Association of Proteinuria and Incident Atrial Fibrillation in Patients With Intact and Reduced Kidney Function

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Background—Early evidence suggests proteinuria is independently associated with incident atrial fibrillation (AF). We sought to investigate whether the association of proteinuria with incident AF is altered by kidney function.

Methods and Results—Retrospective cohort study using administrative healthcare databases in Ontario, Canada (2002–2015). A total of 736 666 patients aged ≥40 years not receiving dialysis and with no previous history of AF were included. Proteinuria was defined using the urine albumin-to-creatinine ratio (ACR) and kidney function by the estimated glomerular filtration rate (eGFR). The primary outcome was time to AF. Cox proportional models were used to determine the hazard ratio for AF censored for death, dialysis, kidney transplant, or end of follow-up. Fine and Grey models were used to determine the subdistribution hazard ratio for AF, with death as a competing event. Median follow-up was 6 years and 44 809 patients developed AF. In adjusted models, ACR and eGFR were associated with AF ($P < 0.0001$). The association of proteinuria with AF differed based on kidney function (ACR × eGFR interaction, $P < 0.0001$). Overt proteinuria (ACR, 120 mg/mmol) was associated with greater AF risk in patients with intact (eGFR, 120) versus reduced (eGFR, 30) kidney function (adjusted hazard ratios, 4.5 [95% CI, 4.0–5.1] and 2.6 [95% CI, 2.4–2.8], respectively; referent ACR 0 and eGFR 120). Results were similar in competing risk analyses.

Conclusions—Proteinuria increases the risk of incident AF markedly in patients with intact kidney function compared with those with decreased kidney function. Screening and preventative strategies should consider proteinuria as an independent risk factor for AF. (*J Am Heart Assoc*. 2017;6:e005685. DOI: 10.1161/JAHA.117.005685.)

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Atrial fibrillation (AF) is the most common arrhythmia worldwide and contributes substantially to morbidity and mortality.[1] Despite considerable therapeutic progress

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regarding the treatment of AF and its associated complications, the return and maintenance of normal sinus rhythm following the onset of AF remains a challenge.[2] As such, early detection, prevention, and screening strategies remain the optimal means for AF reduction. At present, there are well-recognized risk factors for the development of AF, with reduced kidney function being one of the more recently identified and strongest predictors.[3–6]

Proteinuria is a urinary marker often indicative of intrinsic kidney disease and is an important risk factor for the progression of chronic kidney disease.[7] Recently, there is increased awareness of its biological role as a marker of endothelial dysfunction, sympathetic activation, and activation of hemostasis.[8–10] As such, proteinuria has been linked to elevations in the risk of coronary artery disease/acute coronary syndromes, strokes, and venous thromboembolism.[8,11,12] There is early evidence that suggests proteinuria is independently associated with new-onset AF.[3,13–15] However, whether the relationship between proteinuria and new-onset AF differs or is altered by kidney function is unclear.

With the ultimate aim of informing screening and preventative strategies, we undertook a large, population-based study to examine the association of proteinuria with incident

Clinical Perspective

What Is New?

- Proteinuria and reduced kidney function both independently increase the risk of incident atrial fibrillation.
- The association of proteinuria with atrial fibrillation differs based on kidney function.
- Proteinuria increases the risk of incident atrial fibrillation to a much greater degree in patients with intact kidney function compared with those with decreased kidney function.

What Are the Clinical Implications?

- Urine albumin-to-creatinine ratio as a measure of proteinuria and estimated glomerular filtration rate calculated from serum creatinine as a measure of kidney function are readily available measurements in the clinical setting.
- These measures could be incorporated into screening and preventative strategies for atrial fibrillation.
- Further studies to elicit the effectiveness of such strategies and the causal mechanisms of our observed associations are required.

AF and whether this relationship differed based on kidney function. We hypothesized that the risk of incident AF would increase in a graded fashion with increasing proteinuria and that kidney function would be an effect modifier of the association of proteinuria with new-onset AF.

Methods

Design and Setting

We conducted a population-based, retrospective cohort study in the province of Ontario, Canada, using healthcare databases housed at the Institute for Clinical Evaluative Sciences. The study was conducted according to a prespecified protocol that was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada). The reporting of this study follows the RECORD guidelines for observational studies (Table S1).[16]

Data Sources

We ascertained patient characteristics, laboratory data, and outcome data from linked databases. Cerner and Gamma-Dynacare databases were used to obtain outpatient laboratory data. Cerner is a hospital laboratory database that serves a network of 11 hospitals in Southwestern Ontario. Gamma-Dynacare is a laboratory service provider that contains outpatient lab information for individuals who had bloodwork drawn at any of their 148 collection sites in Ontario.

Demographics and vital status information were obtained from the Ontario Registered Persons Database. Diagnostic and procedural information from all hospitalizations was determined using the Canadian Institute for Health Information Discharge Abstract Database. Diagnostic information from emergency room visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan database, which contains all health claims for inpatient and outpatient physician services. We identified patients with a history of kidney transplant or dialysis therapies (exclusion criteria) using the Canadian Organ Replacement Register. These data sets were linked using unique encoded identifiers and analyzed at Institute for Clinical Evaluative Sciences. Whenever possible, we defined patient characteristics and outcomes using validated codes (Table S2).

Study Cohort

We included all patients with at least 1 estimated glomerular filtration (eGFR) value and a urine albumin-to-creatinine-ratio (ACR) test performed within 12 months of each other between April 1, 2002 to March 31, 2015. For each patient, the date of the first eligible ACR test was taken as the index date. We excluded patients aged <40 years (because of the small sample size of younger individuals and their low risk of de novo AF), with any history of kidney transplantation, and evidence of dialysis or AF before their index date (Figure S1).

Exposures, Comorbidities, and Outcomes

Proteinuria was determined by urine ACR measurements and kidney function was determined using eGFR. We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate eGFR.[17] We categorized eGFR and urine ACR using thresholds described in the 2012 KDIGO Guidelines (eGFR: >90 [normal kidney function], 60 to <90, 45 to <60, 30 to <45, 15 to <30, and <15 mL/min per 1.73 m^2; urine ACR: <3, 3–30, and >30 mg/mmol).[7] All enrolled patients were followed forward in time from their index date until the first of: evidence of AF identified during a hospitalization or an emergency department visit, receipt of dialysis, kidney transplantation, death, or the end of study follow-up period (March 31, 2015). Hospitalizations with a diagnosis of AF were identified using validated International Classification for Disease, revisions 9 (pre-2002) and 10 codes, in Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System (Table S2).

