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Incident Atrial Fibrillation and Risk of End-Stage Renal Disease in Adults with Chronic Kidney Disease

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Abstract

Background—Atrial fibrillation (AF) frequently occurs in patients with chronic kidney disease (CKD). However, the long-term impact of development of AF on the risk of adverse renal outcomes in patients with CKD is unknown. In this study, we determined the association between incident AF and risk of end-stage renal disease (ESRD) among adults with CKD.

Methods and Results—We studied adults with CKD (defined as persistent glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2 by the CKD-EPI equation) enrolled in Kaiser Permanente Northern California who were identified between 2002–2010 and who did not have prior ESRD or previously documented AF. Incident AF was identified using primary hospital discharge diagnoses and/or two or more outpatient visits for AF. Incident ESRD was ascertained from a comprehensive health plan registry for dialysis and renal transplant. Among 206,229 adults with CKD, 16,463 developed incident AF. During a mean follow-up of 5.1± 2.5 years, there were 345 cases of ESRD that occurred after development of incident AF (74 per 1000 person-years) compared with 6505 cases of ESRD during periods without AF (64 per 1000 person-years, P<0.001). After adjustment for potential confounders, incident AF was associated with a 67% increase in rate of ESRD (hazard ratio 1.67, 95% confidence interval: 1.46–1.91).

Conclusions—Incident AF is independently associated with increased risk of developing ESRD in adults with CKD. Further study is needed to identify potentially modifiable pathways through which AF leads to a higher risk of progression to ESRD.

Keywords

arrhythmia; fibrillation; kidney

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Introduction

Atrial fibrillation (AF) is estimated to occur in 7–20% among patients with end-stage renal disease (ESRD), which is 2-to-3-fold higher than reported in the general population.[1] Studies have shown that the prevalence of AF is increasing among patients with ESRD and is associated with worse outcomes such as ischemic stroke and death.[2, 3]

Recently, several studies have also found a high incidence and prevalence of AF among the larger population of patients with chronic kidney disease (CKD) not yet requiring dialysis.[4–8] One recent study estimated the prevalence of AF to be 18% in a multicenter cohort with a wide range of kidney function.[8] Although it is well established that AF is associated with poorer clinical outcomes in the general population and in ESRD patients, much less is known about the long-term impact of AF in patients with CKD.

While it is generally accepted that CKD increases the risk of developing AF, few studies have evaluated the potential bidirectional relationship between AF and CKD. One cohort study of Japanese participants found that AF at entry was associated with nearly a twofold increase in the risk of developing CKD or proteinuria.[9] However, the long-term impact of development of AF on the risk of adverse clinical renal outcomes in patients with known CKD is unclear and may have potentially important implications for the management of this high-risk group of patients.

To address this knowledge gap, we examined the association of incident AF on the risk of developing ESRD among a large, diverse, community-based cohort of adults with known CKD.

Methods

Study population

The source population included members of Kaiser Permanente Northern California, a large integrated health care delivery system providing comprehensive care to >3.2 million patients in the San Francisco and greater Bay area. The study sample included all adult members (≥21 years) who had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 as calculated by the CKD-EPI equation[10] between January 1, 2002 and December 31, 2010. Subjects had to have ≥2 eGFR measures of <60 ml/min/1.73 m^2 separated by at least 90 days, as well as all subsequent eGFR measures being <60 ml/min/1.73 m^2 to be included in the analyses. Based on Kidney Disease: Improving Global Outcomes (KDIGO) Committee guidelines, we categorized kidney function as follows: 45–59, 30–44, 15–29 and less than 15 ml/min/1.73 m^2.[11] The date of the first eGFR that qualified as CKD was considered the index date. Among 238,992 participants who met initial inclusion criteria, we excluded 3,078 patients with prior ESRD, and 29,685 with previously documented AF. Prior AF was defined as having ≥1 primary or secondary hospital discharge diagnosis, ambulatory visit and/or emergency department visit with an *International Classification of Diseases, Ninth Edition* (ICD-9) code of 427.31 or 427.32. The final analytic sample included 206,229 subjects.

The study was approved by the institutional review board of the Kaiser Foundation Research Institute. Waiver of informed consent was obtained due to the nature of the study.

