

Cardiovascular Events after New-Onset Atrial Fibrillation in Adults with CKD: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study

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ABSTRACT

Background Atrial fibrillation (AF), the most common sustained arrhythmia in CKD, is associated with poor clinical outcomes in both patients without CKD and patients with dialysis-treated ESRD. However, less is known about AF-associated outcomes in patients with CKD who do not require dialysis.

Methods To prospectively examine the association of new-onset AF with subsequent risks of cardiovascular disease events and death among adults with CKD, we studied participants enrolled in the Chronic Renal Insufficiency Cohort Study who did not have AF at baseline. Outcomes included heart failure, myocardial infarction, stroke, and death occurring after diagnosis of AF. We used Cox regression models and marginal structural models to examine the association of incident AF with subsequent risk of cardiovascular disease events and death, adjusting for patient characteristics, laboratory values, and medication use.

Results Among 3080 participants, 323 (10.5%) developed incident AF during a mean 6.1 years of follow-up. Compared with participants who did not develop AF, those who did had higher adjusted rates of heart failure (hazard ratio [HR], 5.17; 95% confidence interval [95% CI], 3.89 to 6.87), myocardial infarction (HR, 3.64; 95% CI, 2.50 to 5.31), stroke (HR, 2.66; 95% CI, 1.50 to 4.74), and death (HR, 3.30; 95% CI, 2.65 to 4.12). These associations remained robust with additional adjustment for biomarkers of inflammation, cardiac stress, and mineral metabolism; left ventricular mass; ejection fraction; and left atrial diameter.

Conclusions Incident AF is independently associated with two- to five-fold increased rates of developing subsequent heart failure, myocardial infarction, stroke, or death in adults with CKD. These findings have important implications for cardiovascular risk reduction.

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Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide.¹ Patients with CKD comprise nearly 14% of the population² and have even greater burden of AF.^{3,4} The incidence of AF is estimated to be two- to three-fold higher⁵ in patients with CKD compared with the general population.

In the absence of CKD, it is well established that AF is associated with poor outcomes such as ischemic stroke, heart failure (HF), myocardial infarction (MI), and death.^{6–14} Similarly, in patients with ESRD treated with chronic dialysis, studies have

reported that AF is also linked with excess risks of stroke and death.^{15–18} However, less is known about outcomes associated with AF in the substantially

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larger, nondialysis-requiring population of patients with CKD. In a study of patients with CKD in a large health care delivery system, we previously reported that incident AF was associated with greater risk of all-cause death but were not able to address other important individual cardiovascular outcomes.¹⁹

Given the growing population with CKD and AF, a better understanding of clinical outcomes in patients with CKD who develop AF would have potentially important implications for the management of this high-risk group of patients. This study aimed to determine the association of incident AF on the risk of subsequent cardiovascular events, including HF, MI, and deaths among adults with CKD. We hypothesized that CKD participants who developed incident AF would have greater risk of all types of cardiovascular events, particularly HF and stroke, compared with those who did not develop AF.

METHODS

Study Population

A total of 3939 adults were enrolled into the Chronic Renal Insufficiency Cohort (CRIC) study between June 2003 and August 2008 at seven clinical centers nationally (Ann Arbor/Detroit, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland/San Francisco, CA). Men and women were eligible for the study if they were between 21 and 74 years of age and met the following age-specific eGFR criteria: 20–70 ml/min per 1.73 m² for age 21–44 years, 20–60 ml/min per 1.73 m² for age 45–64 years, and 20–50 ml/min per 1.73 m² for age 65–74 years. Exclusion criteria included severe (New York Heart Association class III/IV) HF and polycystic kidney disease, among others previously described.²⁰ Details on study design and baseline characteristics of the participants were previously published.^{20,21} All study participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites.

A total of 3080 participants were included in this analysis after excluding persons with prevalent AF at entry ($n=830$), which was determined by self-report or presence of AF on 12-lead electrocardiogram (ECG) at entry³ and those with missing baseline covariates ($n=29$).