Demographic and clinical risk factors for AF were ascertained in the 5 years preceding the index date, including hypertension, past cerebrovascular disease, past major hemorrhage, cigarette smoking, alcohol abuse, diabetes mellitus, chronic obstructive

pulmonary disease, peripheral vascular disease, congestive heart failure (CHF), and cardiovascular disease.

Statistical Analysis

To assess differences in baseline characteristics across urine ACR categories, we used the chi-square or Cochrane–Armitage tests for categorical variables, and the 1-way ANOVA or Kruskal–Wallis tests for continuous variables. We calculated the crude incidence rate per 1000 person-years of follow-up for new-onset AF diagnosed within a hospitalization or an emergency room visit by eGFR (>90, 60–90, 45–60, 30–45, 15–30, and <15) and urine ACR (<3, 3–30, and >30) categories. We used time-to-event models (Cox proportional and Fine and Grey models) to examine the association of urine ACR with incident AF and whether eGFR was an effect modifier of the association of urine ACR with incident AF (eGFR × ACR). The proportional hazards assumption was assessed visually using plots of the survival function over time by categories of the exposure of interest. Patients were censored upon death, initiation of dialysis, receipt of a kidney transplant, or end of follow-up. The Fine and Grey models accounted for death as a competing risk. Urine ACR was first examined continuously, then categorically (as previously defined). Multivariate models were adjusted for the following factors: age (per year); sex (male referent); income quintile (highest quintile referent); cerebrovascular disease (stroke/transient ischemic attack); myocardial infarction; coronary artery disease; coronary artery bypass grafting; hypertension; CHF; diabetes mellitus; past hemorrhage; chronic obstructive pulmonary disease; peripheral vascular disease; and year of index date (2002 referent). To examine possible nonlinear associations between urine ACR and the hazard of AF, we fit proportional hazards regression models incorporating restricted cubic splines, with knots located at the 5th, 25th, 50th, 75th, and 95th distributions. To illustrate the ACR × eGFR interaction, plots of the adjusted hazard ratio by continuous urine ACR at fixed levels of eGFR (30, 60, 90, and 120) were performed. Because our focus was on lower levels of proteinuria, and also to eliminate the effect of extreme outliers, the highest ACR values were fixed at the 99th percentile (126.4 mg/mmol; N=7361). In a sensitivity analysis, all ACR values were included. We conducted all analyses with SAS software (version 9.4; SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

Of 736 666 patients who met the inclusion and exclusion criteria (Figure S1), 20.0% (n=147 402) had an ACR ≥3 mg/mmol. Baseline characteristics for patients within each albuminuria grouping are presented in Table 1. Patient characteristics differed substantially across urine ACR categories (*P*<0.0001 across all categories). Compared with patients with an ACR <3 mg/mmol, those with an ACR ≥3 mg/mmol were older (63.4 versus 58.9 years) and more likely to be male (58.8% versus 49.7%). Comorbidities, such as diabetes mellitus (63.9%), hypertension (75.6%), a history of stroke (2.6%), CHF (12.4%), coronary artery disease (24.7%), and peripheral vascular disease (2.3%), were all more prevalent in patients with a higher urine ACR. Patients with a higher urine ACR had a lower baseline eGFR (mean eGFR 85.43 and 65.82 mL/min per 1.73 m^2; ACR <3 mg/mmol and ACR >30 mg/mmol, respectively).

Risk of Incident AF by Proteinuria

A total of 44 809 (6.08%) patients developed incident AF over a median follow-up of 6 (interquartile range, 4–8) years. A total of 53 423 (7.3%) died, 5930 (0.8%) developed kidney failure requiring dialysis or kidney transplantation, and 632 504 (85.9%) were censored at the end of follow-up. Among patients with an ACR <3 mg/mmol, 4.8% (n=28 367) developed AF, compared with 10.7% (n=12 895) and 13.2% (n=3547) among those with an ACR 3 to 30 mg/mmol and >30 mg/mmol, respectively (*P* for trend, <0.001).

The association of proteinuria and kidney function with incident AF was examined treating urine ACR and eGFR as continuous variables. When adjusted for demographics, year of cohort entry, comorbidities, and urine ACR, the hazard of incident AF decreased by 0.4% (95% CI, 0.4–0.5) per each 1 mL/min per 1.73 m^2 increase in eGFR. In an analysis adjusted for demographics, year of cohort entry, comorbidities, and eGFR, the hazard of incident AF increased by 0.6% (95% CI, 0.6–0.7) per each 1 mg/mmol increase in urine ACR (*P*<0.0001). An increased risk of AF was noted as soon as urine ACR increased above 0 mg/mmol (referent). The greatest increase in risk occurred when moving from no albuminuria to microalbuminuria (Figure 1). The interaction term for eGFR and urine ACR was highly significant (*P*<0.0001, multiplicative interaction term), indicating that eGFR significantly modified the association between urine ACR and incident AF (Table 2). The significant interaction between urine ACR and eGFR is further illustrated in Figure 2 and Table 3. The presence of proteinuria had a much larger impact on AF risk among patients with preserved compared with reduced kidney function (adjusted hazard ratio [HR] 4.5, 95% CI 4.0–5.1, eGFR 120, and ACR 120 mg/mmol versus adjusted HR 2.6, 95% CI 2.4–2.8, eGFR 30, and ACR 120 mg/mmol; referent ACR 0 and eGFR 120). Similar results were observed when AF risk was examined across eGFR and urine ACR categories (Table 3), except in the eGFR category of