Predictor variable

The primary predictor was diagnosed incident AF from cohort entry through December 2010. Incident AF was defined using previously described, validated approaches[12, 13] based on the first occurrence of: (1) hospitalization with a primary discharge diagnosis of AF or

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(2) two or more ambulatory visits for AF based on ICD-9 codes 427.31 or 427.32 found in health plan inpatient and ambulatory visit databases.

Follow-up and Outcomes

Follow-up occurred until an outcome event was reached, the patient died or disenrolled from the health plan, or the end of the study period on December 31, 2010. The main outcome was progression to ESRD, which was defined as receipt of chronic dialysis or renal transplant and was identified from a comprehensive health plan ESRD treatment registry.[14, 15] Deaths were identified from health plan administrative databases, Social Security Administration vital status files, and California state death certificate registry during the follow-up period.[16]

Covariates

Data were collected on demographic characteristics (age, gender, and self-reported race/ethnicity) from health plan administrative databases and selected socioeconomic features (educational attainment, annual household income) from 2010 U.S. census block data.[16, 17] Targeted comorbid conditions (diabetes mellitus, hypertension, coronary heart disease, stroke, heart failure, peripheral arterial disease, dyslipidemia, lung disease, liver disease and hyperthyroidism) were determined using validated algorithms based on relevant diagnosis and procedures, dispensed prescription medications and/or laboratory results from health plan databases.[18] The most recent outpatient systolic and diastolic blood pressure values before index date were obtained from ambulatory visit databases, which have been shown to reliably reflect chronic blood pressure levels in our population.[19] Hemoglobin level at entry was obtained from ambulatory health plan laboratory databases and categorized (in g/L) as: <9, 9–9.9, 10–10.9, 11–11.9, 12–12.9, 13–13.9 and ≥14. Albuminuria at entry (in the absence of possible concomitant urinary tract infection) was defined based on urine dipstick results obtained from ambulatory health plan laboratory databases and quantified as none/trace, 1+, 2+, 3+ or 4+.[16] Baseline use of anti-hypertensive medications (angiotensin converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARB], calcium channel blockers, diuretics, β-blockers), statins, other lipid lowering agents, warfarin and antiplatelet medications in the 120 days prior to or on the index date were obtained from health plan ambulatory pharmacy databases.

Statistical methods

All analyses were performed using SAS statistical software version 9.1 (Cary, N.C.). Differences between subjects with and without incident AF were compared using Student's t-test for continuous variables and chi-squared test for categorical variables. We performed multivariable extended Cox proportional hazards regression to examine the independent association between development of incident AF during follow-up and risk of ESRD. Follow-up for each subject started on the index date and continued until disenrollment from the health plan, death, end of study period or occurrence of the outcome event (i.e., ESRD). AF was a time-updated exposure. Thus, if a patient developed AF during follow-up, they contributed time to the “no AF” exposure group before being diagnosed with incident AF. After being diagnosed with AF, they would contribute person-time to the “incident AF” exposure group. Variables included in models were based on variables that were significantly different between study population and controls on bivariate analyses or have previously been shown to be associated either with kidney function or AF.[4, 20, 21] We identified *a priori* potential confounder covariates that were time-updated throughout the duration of follow-up or after AF diagnosis as appropriate: age, gender, race, low income status, low educational attainment, diabetes mellitus, stroke/TIA, dyslipidemia and chronic lung disease. We also identified potential mediators in the association between AF and ESRD which were “fixed” at the time of AF diagnosis among patients who developed

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incident AF: eGFR category, proteinuria status, hemoglobin category, hypertension status, systolic blood pressure, history of heart failure, history of coronary heart disease, history of peripheral artery disease and baseline use of relevant medications (β-blockers, ACE inhibitors/ARBs, calcium channel blockers, diuretics, statins, other lipid lowering agents, warfarin, and anti-platelet agents).

Based on *a priori* hypotheses, we conducted stratified multivariable analyses for age (<60, 60–70 and ≥ 70 years), gender (men vs. women), race (white, black and Asian/Pacific Islander) and entry eGFR level (45–59, 30 to <45 and <30 ml/min/1.73 m^2).