Predictor Variable

Incident AF was the main predictor of interest and was determined by identification of hospitalizations or emergency department visits involving AF during study follow-up. Participants were asked twice yearly if they were hospitalized and electronic health records from corresponding hospitals or health care systems were queried for qualifying encounters. Diagnostic codes for AF and other arrhythmias prompted retrieval of medical records and centralized adjudicated review for the presence of AF. At least two study physicians

Significance Statement

Atrial fibrillation, the most common cardiac arrhythmia in adults with kidney disease, is linked with an increased risk of ischemic stroke and death in patients with dialysis-treated ESRD; less is known about outcomes associated with atrial fibrillation among patients with CKD who do not require dialysis. To evaluate whether development of this arrhythmia is linked with other important cardiovascular outcomes among nondialysis patients with CKD, the authors studied a large, well characterized, longitudinal cohort of adult patients with CKD, finding that incident atrial fibrillation was independently associated with two- to five-fold increased risks of developing subsequent heart failure, myocardial infarction, stroke, or death. These findings have important implications for cardiovascular risk reduction in patients with CKD.

reviewed all possible AF events by manual review of relevant medical records and ECGs, if available, using standardized criteria. All discordances were discussed by the two reviewers and resolved. AF was confirmed when both reviewers agreed upon the diagnosis of AF.

Outcomes

The primary outcomes were adjudicated HF, MI, and stroke as well as all-cause death and a composite outcome (HF, MI, stroke, or mortality) that occurred after incident AF and until March 31, 2013. Deaths were identified from report from next of kin, retrieval of death certificates or obituaries, review of hospital and outpatient records, and searching Social Security Death vital status and state death certificate files, if available.

Study participants were queried every 6 months during alternating in-person and telephone visits about whether they were hospitalized, experienced a possible cardiovascular disease (CVD) event, or underwent a selected set of diagnostic tests/procedures. The International Classification of Diseases, Ninth Revision discharge codes were obtained for all hospitalizations and relevant medical records were retrieved for review by at least two study physicians to ascertain events of HF, MI, and stroke.

HF events were determined on the basis of clinical symptoms, radiographic evidence of pulmonary edema, physical examination of the heart and lungs, central venous hemodynamic monitoring data, and echocardiographic imaging in hospitalized patients modeled after Framingham and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial criteria.^{22,23} Diagnosis of probable or definite MI was made on the basis of symptoms consistent with acute ischemia, cardiac biomarker levels, and ECGs as recommended by a consensus statement on the universal definition of MI.²⁴ Two neurologists reviewed all hospitalizations and emergency department visits suggestive of stroke. Outcomes included both probable and definite ischemic stroke. The latter was determined on the basis of autopsy findings or sudden onset of neurologic symptoms supported with computed tomography or magnetic resonance imaging demonstration of

infarction in a territory where an injury or infarction would be expected to create those symptoms. The former was defined as sudden or rapid onset of one major or two minor neurologic signs or symptoms within a cerebrovascular distribution lasting for more than 24 hours or until the patient died, without evidence of hemorrhage or infarction on computed tomography or magnetic resonance imaging performed within 24 hours of the onset of symptoms, and with no alternative explanation.²⁵

Covariates

At the baseline study visit and each subsequent study visit, participants provided information on their sociodemographic characteristics, medical history (including prior CVD and history of hypertension), medication usage (including antiplatelet agents and warfarin), and lifestyle behaviors (e.g., tobacco use). Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other. Diabetes mellitus was defined as a fasting glucose >126 mg/dl, a nonfasting glucose >200 mg/dl, or use of insulin or other antidiabetic medication. Anthropometric measurements and BP were assessed using standard protocols.²⁶ Body mass index (BMI) was derived as weight in kilograms divided by height in meters squared. Serum creatinine concentration was measured using an enzymatic method on an Ortho Vitros 950 at the CRIC study Central Laboratory and standardized to isotope dilution mass spectrometry-traceable values.^{27–29} eGFR was calculated from serum creatinine and cystatin C using the CRIC study equation.²⁹ Additional assays measured 24-hour urine total protein, fibroblast growth factor-23 (FGF23), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hsTnT), and high-sensitivity C-reactive protein (hs-CRP). Transthoracic echocardiograms were performed 1 year after enrollment and provided data on left ventricular ejection fraction and left ventricular mass index,^{30–33} and were quantified centrally by a highly trained, registered diagnostic cardiac sonographer.

Statistical Analyses

All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). We compared baseline characteristics of participants who did versus did not develop incident AF using *t* tests or chi-squared methods, as appropriate. Crude rates of each outcome were calculated per 100 person years for those with and without incident AF with associated 95% confidence intervals (95% CIs).

We performed multivariable Cox proportional hazards regression to examine the association between development of incident AF during follow-up and risk of each type of CVD event and death. AF was classified as 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.