Table 1. Baseline Characteristics of the Study Cohort

	Total Cohort	ACR (<3 mg/mmol)	ACR (3–30 mg/mmol)	ACR (>30 mg/mmol)	P Value for Trend Across Categories
Total (N)	N=736 666	N=589 264	N=120 565	N=26 837	
Age, y					
Mean (±SD)	59.83±12.24	58.94±11.82	63.41±13.20	63.39±13.28	<0.0001
Age <65	212 261 (28.8%)	160 129 (27.2%)	42 601 (35.3%)	9531 (35.5%)	
Age 65-80	481 212 (65.3%)	402 656 (68.3%)	64 306 (53.3%)	14 250 (53.1%)	
Age >80	43 193 (5.9%)	26 479 (4.5%)	13 658 (11.3%)	3056 (11.4%)	
Sex					<0.0001
Female	365 170 (49.6%)	296 377 (50.3%)	57 732 (47.9%)	11 061 (41.2%)	
Male	371 496 (50.4%)	292 887 (49.7%)	62 833 (52.1%)	15 776 (58.8%)	
eGFR, mL/min per 1.73 m^2					
Mean±SD	83.65±19.93	85.43±18.01	78.96±23.44	65.82±28.82	<0.0001
>90	321 227 (43.6%)	268 849 (45.6%)	45 674 (37.9%)	6704 (25.0%)	
60 to 90	320 998 (43.6%)	264 311 (44.9%)	48 234 (40.0%)	8453 (31.5%)	
45 to <60	58 273 (7.9%)	39 530 (6.7%)	14 448 (12.0%)	4295 (16.0%)	
30 to <45	26 186 (3.6%)	13 646 (2.3%)	8,638 (7.2%)	3,902 (14.5%)	
15 to <30	8760 (1.2%)	2810 (0.5%)	3241 (2.7%)	2709 (10.1%)	
<15	1222 (0.2%)	118 (0.0%)	330 (0.3%)	774 (2.9%)	
Neighborhood income quintile					<0.0001
1 (low)	142 964 (19.4%)	110 161 (18.7%)	26 397 (21.9%)	6406 (23.9%)	
2	156 706 (21.3%)	123 115 (20.9%)	27 233 (22.6%)	6358 (23.7%)	
3	151 298 (20.5%)	121 342 (20.6%)	24 572 (20.4%)	5384 (20.1%)	
4	147 001 (20.0%)	119 761 (20.3%)	22 456 (18.6%)	4784 (17.8%)	
5 (high)	136 961 (18.6%)	113 500 (19.3%)	19 621 (16.3%)	3840 (14.3%)	
Missing	1736 (0.2%)	1385 (0.2%)	286 (0.2%)	65 (0.2%)	
Comorbidities					
Diabetes mellitus	312 112 (42.4%)	227 160 (38.5%)	67 798 (56.2%)	17 154 (63.9%)	<0.0001
Hypertension	434 482 (59.0%)	330 608 (56.1%)	83 582 (69.3%)	20 292 (75.6%)	<0.0001
Stroke/TIA	7377 (1.0%)	4640 (0.8%)	2047 (1.7%)	690 (2.6%)	<0.0001
Hemorrhage	19 718 (2.7%)	14 976 (2.5%)	3739 (3.1%)	1003 (3.7%)	<0.0001
CHF	32 143 (4.4%)	19 509 (3.3%)	9299 (7.7%)	3335 (12.4%)	<0.0001
Myocardial infarction	14,901 (2.0%)	10,252 (1.7%)	3,501 (2.9%)	1,148 (4.3%)	<0.0001
CAD	112 977 (15.3%)	81 795 (13.9%)	24 545 (20.4%)	6637 (24.7%)	<0.0001
CABG	7278 (1.0%)	4931 (0.8%)	1751 (1.5%)	596 (2.2%)	<0.0001
PAD/PVD	5038 (0.7%)	2838 (0.5%)	1582 (1.3%)	618 (2.3%)	<0.0001
COPD	8606 (1.2%)	5344 (0.9%)	2487 (2.1%)	775 (2.9%)	<0.0001

Data presented as number (percent), except for age and eGFR, which are presented as mean (SD). ACR indicates albumin to creatinine ratio; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; mg, milligrams; PAD, peripheral artery disease, PVD, peripheral vascular disease; TIA, transient ischemic attack.

<15 mL/min per 1.73 m^2 (end-stage kidney disease). In end-stage kidney disease, the increased risk observed with a higher urine ACR was comparable with patients with preserved kidney function.

The crude number of events, incidence rate (IR), and crude and adjusted HRs for incident AF by urine ACR and eGFR categories according to the KDIGO chronic kidney disease classification scheme are presented in Tables S3 through S5,
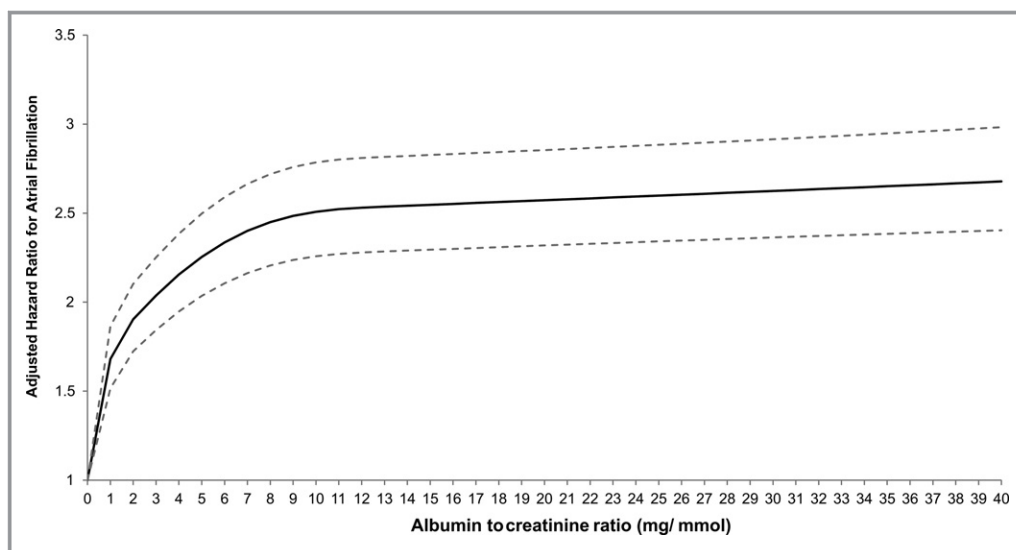
Figure 1. Adjusted continuous hazard ratio for incidence of atrial fibrillation by urine ACR. The solid black line represents the hazard ratio and the dashed lines represent the 95% CI. Data adjusted for age, sex, income quintile, index year, comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, stroke/transient ischemic attack, hemorrhage, congestive heart failure, peripheral vascular disease, and coronary artery bypass grafting), and eGFR. ACR was analyzed using restricted cubic splines with knots at the 5th, 25th, 50th, 75th, and 95th percentile. ACR indicates albumin-to-creatinine ratio.

