pressure.

Our findings from a large population-level cohort with access to universal healthcare are generalizable and build on previous findings. Using well-validated definitions we were able to capture a large number of STEMI and NSTEMI events, which allowed us to determine the relative risks across multiple eGFR/ACR combinations. Despite these strengths, our study does have limitations. We defined CKD by single outpatient measures of eGFR and ACR, which could lead to a potential misclassification, of acute kidney injury as CKD. However, previous validation studies demonstrate an improved degree of accuracy when utilizing outpatient rather than inpatient serum creatinine measures.[13] We included a large number of clinically important covariates in our models, including medications and healthcare utilization; however, some important potential confounders were unavailable. Certain antiplatelet agents (acetylsalicylic acid) are available without a prescription in Ontario; thus, we may have underestimated its use in our population. However, we adjusted for proxies in our models such as angina and stroke that often are associated with antiplatelet use. We lacked specific information on blood pressure and again used proxies of a previous diagnosis of hypertension or prescription of an

antihypertensive medication in our analysis. There is a potential for misclassification of acute coronary syndrome type, as the outcome definition for STEMI and NSTEMI we used reported misclassification of 7.7% of patients with STEMI as NSTEMI in the original validation study. Albuminuria measures are more commonly performed in patients with diabetes mellitus, which has likely resulted in these patients being oversampled in this study.

In this population-level study, we have shown specifically that isolated albuminuria confers a higher risk of both types of MI (STEMI and NSTEMI), regardless of eGFR, whereas isolated declines in eGFR are associated with a higher risk of NSTEMI. Taken together, our results suggest that albuminuria and eGFR may be helpful in predicting the risk of MI type in individuals, and this may aid clinicians in targeting appropriate therapies and preventative measures.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement[1].

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title page & abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses.		Introduction
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods: Study Design & Setting
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods: Study Design & Setting
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods: Participants Results
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be	Methods: Variables

			provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods: Participants, Variables
Bias	9	Describe any efforts to address potential sources of bias.		Methods: Variables
Study size	10	Explain how the study size was arrived at.		Methods: Participants
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods: Statistical Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods: Statistical Methods
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Methods: Participants
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods: Study Design & Setting
Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders.		Results

		(b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		
Outcome data	15	Report numbers of outcome events or summary measures over time.		Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		Results
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		n/a
Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Acknowledgment

Supplemental Reference:

1. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, Committee RW. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med.* 2015; 12:e1001885.