Covariates in the models were selected on the basis of biologic plausibility. Only participants with all covariates available at baseline were included in the analyses. Baseline variables included in models were sociodemographic characteristics; clinical center; diabetes; hypertension; self-reported history of HF, coronary heart disease, or stroke (*i.e.*, prevalent CVD); tobacco use; systolic BP; BMI; eGFR; proteinuria level; BMI; LDL cholesterol; HDL cholesterol; use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ARBs); and use of β -blockers and diuretics. For this analysis, patients were censored at occurrence of the outcome event, death, loss to follow-up, or end of administrative follow-up on March 31, 2013.

In a secondary analysis, given the concern for potential time-dependent confounding, we fit marginal structural models (MSMs), which applies inverse probability weighting in a discrete time failure causal inference model structure.³⁴ A substantial body of work has emerged demonstrating the usefulness of statistical tools like MSMs in the areas of CKD.^{35,36} Briefly, a MSM is a two-step approach wherein models are first fit to predict the probability of AF during follow-up (*i.e.*, the exposure of interest) and the probability of noncensoring in each time window, and second, inverse-probability weighted models are then fit for the outcomes. Inverse-probability weighting was also used to handle censoring events and missing data. For extreme weights, an upper and lower bound was set and any values above or below those thresholds were assigned to those limit values. In the MSM, both AF and covariates were time-updated with the exception of sex, race/ethnicity, and education level.³⁷ Missing covariates during follow-up were assumed to be the same as the last observation. Hazards ratios (HRs) and 95% CIs were reported for all models.

We performed several additional sensitivity analyses. First, we repeated our analyses stratifying (and testing for interaction) by demographic features and prevalent CVD: age (\leq or $>$ 45 years), sex, race (black and nonblack), history of HF, history of MI, and history of stroke. Second, we adjusted for use of warfarin and antiplatelet agents to determine whether treatment for AF attenuated the observed associations. Third, we adjusted for levels of targeted biomarkers reflecting altered mineral metabolism (FGF23), cardiac stress (NT-proBNP and hsTnT), and inflammation (hs-CRP). These biomarkers have all been shown to be associated with AF in prior studies.^{38–42} Fourth, we adjusted for measures of subclinical HF as ascertained by echocardiograms 1 year after entry, including left ventricular hypertrophy, left ventricular ejection fraction, and left atrial diameter, because these measures are associated with incident AF and many of our outcomes of interest and thus may be important confounders. Finally, we excluded participants in whom incident AF and either HF or MI occurred during the same hospitalization.

RESULTS

Participant Characteristics

There were 323 patients with incident AF (10.5% of study population) observed during follow-up. Participants who developed incident AF were more likely to be older, men, white, have a prior history of CVD, higher BP and BMI, and lower entry eGFR (Table 1). Furthermore, those who developed incident AF were also more likely to use antiplatelet agents or warfarin, and have higher levels of circulating FGF23, hs-CRP, NT-proBNP, and hsTnT. They also had higher left ventricular mass index, higher left atrial diameter, and lower left ventricular ejection fraction on ECG (Table 1).

Rates of Cardiovascular Events after Incident AF

Mean (SD) follow-up time was 6.10 (2.7) years. Among patients without a history of HF, the crude rate of HF hospitalization was several-fold higher among patients who developed incident AF compared with those who did not (Figure 1,

Table 2). Similarly, rates of MI and stroke were higher among incident AF participants. The overall rate of death along or the composite of death or any incident CVD event was nearly five-fold higher among participants with incident AF versus those without AF.

Association of Incident AF with Subsequent Cardiovascular Events

In multivariable Cox models, incident AF was significantly associated with three- to six-fold greater rate of HF, MI, stroke, and death in all models (Table 2). After adjustment for demographics, comorbidity, medication use, and kidney function level, incident AF was associated with substantially higher adjusted rates of HF (HR, 5.17; 95% CI, 3.89 to 6.87), MI (HR, 3.64; 95% CI, 2.50 to 5.31), and stroke (HR, 2.66; 95% CI, 1.50 to 4.74). Furthermore, the adjusted rate of all-cause death and the composite of death or CVD event was greater among participants who developed incident AF (adjusted HR, 3.30 [95% CI, 2.65 to 4.12] and 3.68 [95% CI, 2.99 to 4.53], respectively).