Table 3, and Figure 3. Risk of incident AF increased with declining eGFR and increasing urine ACR categories. Patients in the lowest eGFR (<15 mL/min per 1.73 m^2) and highest urine ACR (>30 mg/mmol) category had the highest risk of developing AF (number of events=88 [11.4%]; IR, 62.7 [95% CI, 50.2–77.2] per 1000 person-years; adjusted HR, 3.4 [95% CI, 2.8–4.2] as compared with those with referent eGFR >90 and ACR <3 mg/mmol). Among patients with a urine ACR <3 mg/mmol, the IR of AF increased 14.3-fold (IR, 3.3 versus 46.9 per 1000 person-years), and for those with a urine ACR >30 mg/mmol, the IR of AF increased 6.2-fold (IR, 10.1 versus 62.7 per 1000 person-years) as eGFR declined. Among patients with normal kidney function (eGFR >90), the IR of AF increased 3.1-fold (IR, 3.3 versus 10.1 per 1000 person-years), and among those with kidney failure (eGFR, <15), the IR of AF increased 1.3-fold (IR, 46.9 versus 62.7 per 1000 person-years) across categories of increasing ACR (Figure 3; Table S4). The increased risk of incident AF observed with increasing urine ACR and declining eGFR categories attenuated, but still remained significant, after adjustment for patient demographics, year of cohort entry, and comorbidities. For example, the unadjusted and adjusted HRs for AF in the urine ACR >30 mg/mmol and eGFR 15 to <30 category were HR 13.2 (95% CI, 12.0–14.6) and adjusted HR 2.1 (95% CI, 1.9–2.3; referent category ACR <3 mg/mmol and eGFR >90; Table 3 and Table S5). When accounting for death as a competing risk, there was a slight attenuation in the subdistribution HRs, but the overall findings were similar (Table S6).

Discussion

In this large, population-based, retrospective cohort study that included 736 666 individuals with 44 809 incident AF events, we found that risk of incident AF increased in a graded fashion with increasing proteinuria, and that the greatest increase in risk occurred at low levels of proteinuria (microalbuminuria or lower). There was a significant interaction between urine ACR and eGFR, such that proteinuria had the greatest impact on increasing AF risk among individuals with intact kidney function. The presence of proteinuria had a much smaller impact on increasing AF risk in patients with significant kidney dysfunction (eGFR, 30) except in patients with end-stage kidney disease (eGFR, <15). These associations were independent of demographics and comorbidities, including those that are known risk factors for AF.[1,5]

Previous cross-sectional studies have shown that patients with microalbuminuria have a heightened prevalence of AF.[11,18–22] Four published studies have examined the association of proteinuria with incident AF, with 3 studies demonstrating a significant positive association.[3,13–15] The 1 study that failed to demonstrate a positive association, conducted in a subset of participants from the Framingham Heart Study, had limited statistical power with only 135 AF events.[14] Our findings add to the growing body of literature demonstrating an independent association between proteinuria and incident AF. To our knowledge, our study is the largest to date and was conducted in a broad, generalizable

Table 2. Adjusted Associations of Kidney Function, Proteinuria, and Incidence of AF

Model Term (All Continuous)	Adjusted HR (95% CI)	P Value
eGFR		<0.0001
ACR		<0.0001
eGFR×ACR		<0.0001
Age	1.07 (1.07–1.07)	<0.0001
Urban (rural referent)	0.84 (0.82–0.87)	0.356
Year (of ACR)	1.01 (1.01–1.02)	<0.0001
Sex (male referent)	0.72 (0.71–0.74)	<0.0001
Diabetes mellitus	1.13 (1.11–1.15)	<0.0001
COPD	1.59 (1.52–1.66)	<0.0001
Hypertension	1.26 (1.23–1.29)	<0.0001
CHF	2.62 (2.55–2.69)	<0.0001
Major hemorrhage	1.27 (1.22–1.33)	<0.0001
Myocardial infarction	0.89 (0.85–0.93)	<0.0001
Coronary artery disease	1.65 (1.62–1.69)	<0.0001
Peripheral vascular disease	1.29 (1.22–1.38)	<0.0001
CABG	0.86 (0.81–0.91)	<0.0001
Income quintile		0.6017
1 (low)	0.99 (0.96–1.02)	
2	0.99 (0.96–1.02)	
3	0.74 (0.94–1.00)	
4	0.98 (0.95–1.01)	
5 (high-referent)	1	

ACR is in milligrams per millimole. eGFR is in milliliters per minute per 1.73 m^2. ACR indicates albumin-to-creatinine ratio; AF, atrial fibrillation; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder, eGFR, estimated glomerular filtration rate, HR, hazard ratio.

patient population. Our results agree with those of Alonso et al, whose study in the ARIC (Atherosclerosis Risk in Communities) cohort (n=10 328) showed a similar graded increase in the HR for AF with increasing urine ACR categories. Similar to our findings, Alonso et al observed a substantial increase in the risk for incident AF among patients with normal kidney function (eGFR >90) and high-level albuminuria (ACR, >30 mg/mmol).[3] This finding highlights the underappreciated, yet highly clinically significant, risk for AF among patients with proteinuria that is independent of kidney function. We are also the first to report that eGFR significantly modifies the association of proteinuria with AF. Previously, Alonso et al reported that the multiplicative interaction between eGFR and urine ACR was not significant, but their study was limited by a smaller sample size and the exclusion of patients with an eGFR <15 mL/min per 1.73 m^2.[3] We found a high risk of incident AF in end-stage kidney disease patients that increased across proteinuria

categories. This is likely attributed to worsening hypertension and volume overload as patients approach the need for dialysis. Our finding that the effect of proteinuria on AF risk is modified by a patient's eGFR is important because it highlights the significance of both proteinuria and reduced kidney function as risk factors for AF, and that proteinuria is a particularly important risk factor among patients with preserved kidney function.

Several possible mechanisms may account for our observed associations. Patients with proteinuria had a higher prevalence of other risk factors for AF, such as hypertension, CHF, and cardiovascular disease. The confounding effect of these factors is demonstrated by significant attenuation of the association of urine ACR with AF in the fully adjusted model (urine ACR and eGFR categorical analysis). However, a significant association still persisted after adjustment, suggesting that albuminuria independently increases AF risk.