We also performed two sensitivity analyses. In the first sensitivity analysis, to determine whether the progression of AF was a proxy for progression of kidney disease, we conducted a parallel matched cohort analysis using a highly stratified extended Cox regression model of a subgroup of 80,803 patients who had persistent CKD throughout the entire duration of follow-up. In this parallel matched cohort analysis, t_1 was the time of incident AF diagnosis for patients who developed incident AF. We matched each incident AF patient (N=6,257) with patients who did not have AF at t_1 based on gender, age (± 5 years), eGFR category (<30, 30–44, 45–59 ml/min/1.73 m^2), and being alive at the time of t_1 (N=48,989), with an average matching ratio of 1:7. We followed both the AF and non-AF controls until the end of follow-up, death or disenrollment. We adjusted for covariates in the models based on the specifications outlined above for the primary analysis. In the second sensitivity analysis, we studied whether adjustment interim heart failure and myocardial infarction hospitalizations after diagnosis of AF would attenuate the association between incident AF and ESRD.

Results

Baseline characteristics

The total study population included 206,229 adults with CKD. At cohort entry, mean age was 70.7 ± 11.0 years, approximately half were women and two thirds were white. Overall most patients had hypertension and eGFR of 45–59 ml/min/1.73 m^2 at study entry., (Table 1).

During follow-up through 2010, a total of 16,463 subjects developed incident AF. In univariate analyses, younger age, Black and Hispanic race, co-morbid diseases such as diabetes, lower eGFR, higher blood pressure, and lower hemoglobin were strongly associated with incident AF (Table 1).

Incident AF and Risk of ESRD

Mean follow-up among all subjects was 5.1 ± 2.5 years. During follow-up, 40,579 (19.7%) died and 30,411 (14.8%) disenrolled before the end of the study period. There were 345 cases of ESRD that occurred after development of incident AF (74 per 1000 person-years) compared with 6505 cases of ESRD during periods without AF (64 per 1000 person-years, P<0.001).

In unadjusted analyses, there was a 18% increased rate of ESRD associated with incident AF in patients with CKD (Table 2). After adjustment for age, sex, race, household income, educational status, entry eGFR level, comorbid diseases, blood pressure level, albuminuria, hemoglobin level and medication use, incident AF was associated with a 67% higher relative rate of ESRD among patients with CKD (Table 2).

In adjusted models stratified by age, gender, race and baseline eGFR level, we found a consistently higher adjusted rate of ESRD associated with incident AF in all of the targeted patient subgroups, except for baseline eGFR <30 ml/min/1.73 m^2 (Figure 1).

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In sensitivity analyses among a subgroup of CKD patients within our cohort, each incident AF patient was matched with patients who did not develop AF based on age, gender, eGFR category and vital status at the time of the incident AF diagnosis. In this parallel matched cohort analysis, the multivariable association of incident AF with ESRD was similar to the main analysis (HR 1.63 [1.39 – 1.91]).

In an additional sensitivity analysis, adjustment for interim hospitalizations for heart failure (N=1,978) and myocardial infarction (N=613) between diagnosis of incident AF and ESRD only slightly attenuated the association between incident AF and ESRD among patients with CKD (HR 1.60 [1.41, 1.83]).

Discussion

Among a large, diverse cohort of adults with CKD, we found that incident AF was independently associated with a 67% higher relative rate of subsequent ESRD, even after adjustment for a broad set of potential confounders. Furthermore, this association was consistent among all age, gender, racial and baseline eGFR subgroups. While previous literature has shown that CKD is associated with a high incidence and prevalence of AF,[4–8] our novel results support that AF may contribute to an accelerated progression of CKD to ESRD independent of other known risk factors.

We found that the incidence of documented AF was high among patients with CKD, which supports and extends results from previous studies. For example, within the Atherosclerosis Risk in Community (ARIC) Study, during 10 years of follow-up, there was a graded, increased risk of incident AF with lower baseline eGFR or higher level of albuminuria, even after adjustment for other risk factors.[4] In contrast, a study of patients with CKD with prevalent AF found that the graded association between lower eGFR and prevalent AF was no longer significant after adjustment for age, sex, race/ethnicity and study center.[8]