Table 1. Characteristics at study entry in participants who did or did not develop incident AF

Characteristic	Incident AF, n=323	No Incident AF, n=2757	P Value
Age, mean (SD), yr	61.6 (9.2)	57.3 (11.2)	<0.001
Women, N (%)	129 (39.9)	1258 (45.6)	0.05
Race/ethnicity, N (%)			
Non-Hispanic white	165 (51.1)	1156 (41.9)	0.009
Non-Hispanic black	119 (36.8)	1120 (40.6)	
Hispanic	30 (9.3)	365 (13.2)	
Other	9 (2.8)	116 (4.2)	
Diabetes mellitus, N (%)	171 (52.9)	1290 (46.8)	0.04
Hypertension, N (%)	298 (92.3)	2341 (84.9)	<0.001
Prior MI or coronary revascularization, N (%)	103 (31.9)	449 (16.3)	<0.001
History of stroke, N (%)	36 (11.1)	231 (8.4)	0.10
History of HF, N (%)	38 (11.8)	145 (5.3)	<0.001
History of peripheral vascular disease, N (%)	24 (7.4)	158 (5.7)	0.22
Any prior CVD, N (%)	143 (44.3)	723 (26.2)	<0.001
Current smoker, N (%)	41 (12.7)	361 (13.1)	0.84
Systolic BP, mean (SD), mm Hg	131.9 (21.9)	127.7 (21.7)	0.001
BMI, mean (SD), kg/m ²	33.0 (7.9)	31.8 (7.7)	0.01
eGFR, ml/min per 1.73 m ² , N (%)			
<30	78 (24.1)	514 (18.6)	<0.001
30–44	127 (39.3)	885 (32.1)	
45–59	81 (25.1)	814 (29.5)	
≥60	37 (11.5)	544 (19.7)	
Urine protein, median (IQR), g/24 h	0.2 (0.1–0.9)	0.2 (0.1–1.0)	0.27
Aspirin use, N (%)	167 (51.7)	1130 (41.0)	<0.001
Antiplatelet use, N (%)	177 (54.8)	1212 (44.0)	<0.001
Warfarin use, N (%)	20 (6.2)	59 (2.1)	<0.001
FGF23, median (IQR), RU/ml	163.7 (109.2–255.0)	135.5 (91.7–219.3)	<0.001
hs-CRP, median (IQR), mg/L	3.4 (1.3–7.6)	2.4 (1.0–5.9)	<0.001
NT-proBNP, median (IQR), pg/ml	326.7 (120.2–678.2)	120.2 (53.8–291.6)	<0.001
hsTnT, median (IQR), pg/ml ECG parameters	16.5 (9.1–32.5)	10.7 (5.1–20.9)	<0.001
Left ventricular hypertrophy, N (%)	158 (65.3)	969 (47.4)	<0.001
Left ventricular mass index, median (IQR), g/m ²	55.4 (46.7–64.3)	47.8 (40.7–57.3)	<0.001
Left atrial diameter, mean (SD), cm	4.1 (0.7)	3.9 (0.6)	<0.001
Left ventricular ejection fraction, median (IQR)	54.5 (49.0–57.8)	55.5 (51.9–59.3)	<0.001

IQR, interquartile range.

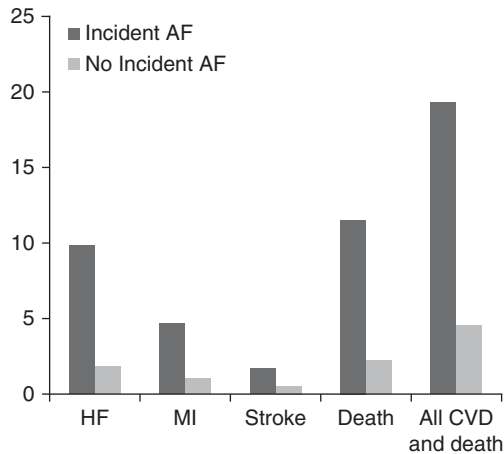


Figure 1. Incidence rates of cardiovascular events and death are higher in participants who developed incident atrial fibrillation versus those who did not.

Incident AF and Subsequent Cardiovascular Events using MSMs

Using MSM, the direction and strength of associations of incident AF with subsequent CVD events and death were similar to those observed using our primary analytic approach (Supplemental Table 1).

Sensitivity Analyses: Subgroup Analyses

We stratified and tested for potential interactions by age (\leq or >45 years), sex, race (black and nonblack), history of HF, history of MI, and history of stroke. The association of incident AF with HF, MI, stroke, and death were consistent across participant subgroups, and none of the interaction tests were statistically significant (Figure 2, A, D, and E).

Sensitivity Analyses: Incident AF and Subsequent Cardiovascular Events, Adjusting for Potential Mediators

We first adjusted for longitudinal use of antiplatelet and anti-coagulant agents in addition to the fully adjusted models, and this yielded very similar associations of incident AF with subsequent incident CVD events (Table 3). With adjustment for circulating biomarkers of inflammation, mineral metabolism, and cardiac biomarkers of stress, the associations of incident AF with subsequent CVD events remained statistically significant. Adjustment for left ventricular hypertrophy, left ventricular ejection fraction, and left atrial diameter led to modest attenuation in the models; however, even with these additional adjustments, the associations of incident AF with HF, MI, and death remained statistically significant, whereas the association with stroke did not (Table 3).