Albuminuria may serve as a marker of hypertensive end-organ and vascular damage, endothelial dysfunction, or cardiometabolic syndrome.[11,12,23] In this regard, urine ACR may act as a marker of subclinical cardiovascular disease.[18] Our further finding of reduced eGFR being a risk factor for AF agrees with previously published studies.[6] A reduction in eGFR results in impaired sodium handling, which leads to salt-sensitive hypertension and expansion of extracellular fluid volume.[24] This can ultimately result in cardiac remodeling, including left ventricular hypertrophy and left atrial enlargement, that favor development of AF.[25] Impaired eGFR leads to pathological upregulation of the sympathetic nervous system.[26] Increasing evidence supports the important role of the autonomic nervous system in the induction and maintenance of AF.[27] A reduction in eGFR also leads to upregulation of the renin-angiotensin system, which may contribute to the development of AF through induction of atrial fibrosis and atrial electrical remodeling. The important role of the renin-angiotensin system is supported by clinical studies demonstrating a reduction in AF among patients administered angiotensin-converting enzyme inhibitors.[28]

In light of our findings, strategies to prevent AF may be targeted in patients with both a reduced eGFR and elevated urine ACR. The feasibility of AF prevention was highlighted in patients undergoing cardiac surgery, where therapeutic interventions have successfully demonstrated a reduction of incident AF.[29,30] Observational data suggest an extension of these findings in patients on dialysis.[31,32] Whether these interventions attenuate AF among patients with low levels of eGFR and high urine ACR remains uncertain. The importance of AF prevention is further underscored by the uncertainty regarding the risk-benefit ratio of thromboembolism prophylaxis in AF patients with an eGFR <30 mL/min per 1.73 m^2 and the association of AF with increased morbidity, mortality, and healthcare costs.[1,2,33]
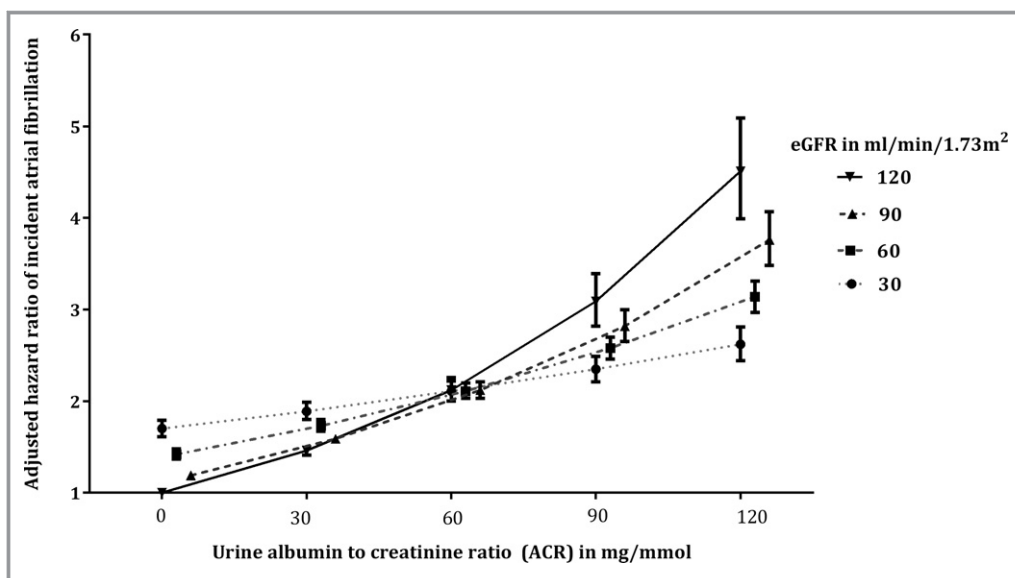
Figure 2. Adjusted hazard ratio of incident atrial fibrillation by proteinuria at fixed levels of kidney function. Albumin-to-creatinine ratio (ACR) is in milligrams per millimole. eGFR is in milliliters per minute per 1.73 m^2. Data adjusted for age, sex, income quintile, index year, and comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, stroke/transient ischemic attack, hemorrhage, congestive heart failure, peripheral vascular disease, and coronary artery bypass grafting). eGFR indicates estimated glomerular filtration rate.

Our study has important limitations. A diagnosis of AF was identified using emergency room visits or hospital discharge records; therefore, cases of asymptomatic AF or AF in patients managed solely in an outpatient setting may have been missed. Ascertainment bias for AF is a consideration among patients with chronic kidney disease attributed to a higher prevalence of comorbidities, which could lead to increased hospitalizations and cardiac testing. However, others have previously shown that AF ascertainment using only inpatient records, as opposed to both outpatient and inpatient records, is acceptable and does not introduce significant bias.[34] As well, we excluded outpatient records because of inaccurate capture of cardiac arrhythmias in the outpatient setting, where the diagnosis is coded simply as "arrhythmia" as opposed to the specific diagnosis of AF coded in hospital and emergency room discharge records. Another important limitation is the absence of echocardiographic data. Although we were able to adjust for a number of important confounders (ie hypertension and CHF), residual confounding is always a possibility and therefore the observed associations may not be causal. Despite these limitations, our study has the important strength of its very large sample size with a large number of events in a diverse, generalizable patient population.

Table 3. Adjusted Associations of Kidney Function, Proteinuria, and Incidence of AF by Cox Proportional Hazards

Categories	Referent: eGFR >90 and ACR <3			Referent ACR <3 Across eGFR Categories		
	ACR<3	ACR 3 to 30	ACR>30	ACR<3	ACR 3 to 30	ACR>30
eGFR >90	1 (ref)	1.53 (1.45–1.61)	2.55 (2.31–2.80)	1 (ref)	1.52 (1.45–1.6)	2.54 (2.31–2.79)
eGFR 60 to 90	1.09 (1.06–1.13)	1.68 (1.62–1.75)	2.22 (2.08–2.37)	1 (ref)	1.54 (1.49–1.59)	2.04 (1.92–2.16)
eGFR 45 to <60	1.27 (1.21–1.32)	1.76 (1.67–1.85)	2.09 (1.93–2.26)	1 (ref)	1.39 (1.32–1.45)	1.66 (1.54–1.79)
eGFR 30 to <45	1.43 (1.36–1.51)	1.77 (1.67–1.88)	1.97 (1.82–2.14)	1 (ref)	1.24 (1.17–1.32)	1.39 (1.27–1.51)
eGFR 15 to <30	1.55 (1.41–1.69)	1.81 (1.66–1.96)	2.08 (1.88–2.31)	1 (ref)	1.18 (1.05–1.31)	1.36 (1.20–1.54)
eGFR <15	1.69 (1.12–2.54)	2.47 (1.88–3.26)	3.41 (2.76–4.22)	1 (ref)	1.49 (0.91–2.44)	2.04 (1.29–3.22)

Data adjusted for age, sex, income quintile, index year, and comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, stroke/transient ischemic attack, hemorrhage, congestive heart failure, peripheral vascular disease, and coronary artery bypass grafting). ACR is in milligrams per millimole. eGFR is in milliliters per minute per 1.73 m^2. ACR indicates albumin to creatinine ratio; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate.