Previous studies have reported that AF is associated with worse long-term clinical outcomes in patients with ESRD.[2] For example, among >17,000 dialysis patients enrolled in the international Dialysis Outcomes and Practice Patterns Study (DOPPS), AF at study enrollment was associated with higher rates of stroke (adjusted hazard ratio 1.28, 95% CI: 1.01–1.63) and death (adjusted hazard ratio 1.16, 95% CI: 1.08–1.25).[3] Within the nationally representative U.S. Renal Data System between 1989 and 2006, the adjusted 1-year risk of death was 45% higher in dialysis patients with AF compared with those who did not have documented AF.[1] In our study based on a large, diverse community-based cohort of adults with CKD, we found a higher mortality rate among those who developed incident AF. Even taking this into account, we demonstrated that incident AF was independently linked to a higher rate of ESRD, which is associated with tremendous morbidity and mortality. To our knowledge, there are no previously published studies that have evaluated the relation between incident AF and adverse renal events. In addition, we found relatively similar associations between incident AF and risk of ESRD in various patient subgroups (Figure 1), including those *without* a high burden of cardiovascular risk factors (e.g., younger age, female gender, higher eGFR level). While we focused on ESRD as a definitive clinical outcome, it is possible that AF may also be associated with the development and progression of CKD at earlier stages.

Several possible mechanisms may contribute to how AF could increase the risk of ESRD. AF promotes systemic inflammation,[22–26] which has been strongly associated with progression of ESRD in patients with CKD.[27, 28] Given that AF can also induce fibrosis within the myocardium,[29] it is possible that this same fibrosis process is activated within the kidney as well, perhaps through a systemic pro-fibrotic tendency (although there is not

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definitive evidence for this mechanism). AF also contributes to decline of left ventricular systolic and diastolic function over time,[30, 31] which may promote progression of CKD through altered hemodynamics,[31, 32] venous congestion and activation of the renin-angiotensin-aldosterone system.[33, 34] It is also possible that AF may be prothrombotic, leading to renal micro-infarcts, similar to silent cerebral infarcts that have been noted in patients with AF.[35] It is possible that some of the medications used to treat AF may contribute to decline in renal function (e.g., diuretics).

Our study had several strengths. We examined a very large and diverse sample of well-characterized community-based adults across the spectrum of CKD, with outcomes through 2010. We were able to capture documented incident AF in both the inpatient and outpatient setting through validated diagnosis codes in health plan automated databases. We also had serial calibrated outpatient serum creatinine measurements available on entry into the study cohort to confirm the presence and severity of CKD. Our primary endpoint was ESRD requiring dialysis or renal transplant which was comprehensively captured, and we did not depend on outcomes based only on changes in estimated glomerular filtration rate which could be susceptible to ascertainment bias within a clinical practice population. Our study also had several limitations. As systematically timed measures of eGFR were not available in this cohort of CKD patients treated in a “real world” clinical practice setting, we were unable to evaluate intermediate outcomes such as the specific rate of decline of eGFR. We were not able to quantify accurately the severity of proteinuria as only urine dipstick results were available. We were also unable to determine the exact mechanisms explaining the association between AF and ESRD. We cannot completely rule out residual confounding, although we were able to statistically adjust for a wide range of potential explanatory factors, including differential exposure to relevant medications, blood pressure and hemoglobin level. We conducted our study among health plan members within a large integrated health care delivery system in northern California, so our findings may not be completely generalizable to other health care settings or to uninsured patients.

In conclusion, incident AF is associated with 67% higher relative rate of ESRD among patients with CKD, independent of known clinical risk factors and medical therapies. Further study is needed to delineate the contributing factors leading to the development of AF in the setting of CKD and potentially modifiable pathways through which AF leads to a higher risk of progression to ESRD.