Sensitivity Analysis: Exclusion of Participants with Incident AF and MI or HF during the Same Hospitalization

A total of 28 participants had a diagnosis of incident AF and HF and 20 participants had a diagnosis of incident AF and MI during the same hospitalization. Excluding these participants, the adjusted multivariable association of incident AF with HF remained robust (adjusted HR, 2.87; 95% CI, 2.02 to 4.08). The association of incident AF with MI was attenuated and no longer statistically significant (adjusted HR, 1.56; 95% CI, 0.92 to 2.65).

DISCUSSION

Among a large, well characterized, and diverse prospective cohort of patients with CKD without AF, we found strong

Table 2. Association of time-updated incident AF with risk of subsequent cardiovascular events and death in adults with CKD

Cardiovascular Events	Number of Events	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
HF				
No incident AF	344	Ref	Ref	Ref
Incident AF	66	5.99 (4.55–7.89)	6.06 (4.59–8.01)	5.17 (3.89–6.87)
Acute MI				
No incident AF	198	Ref	Ref	Ref
Incident AF	36	4.81 (3.33–6.95)	4.28 (2.95–6.22)	3.64 (2.50–5.31)
Stroke				
No incident AF	106	Ref	Ref	Ref
Incident AF	15	3.47 (1.98–6.09)	3.14 (1.78–5.54)	2.66 (1.50–4.74)
Death				
No incident AF	461	Ref	Ref	Ref
Incident AF	111	4.50 (3.64–5.57)	4.14 (3.33–5.15)	3.30 (2.65–4.12)
Composite outcome of HF, acute MI, stroke, and death				
No incident AF	827	Ref	Ref	Ref
Incident AF	112	4.38 (3.57–5.36)	4.20 (3.42–5.15)	3.68 (2.99–4.53)

Model 1: adjusted for age, sex, race/ethnicity, clinical site. Model 2: adjusted for model 1 plus diabetes, hypertension, any history of CVD, tobacco use, systolic BP, BMI, eGFR, proteinuria, BMI, LDL cholesterol, HDL cholesterol, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, β -blocker use, and diuretic use. Ref, reference value.