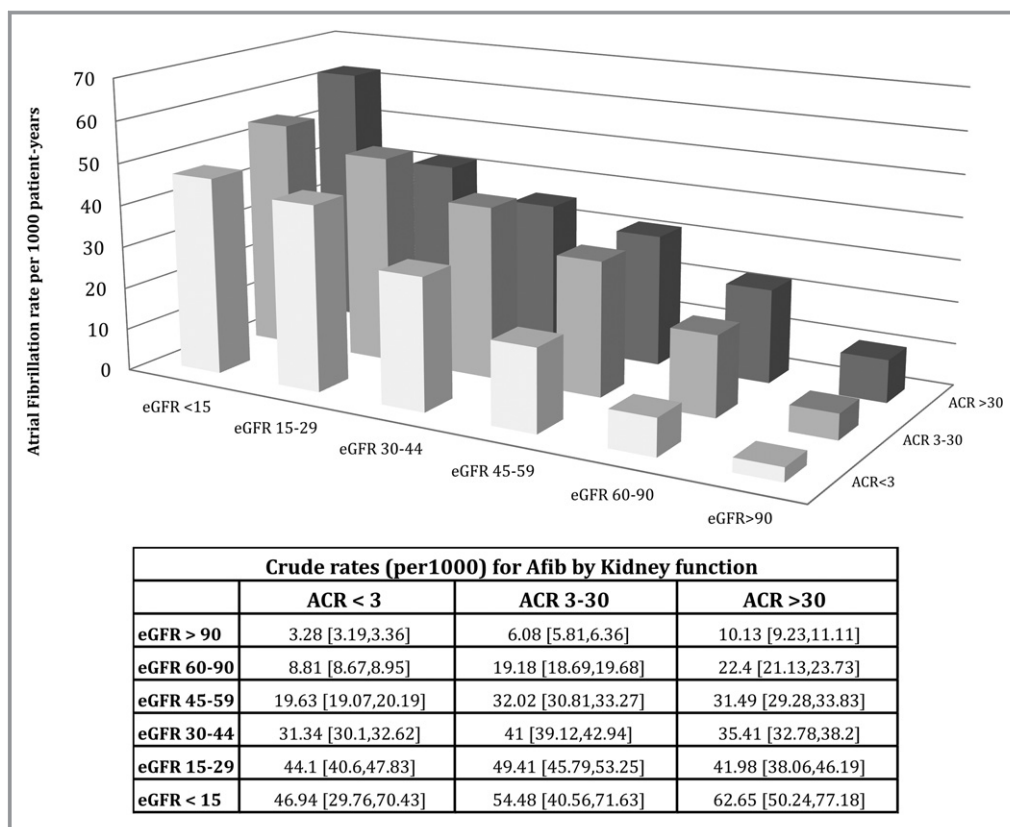| Crude rates (per1000) for Afib by Kidney function		
	ACR < 3	**ACR 3-30**	**ACR >30**
eGFR > 90	3.28 [3.19,3.36]	6.08 [5.81,6.36]	10.13 [9.23,11.11]
eGFR 60-90	8.81 [8.67,8.95]	19.18 [18.69,19.68]	22.4 [21.13,23.73]
eGFR 45-59	19.63 [19.07,20.19]	32.02 [30.81,33.27]	31.49 [29.28,33.83]
eGFR 30-44	31.34 [30.1,32.62]	41 [39.12,42.94]	35.41 [32.78,38.2]
eGFR 15-29	44.1 [40.6,47.83]	49.41 [45.79,53.25]	41.98 [38.06,46.19]
eGFR < 15	46.94 [29.76,70.43]	54.48 [40.56,71.63]	62.65 [50.24,77.18]

Figure 3. Crude incidence rate of atrial fibrillation by urine albumin-to-creatinine ratio and eGFR category. ACR is in milligrams per millimole. eGFR is in milliliters per minute per 1.73 m^2. ACR and eGFR categories correspond to KDIGO categories for chronic kidney disease.[7] ACR indicates albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Conclusions

Our data show that the risk of incident AF increases in a graded fashion with increasing proteinuria and that kidney function modifies the association of proteinuria with incident AF. Urine ACR and eGFR calculated from serum creatinine are readily available measurements in the clinical setting and could thus be easily incorporated into screening and preventative strategies for AF. Further studies to elicit the effectiveness of such strategies and the causal mechanisms for our observed associations are required.

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) Statement1

	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.	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
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods

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, Supplemental Figure 1 & Supplemental Table 2
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 provided. If these cannot be reported, an explanation should be provided.	Methods & Supplemental Table 2
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

Bias	9	Describe any efforts to address potential sources of bias.		Methods
Study size	10	Explain how the study size was arrived at.		Methods and Supplemental Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		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
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
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

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.	Supplemental Figure 1 & Results
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		Results
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		Results

		relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		Results
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.		Acknowledgments & Funding
Accessibility of protocol, raw data, and		N/A	(22.1) Authors should provide information on how to access any supplemental information	

programming code	such as the study protocol, raw data, or programming code.

Table S2. Coding definitions for demographic and comorbid conditions

Characteristic	Database	Code
Age, sex, income	RPDB	
Diabetes	DAD OHIP	ICD9: "250" ICD10: "E10", "E11", "E12", "E13", "E14" OHIP DX: "250" OHIP FEE: "Q040", "K029", "K030", "K045", "K046"
Hypertension	DAD OHIP	ICD9: "401", "402", "403", "404", "405" ICD10: "I10", "I11", "I12", "I13", "I15" OHIP DX: "401", "402", "403"
Ischemic stroke	DAD OHIP	ICD9: "433", "434", "436" ICD10: "H341", "I630", "I631", "I632", "I633", "I634", "I635", "I638", "I639", "I64"
Transient ischemic attack	DAD OHIP	ICD9: "435" ICD10: "H340", "G450", "G451", "G452", "G453", "G458", "G459"

Major hemorrhage- Subarachnoid hemorrhage	DAD	ICD9: "430" ICD10: "I600", "I601", "I602", "I603", "I604", "I605", "I606", "I607", "I609"
Major hemorrhage- Intracranial hemorrhage	DAD	ICD9: "431" ICD10: "I61"
Major hemorrhage- other non-traumatic intracranial hemorrhage	DAD	ICD9: "432" ICD10: "I62"
Major hemorrhage- upper gastrointestinal	DAD	ICD9: "5307", "5310", "5312", "5314", "5316", "5320", "5322", "5324", "5326", "5330", "5332", "5334", "5336", "5340", "5342", "5344", "5346", "5780", "5781" ICD10: "I850", "I9820", "I983", "K2210", "K2211", "K2212", "K2214", "K2216", "K226", "K228", "K250", "K252", "K254", "K256", "K260", "K262", "K264", "K266",