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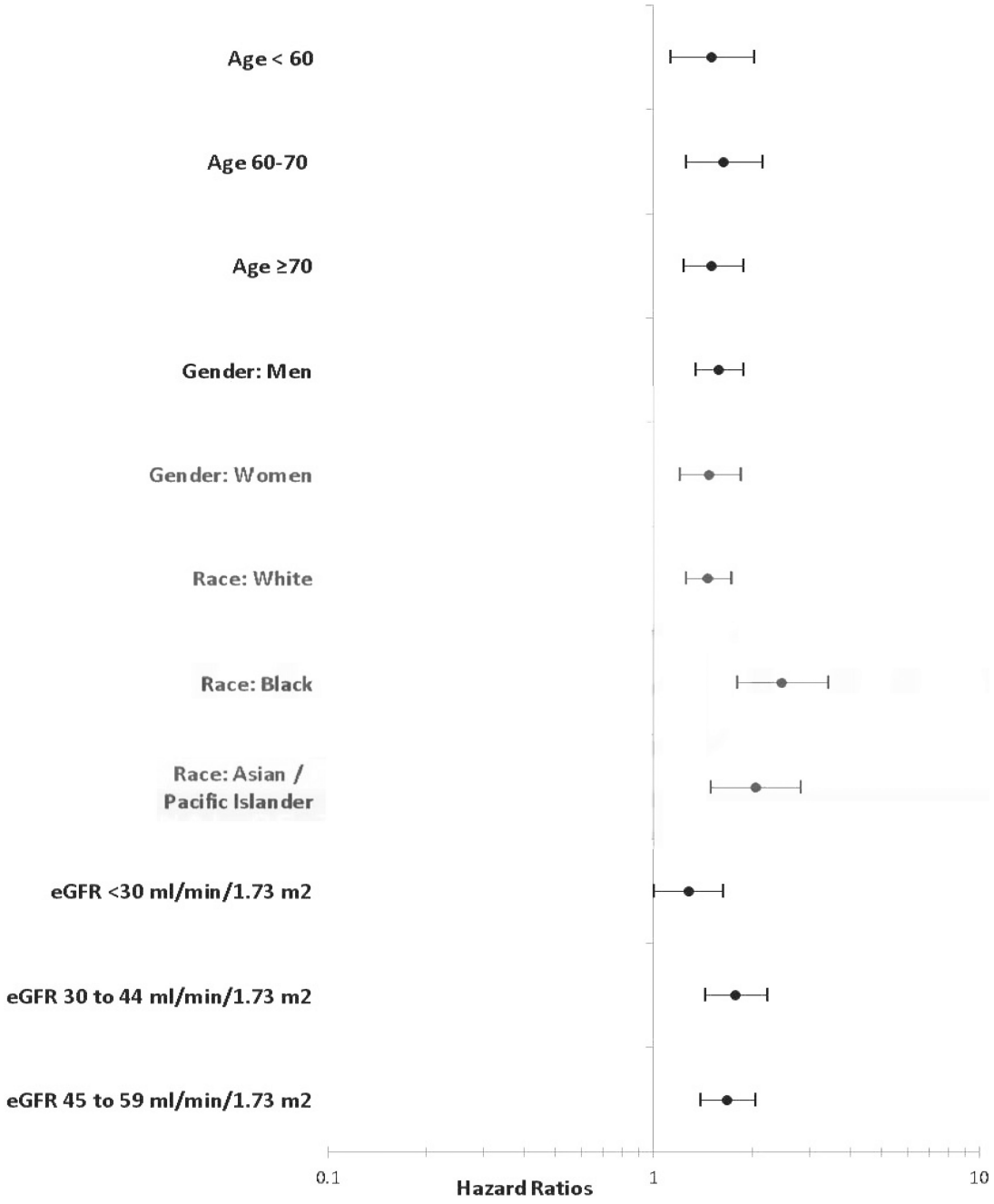

Figure 1.

Multivariable association between atrial fibrillation and risk of end-stage renal disease among chronic kidney disease subgroups. Models included patient age, gender, race, education, income level, eGFR level, albuminuria, hemoglobin level, diabetes mellitus, hypertension, coronary heart disease, ischemic stroke, transient ischemic attack, heart failure, peripheral arterial disease, dyslipidemia, chronic lung disease, chronic liver disease, hyperthyroidism and baseline medication use (β-blockers, ACE inhibitors/ARBs, calcium channel blockers, diuretics, statins, other lipid lowering agents, warfarin, antiplatelet agents).