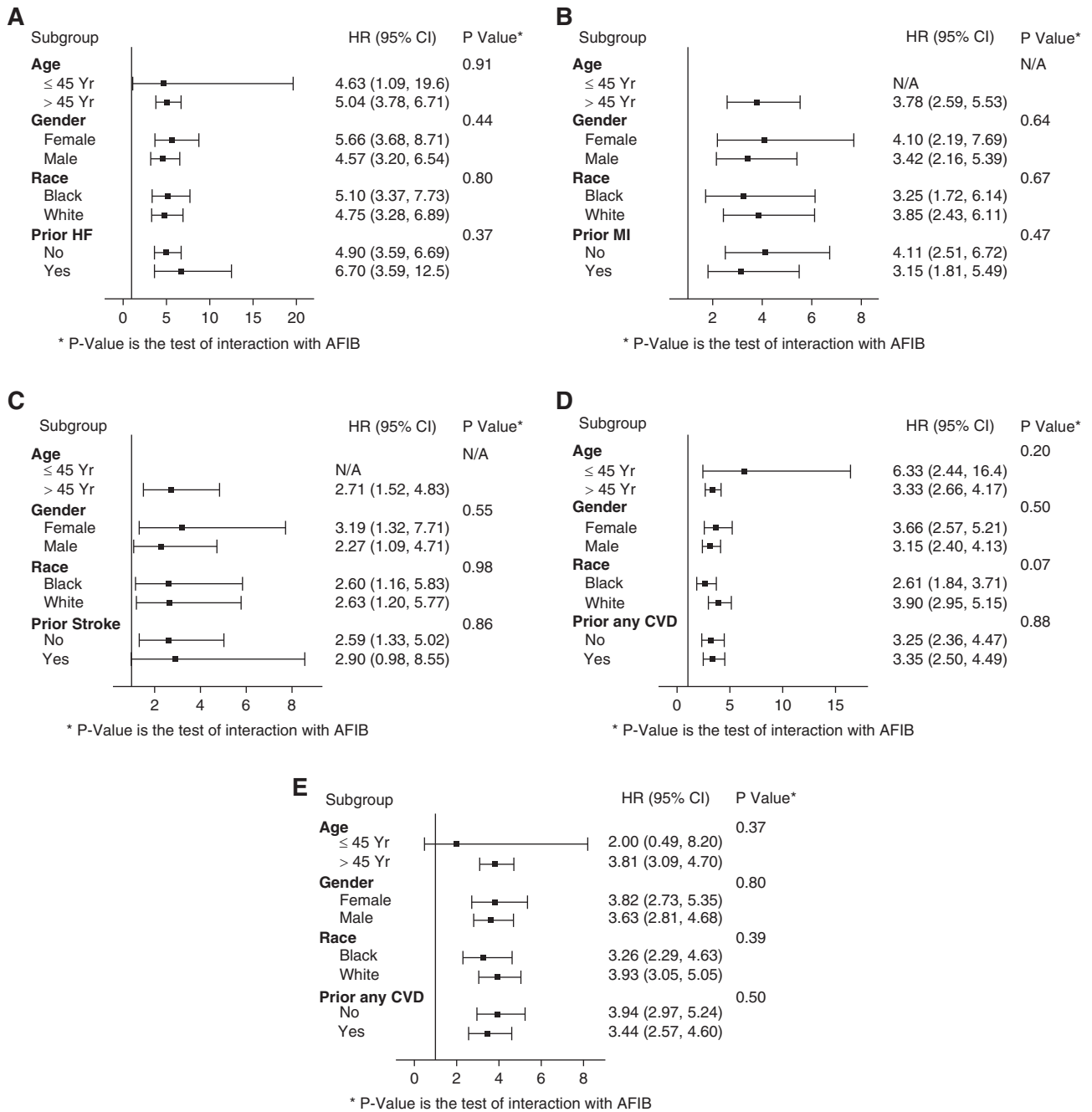


Figure 2. Adjusted association of incident atrial fibrillation with risk of heart failure is similar across patient subgroups. (B) Adjusted association of incident atrial fibrillation with risk of acute myocardial infarction is similar across patient subgroups. (C) Adjusted association of incident atrial fibrillation with risk of stroke is similar across patient subgroups. (D) Adjusted association of incident atrial fibrillation with risk of death from any cause is similar across patient subgroups. (E) Adjusted association of incident atrial fibrillation with risk of the composite of heart failure, acute myocardial infarction, stroke or death is similar across patient subgroups. All models adjusted for age, sex, race/ethnicity, clinical site, diabetes, hypertension, any history of cardiovascular disease, tobacco use, systolic blood pressure, BMI, eGFR, proteinuria, BMI, LDL cholesterol, HDL cholesterol, ACEi/ARB use, β -blocker use, and diuretic use. ACEi, angiotensin-converting enzyme inhibitor; AFIB, atrial fibrillation; ARB, angiotensin receptor blocker; N/A, no events observed in subgroup.

associations of incident AF with subsequent CVD events. Incident AF was associated with a two- to six-fold increased rate of HF, MI, stroke, and death, even accounting for a broad range of potential confounders. These associations

were consistent across demographic and clinical characteristics and remained robust even after adjustment for use of antiplatelet and anticoagulant therapies; circulating biomarkers of inflammation, cardiac stress, and mineral metabolism; and measures of

Table 3. Association of time-updated incident AF with risk of subsequent cardiovascular events and death after adjustment for potential mediators among adults with CKD

Cardiovascular Events	Adjusted Model ^a	Adjusted Model ^a Plus Adjustment for Warfarin and Antiplatelet Agent Use HR (95% CI)	Adjusted Model ^a Plus Adjustment for Baseline hs-CRP, NT-proBNP, hsTnT, and FGF23 Levels HR (95% CI)	Adjusted Model ^a Plus Adjustment for ECG Measures: LVM, LVEF, and LA Diameter HR (95% CI)
HF				
No incident AF	Ref	Ref	Ref	Ref
Incident AF	5.17 (3.89–6.87)	5.17 (3.89–6.88)	4.91 (3.68–6.56)	4.54 (3.23–6.39)
Acute MI				
No incident AF	Ref	Ref	Ref	Ref
Incident AF	3.64 (2.50–5.31)	3.65 (2.50–5.34)	3.60 (2.47–5.26)	3.05 (1.94–4.78)
Stroke				
No incident AF	Ref	Ref	Ref	Ref
Incident AF	2.66 (1.50–4.74)	2.57 (1.44–4.61)	2.71 (1.52–4.84)	1.86 (0.91–3.77)
Death				
No incident AF	Ref	Ref	Ref	Ref
Incident AF	3.30 (2.65–4.12)	3.28 (2.63–4.09)	3.14 (2.51–3.93)	3.12 (2.36–4.11)
Composite outcome of HF, acute MI, stroke, and death				
No incident AF	Ref	Ref	Ref	Ref
Incident AF	3.68 (2.99–4.53)	3.69 (2.99–4.55)	3.45 (2.79–4.26)	3.40 (2.64–4.38)

LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LA, left atrial; Ref, reference value.