		"K270", "K272", "K274", "K276", "K280", "K282", "K284", "K286", "K290", "K3180", "K31811", "K6380", "K920", "K921"
Major hemorrhage-Lower gastrointestinal	DAD	ICD9: "5693", "5789" ICD10: "K5520", "K625", "K922"
Congestive heart failure	DAD OHIP	ICD9: "425", "5184", "514", "428" ICD10: "I500", "I501", "I509", "I255", "J81" CCP: "4961", "4962", "4963", "4964" CCI: "1HP53", "1HP55", "1HZ53GRFR", "1HZ53LAFR", "1HZ53SYFR" OHIP FEE: "R701", "R702", "Z429" OHIP DX: "428"
Myocardial infarction (MI)	DAD	ICD9: "410" ICD10: "I21", "I22"

Coronary artery disease (excluding Angina)	DAD OHIP	ICD9: "412", "410", "411" ICD10: "I21", "I22", "Z955", "T822" CCI: "1IJ50", "1IJ76" CCP: "4801", "4802", "4803", "4804", "4805", "481", "482", "483" OHIPFee: "R741", "R742", "R743", "G298", "E646", "E651", "E652", "E654", "E655", "Z434", "Z448" OHIPDx: "410", "412"
Coronary artery bypass grafting (CABG)	DAD OHIP	CCI: "1IJ76" CCP: "4811", "4812", "4813", "4814", "4815", "4816", "4817", "4819" OHIP FEE: "R742", "R743", "E654", "E645", "E652", "E646"
Peripheral vascular disease	DAD OHIP	ICD 9: "4402", "4408", "4409", "5571", "4439", "444"

		ICD 10: "I700", "I702", "I708", "I709", "I731", "I738", "I739", "K551"
		CCP: "5125", "5129", "5014", "5016", "5018", "5028", "5038", "5126", "5159"
		CCI: "1KA76", "1KA50", "1KE76", "1KG50", "1KG57", "1KG76MI", "1KG87", "1IA87LA", "1IB87LA", "1IC87LA", "1ID87", "1KA87LA", "1KE57"
		OHIP fee codes: "R787", "R780", "R797", "R804", "R809", "R875", "R815", "R936", "R783", "R784","R785", "E626", "R814", "R786", "R937", "R860", "R861", "R855", "R856", "R933", "R934", "R791", "E672", "R794", "R813", "R867", "E649"

Chronic obstructive pulmonary disorder (COPD)	DAD	ICD9: "491", "492", "496" ICD10: "J41", "J43", "J44"

Outcome definitions

Outcome	Database	Codes
Atrial Fibrillation	DAD NACRS	ICD9:"4273" ICD10: "I48"
Dialysis	OHIP	Fee code: "R849","G323","G325","G326","G860","G862", "G863","G865","G866","G330","G331","G332", "G861","G864"
Kidney transplant	CORR	Transplanted_organ_type_code: "10", "11", "12", "18", "19",
Death	RPDB	

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

Table S3. Crude counts of atrial fibrillation by eGFR and urine ACR category

	ACR <3 N=589,264	ACR 3-30 N=120,565	ACR >30 N=26,837
eGFR >90 (N=321,227)	5708 (2.12)	1906 (4.17)	459 (6.85)
eGFR 60-90 (N=320,998)	14873 (5.63)	5826 (12.08)	1161 (13.73)
eGFR 45-<60 (N=58,273)	4769 (12.06)	2626 (18.18)	749 (17.44)
eGFR 30-<45 (N=26,186)	2411 (17.67)	1798 (20.82)	670 (17.17)
eGFR 15-<30 (N=8760)	583 (20.75)	688 (21.23)	420 (15.5)
eGFR <15 (N=1222)	23 (19.49)	51 (15.45)	88 (11.37)

Each box presents number with atrial fibrillation and percentage of category total. The ACR is in milligram per millimole. The eGFR is in millilters per minute per 1.73 meter squared.

Abbreviations: ACR: albumin-to-creatinine-ratio, eGFR: estimated glomerular filtration rate, N: number

Table S4. Crude rates (per 1000 person-years) for the incidence of atrial fibrillation by eGFR and urine ACR category

	ACR<3	ACR 3-30	ACR>30
eGFR >90	3.28 [3.19-3.36]	6.08 [5.81-6.36]	10.13 [9.23-11.11]
eGFR 60-90	8.81 [8.67-8.95]	19.18 [18.69-19.68]	22.4 [21.13-23.73]
eGFR 45-<60	19.63 [19.07-20.19]	32.02 [30.81-33.27]	31.49 [29.28-33.83]
eGFR 30-<45	31.34 [30.1-32.62]	41 [39.12-42.94]	35.41 [32.78-38.2]
eGFR 15-<30	44.1 [40.6-47.83]	49.41 [45.79-53.25]	41.98 [38.06-46.19]
eGFR <15	46.94 [29.76-70.43]	54.48 [40.56-71.63]	62.65 [50.24-77.18]

The ACR is in milligram per millimole. The eGFR is in millilters per minute per 1.73 meter squared.

Abbreviations: ACR: albumin-to-creatinine-ratio, eGFR: estimated glomerular filtration rate.

Table S5. Crude hazard ratios for the incidence of atrial fibrillation by eGFR and urine ACR category

	ACR<3	ACR 3-30	ACR>30
eGFR >90	1[ref]	1.83 [1.73-1.92]	3.05 [2.77-3.35]
eGFR 60-90	2.70 [2.62-2.78]	5.82 [5.61-6.03]	6.80 [6.39-7.25]
eGFR 45-<60	6.01 [5.79-6.25]	9.80 [9.36-10.27]	9.67 [8.96-10.44]
eGFR 30-<45	9.65 [9.20-10.12]	12.68 [12.02-13.37]	10.99 [10.14-11.9]
eGFR 15-<30	13.73 [12.61-14.96]	15.42 [14.25-16.69]	13.21 [11.96-14.59]
eGFR <15	14.60 [9.70-22.00]	16.92 [12.85,22.30]	19.36 [15.68-23.90]

The ACR is in milligram per millimole. The eGFR is in millilters per minute per 1.73 meter squared.