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Table 1

Baseline characteristics of 206,229 adults with chronic kidney disease*

Characteristic	Mean (SD) or Percentage	Univariate Hazard Ratio (95% Confidence Interval)
Mean (SD) age, year	70.7 (11.0)	0.93 (0.92, 0.93)
Women (%)	51.1	0.74 (0.71, 0.78)
Race (%)		
White	66.1	Ref
Black	7.7	3.82 (3.57, 4.09)
Hispanic	0.2	7.62 (5.85, 9.92)
Asian/Pacific Islander	9.7	2.97 (2.77, 3.18)
Socioeconomic status		
Annual household income < $35,000 (%)	13.2	1.31 (1.23, 1.40)
Less than 9th grade education (%)	4.1	1.81 (1.65, 1.99)
Medical history (%)		
Diabetes mellitus	28.4	4.28 (4.08, 4.49)
Hypertension	79.1	1.92 (1.79, 2.07)
Coronary disease	6.0	1.33 (1.21, 1.45)
Ischemic stroke	1.6	1.78 (1.53, 2.07)
Transient ischemic attack	0.6	1.40 (1.07, 1.83)
Chronic heart failure	7.3	2.10 (1.96, 2.26)
Peripheral arterial disease	2.3	1.72 (1.51, 1.95)
Dyslipidemia	55.6	1.39 (1.33, 1.46)
Chronic lung disease	28.2	1.10 (1.04, 1.16)
Chronic liver disease	2.2	2.26 (2.00, 2.56)
Hyperthyroidism	4.3	0.86 (0.76, 0.97)
Estimated GFR category, ml/min/1.73 m^2 (%)		
45–59	79.3	Ref
30–44	16.3	3.98 (3.75, 4.23)
15–29	3.8	21.22 (19.94, 22.57)
<15	0.7	95.16 (85.69, 105.67)
Dystolic blood pressure category, mm Hg (%)		
≤ 120	22.8	Ref
121–129	15.2	1.12 (1.01, 1.24)
130–139	24.8	1.18 (1.08, 1.29)
140–159	24.3	1.81 (1.67, 1.97)
160–179	9.6	2.63 (2.40, 2.88)
≥180	3.3	4.64 (4.18, 5.15)
Diastolic blood pressure category, mm Hg (%)		
≤ 80	72.4	Ref
81–84	9.9	1.24 (1.14, 1.35)
85–89	7.6	1.46 (1.30, 1.60)

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Characteristic	Mean (SD) or Percentage	Univariate Hazard Ratio (95% Confidence Interval)
90–99	7.6	1.99 (1.85, 2.15)
100–109	2.0	2.64 (2.34, 2.98)
≥110	0.5	4.95 (4.19, 5.88)
Hemoglobin category, g/dL (%)		
<9.0	0.9	9.0 (7.79, 10.41)
9.0–9.9	1.8	8.15 (7.21, 9.21)
10.0–10.9	4.7	5.42 (4.92, 5.97)
11.0–11.9	10.3	3.17 (2.91, 3.46)
12.0–12.9	18.6	1.62 (1.48, 1.77)
13.0–13.9	24.0	Ref
≥14.0	39.7	0.57 (0.52, 0.62)
Albuminuria by urine dipstick (%)		
Negative/trace	92.9	Ref
1+	3.6	5.09 (4.51, 5.74)
2+	2.2	16.19 (14.60, 17.96)
3+	0.4	47.47 (41.03, 54.91)
4+	0.9	54.04 (48.67, 60.01)
Medication use (%)		
β-blocker	39.4	1.17 (1.12, 1.23)
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	47.2	1.72 (1.64, 1.80)
Calcium channel blockers	20.6	2.47 (2.36, 2.60)
Diuretics	53.9	1.18 (1.12, 1.23)
Statin	39.2	1.26 (1.20, 1.32)
Other lipid-lowering therapy	3.9	1.53 (1.38, 1.70)
Warfarin	2.2	0.94 (0.79, 1.12)
Antiplatelet agents	3.2	1.18 (1.04, 1.35)

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Table 2

Association between incident atrial fibrillation and subsequent risk of end-stage renal disease among adults with chronic kidney disease

	Hazard Ratio (95% Confidence Interval)
Unadjusted	1.18 (1.06 –1.31)
Adjusted for patient characteristics, cardiovascular risk factors and medication use[†]	1.67 (1.46 – 1.91)

[*] Included patient age, gender, race, education, income level, eGFR level, albuminuria, hemoglobin level, diabetes mellitus, hypertension, coronary heart disease, ischemic stroke, transient ischemic attack, heart failure, peripheral arterial disease, dyslipidemia, chronic lung disease, chronic liver disease, hyperthyroidism and baseline medication use (β-blockers, ACE inhibitors/ARBs, calcium channel blockers, diuretics, statins, other lipid lowering agents, warfarin, antiplatelet agents).