^aAdjusted for age, sex, race/ethnicity, clinical site, diabetes, hypertension, any history of CVD, tobacco use, systolic BP, BMI, eGFR, proteinuria, BMI, LDL cholesterol, HDL cholesterol, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, β -blocker use, and diuretic use.

structural cardiac impairment that may mediate the observed associations.

We found that incident AF was associated with a nearly six-fold increased adjusted rate of HF and a four-fold increased adjusted rate of MI in a large, multicenter CKD population, in whom the clinical consequences of AF have been less well defined. Our findings are novel in that we focused on other outcomes (beyond stroke and death) such as HF and MI, which are less studied in relation to AF, particularly in CKD. One recent study of 1.4 million patients from Ontario with eGFR < 90 ml/min per 1.73 m² (mean eGFR 69 ml/min per 1.73 m²) also found that development of incident AF was significantly associated with greater risk of HF, MI, and mortality, particularly in the first 6 months from diagnosis.⁴³ The findings were largely similar to our study, with some key differences. Our study population had more advanced CKD with higher burden of comorbidity such as diabetes and hypertension compared with the Ontario population, likely contributing to the higher event rate in our study. The events in our study were ascertained by physician adjudication versus use of administrative codes in the Ontario study. We were able to adjust for a larger number of systematically collected covariates including relevant medications, key laboratory values including proteinuria, and measures from transthoracic echocardiograms. Our study materially extends the literature by providing more rigorous support for the strong association between incident AF and subsequent CVD events in adults with CKD.

Prior studies in the non-CKD population have also reported strong links between AF and HF.^{6–12,44,45} Among participants

in the Framingham study, AF was associated with a two-fold increased risk of incident HF,⁴⁶ and HF was the most common nonfatal CVD outcome after AF in Medicare beneficiaries.¹⁴ Other studies in non-CKD cohorts have also noted an association between AF and risk of MI.^{7,47} In a meta-analysis of 104 cohorts, AF was associated with a 1.5- to five-fold increased risk of death, stroke, coronary heart disease, and HF.⁶ In the Ontario study, there was a statistically significant interaction by eGFR level, with stronger associations of incident AF with CVD events among those with higher eGFR/without CKD, particularly for the outcome of HF within the first 6 months of diagnosis of AF for which the risk was 14-fold higher compared with those without AF.⁴³ It is unclear why the magnitude of this association is so large compared with previous studies of patients without CKD. Possible reasons include residual confounding because some key covariates were not available, differences in treatment among patients with lower eGFR (greater use of cardioprotective medications), or misclassification of the outcome at lower eGFR (HF versus volume overload for example).

There are several plausible mechanisms to explain our findings. AF and HF have shared risk factors such as abnormal left ventricular structure/function, cardiac stretch from volume expansion, and inflammation, all of which are more common in CKD.^{48–52} Thus, it is possible that AF may reflect impending clinical HF. Patients with CKD have greater burden of vascular calcification, which in combination with greater cardiac demand, may contribute to subsequent MI.⁵³ It is also possible that shared risk factors between MI

and AF, such as hypertension and others, also help to explain the observed associations. Alternatively, AF over time may lead to structural and functional cardiac abnormalities and thus may be a precipitating factor for both HF and MI. Our study supports further efforts to elucidate these mechanisms to reduce AF-related complications in patients with CKD.

We found that incident AF was associated with ischemic stroke and death in patients with CKD. Among patients on dialysis, prior reports have also confirmed an association between AF and ischemic stroke^{18,54}; however, evidence in nondialysis-requiring CKD is limited. Our study augments previous literature reporting an association between incident AF and ischemic stroke in patients with CKD. In addition to stroke, studies of CKD and non-CKD populations have also shown a strong association of AF with risk of death.^{19,44,55}

We adjusted for several biologic shared risk factors that may contribute to the association of incident AF with subsequent CVD events. Inflammation and cardiac stress have been implicated in the pathogenesis of AF and other types of CVD, yet our results remained strong with adjustment for hs-CRP, NT-proBNP, and hsTnT.^{38–42} Alterations in mineral metabolism represent a novel mechanism linking kidney disease and AF and HF.^{39,56,57} The observed associations remained strong with adjustment for FGF23. Adjustment for echocardiographic measures led to the greatest attenuation of the observed associations, although they remained statistically significant. Prior reports have also noted strong associations of elevated left ventricular mass and decreased left ventricular ejection fraction with risk of developing AF.^{58,59} As noted above, it is possible that ventricular dysfunction may lead to AF, or alternatively, AF may contribute to ventricular dysfunction.