Abbreviations: ACR: albumin-to-creatinine-ratio, eGFR: estimated glomerular filtration rate.

Table S6. The adjusted hazard and sub-distribution hazard ratio for the incidence of atrial fibrillation by eGFR and urine ACR category

	Cox model			Fine and Grey Model		
Categories:	ACR<3	ACR 3-30	ACR>30	ACR<3	ACR 3-30	ACR>30
eGFR >90	1 (ref)	1.53 [1.45-1.61]	2.55 [2.31-2.80]	1 [ref]	1.51 [1.44-1.59]	2.42 [2.20-2.66]
eGFR 60-90	1.09 [1.06-1.13]	1.68 [1.62-1.75]	2.22 [2.08-2.37]	1.16 [1.12-1.20]	1.72 [1.65-1.79]	2.14 [2.00-2.29]
eGFR 45-<60	1.27 [1.21-1.32]	1.76 [1.67-1.85]	2.09 [1.93-2.26]	1.35 [1.29-1.41]	1.74 [1.65-1.84]	2.00 [1.84-2.17]
eGFR 30-<45	1.43 [1.36-1.51]	1.77 [1.67-1.88]	1.97 [1.82-2.14]	1.46 [1.38-1.54]	1.66 [1.56-1.77]	1.73 [1.58-1.89]
eGFR 15-<30	1.55 [1.41-1.69]	1.81 [1.66-1.96]	2.08 [1.88-2.31]	1.42 [1.29-1.56]	1.54 [1.40-1.68]	1.64 [1.46-1.83]
eGFR <15	1.69 [1.12-2.54]	2.47 [1.88-3.26]	3.41 [2.76-4.22]	1.50 [0.97-2.33]	1.59 [1.17-2.18]	2.16 [1.69-2.76]

Data adjusted for age, sex, income quintile, index year, comorbidities (diabetes, hypertension, Chronic

obstructive pulmonary disease, coronary artery disease, myocardial infarction, stroke/transient ischemic

attack, hemorrhage, congestive heart failure, peripheral vascular disease, coronary artery bypass graft).

Death was the competing event for Fine & Grey models. The ACR is in milligram per millimole. The eGFR is

in millilters per minute per 1.73 meter squared.

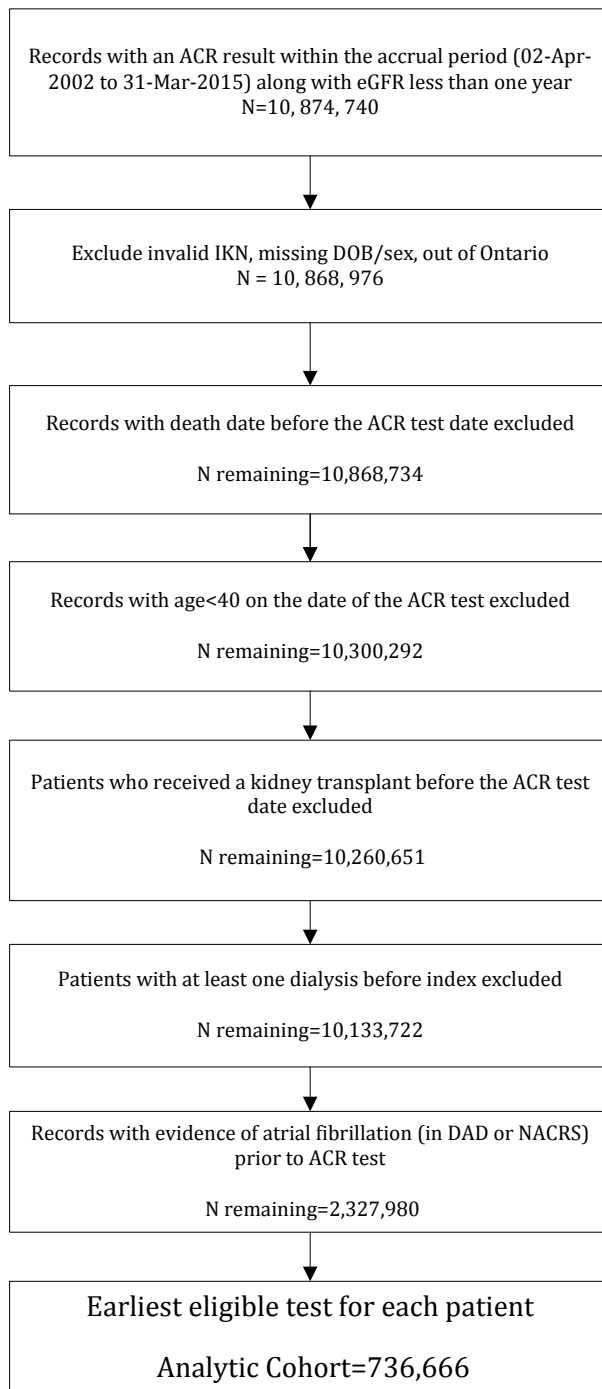Abbreviations: ACR: albumin-to-creatinine-ratio, eGFR: estimated glomerular filtration rate.

```
┌─────────────────────────────────────────────────────┐
│ Records with an ACR result within the accrual period │
│ (02-Apr-2002 to 31-Mar-2015) along with eGFR less    │
│ than one year                                        │
│ N=10, 874, 740                                       │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Exclude invalid IKN, missing DOB/sex, out of Ontario │
│ N = 10, 868, 976                                     │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Records with death date before the ACR test date     │
│ excluded                                             │
│                                                      │
│ N remaining=10,868,734                               │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Records with age<40 on the date of the ACR test      │
│ excluded                                             │
│                                                      │
│ N remaining=10,300,292                               │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Patients who received a kidney transplant before the │
│ ACR test date excluded                               │
│                                                      │
│ N remaining=10,260,651                               │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Patients with at least one dialysis before index     │
│ excluded                                             │
│                                                      │
│ N remaining=10,133,722                               │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Records with evidence of atrial fibrillation (in DAD │
│ or NACRS) prior to ACR test                          │
│                                                      │
│ N remaining=2,327,980                                │
└─────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────┐
│ Earliest eligible test for each patient              │
│                                                      │
│ Analytic Cohort=736,666                              │
└─────────────────────────────────────────────────────┘
```

Figure S1. Analytic cohort creation

Abbreviations: ACR: albumin-to-creatinine-ratio, DAD: discharge abstract database, DOB: date of birth,

eGFR: estimated glomerular filtration rate, IKN: institute for clinical evaluative sciences key number, N:

number, NACRS: national ambulatory care reporting system