The strong associations of incident AF with HF, MI, stroke, and death were consistent across subgroups by age, sex, race, and prevalent CVD. These findings are interesting because older adults, men and white patients are at significantly higher risk for developing AF.^{60–64} Our findings showing similar results in white and black patients with CKD are in contrast with certain previous studies suggesting a higher risk of AF-related complications in blacks compared with whites in the general population.^{7,54}

Our study was strengthened by examination of a carefully followed cohort with extensive cardiovascular measures and long follow-up time. Incident AF and the CVD events of interest were systematically ascertained and confirmed by adjudication using standardized criteria. We were able to adjust for a large number of relevant covariates, including echocardiographic measures, as well as multiple circulating biomarkers that may be important confounders or mediators. In sensitivity analyses using MSMs, we did not find evidence of strong time-dependent confounding. We also recognize several limitations. The number of outcomes that occurred after development of incident AF was modest, particularly for

stroke, which may have affected the precision for that outcome. We were not able to characterize the type of AF (*e.g.*, paroxysmal, persistent, *etc.*). This was a cohort of patients with CKD only, so we were not able to directly compare our findings in patients without CKD. We did not have detailed data on adherence to or dosages of medications (including antiplatelet and anticoagulant medications). As an observational study, we cannot determine causality, and given that our study involved research volunteers and a significant proportion of participants were followed by nephrologists, our results may not be generalizable to all CKD populations.

In conclusion, incident AF was independently associated with notably higher rates of HF, MI, stroke, and death in a diverse adult population with CKD. Further studies should delineate mechanisms that may link AF with these cardiovascular complications and to investigate whether AF therapies can mitigate the observed excess risks of adverse outcomes.

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N.B. and A.S.G. designed the study. D.X. and D.S. conducted statistical analyses. N.B., D.X., D.S., and A.S.G. were responsible for interpretation of data. N.B., D.X., D.S., L.J.A., R.D., H.I.F., J.H., K.J., J.W.K., S.M., S.D.N., M.R., A.C.R., E.Z.S., R.T., and A.S.G. drafted and revised the manuscript. All authors approved the final version of the manuscript.

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DISCLOSURES

None.

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SUPPLEMENTAL TABLE

Supplemental Table 1. Marginal structural model* results for the association of incident atrial fibrillation with subsequent incident cardiovascular events in adults with chronic kidney disease.

<i>Outcome</i>	<i>Estimated HR (95% CI)</i>	<i>p-value</i>
Incident heart failure		
No Incident AF	Ref	
Incident AF	4.80 (3.51 - 6.56)	<.0001
Incident MI		
No Incident AF	Ref	
Incident AF	3.10 (2.11 - 4.54)	<.0001
Incident stroke		
No Incident AF	Ref	
Incident AF	1.75 (0.99 - 3.09)	0.02
Death		
No Incident AF	Ref	
Incident AF	3.69 (2.93 - 4.64)	<.0001
Composite of death and incident CVD		
No Incident AF	Ref	
Incident AF	3.68 (2.91 - 4.66)	<.0001

*Adjusted for age, sex, race/ethnicity, clinical site, diabetes, hypertension, any history of cardiovascular disease, tobacco use, systolic blood pressure, BMI, eGFR, proteinuria, BMI, LDL cholesterol, HDL cholesterol, ACEi/ARB use, β -blocker use and diuretic use

SIGNIFICANCE STATEMENT

Atrial fibrillation, the most common cardiac arrhythmia in adults with kidney disease, is linked with an increased risk of ischemic stroke and death in patients with dialysis-treated ESRD; less is known about outcomes associated with atrial fibrillation among patients with CKD who do not require dialysis. To evaluate whether development of this arrhythmia is linked with other important cardiovascular outcomes among nondialysis patients with CKD, the authors studied a large, well characterized, longitudinal cohort of adult patients with CKD, finding that incident atrial fibrillation was independently associated with two- to five-fold increased risks of developing subsequent heart failure, myocardial infarction, stroke, or death. These findings have important implications for cardiovascular risk reduction in patients with CKD.