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Atrial Fibrillation and Longitudinal Change in Cognitive Function in CKD

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Background: Studies in the general population suggest that atrial fibrillation (AF) is an independent risk factor for decline in cognitive function, but this relationship has not been examined in adults with chronic kidney disease (CKD). We investigated the association between incident AF and changes in cognitive function over time in this population.

Methods and Results: We studied a subgroup of 3254 adults participating in the Chronic Renal Insufficiency Cohort Study. Incident AF was ascertained by 12-lead electrocardiogram (ECG) obtained at a study visit and/or identification of a hospitalization with AF during follow-up. Cognitive function was assessed biennially using the Modified Mini-Mental State Exam. Linear mixed effects regression was used to evaluate the association between incident AF and longitudinal change in cognitive function. Compared with individuals without incident AF ($n = 3158$), those with incident AF ($n = 96$) were older, had a higher prevalence of cardiovascular disease and hypertension, and lower estimated glomerular filtration rate. After median follow-up of 6.8 years, we observed no significant multivariable association between incident AF and change in cognitive function test score.

Conclusion: In this cohort of adults with CKD, incident AF was not associated with a decline in cognitive function.

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AF is the most common clinically significant arrhythmia worldwide, and evidence suggests that it is highly prevalent in persons with CKD.[1] Furthermore, clinical studies in populations without CKD have shown that AF is an independent risk factor for stroke and mortality.[2] Previous studies suggest that AF may increase the risk for cognitive decline in non-CKD populations.[3–5] Potential pathways linking AF with cognitive decline include brain hypoperfusion, subclinical strokes, and inflammation.[5] However, the impact of AF on cognitive decline in CKD remains unclear. This is a question of particular relevance because individuals with CKD are at substantially higher risk for developing cognitive impairment compared with the general population.[6,7] To address this question, we investigated the association between incident AF and changes in cognitive function over time in adults enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study, a large multicenter prospective cohort study of adults with CKD. We

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hypothesized that incident AF would be associated with decline in cognitive function.

METHODS

Study Participants

The CRIC Study is an ongoing multicenter study of 3939 adults with CKD enrolled between June 2003 and August 2008 at 7 medical centers in the United States (Chicago, Illinois; Oakland/San Francisco, California; Ann Arbor/Detroit, Michigan; Baltimore, Maryland; Cleveland, Ohio; New Orleans, Louisiana; Philadelphia, Pennsylvania).[8] All study participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites.

For this study, we excluded 673 participants with prevalent AF (determined by self-report or presence of AF on 12-lead ECG at study entry) and 12 missing cognitive function measurements (Figure 1). In addition, we conducted exploratory analyses in a smaller subset of 825 individuals who participated in an ancillary study (CRIC Cognition Study).[9] This ancillary study began in 2006 and enrolled participants aged 55 years or older from 4 CRIC centers.

Measurements and Variable Definition

Demographic characteristics (age, sex, race/ethnicity [non-Hispanic White, non-Hispanic Black, Hispanic, or other], education, marital status, annual household income, and health insurance) were ascertained at baseline; clinical and laboratory data were obtained at baseline and updated annually.[8] At baseline and annually, information was collected on medical history (hypertension, diabetes, previous myocardial infarction/coronary revascularization, heart failure, stroke, peripheral artery disease [defined as self-report of claudication, amputation, or revascularization procedure of the extremities]), smoking habits, alcohol intake (defined as participant self-report of current or former use of beer, wine, or liquor), and medication use (including antiplatelet agents [aspirin, clopidogrel, and other platelet aggregation inhibitors] and warfarin). Body mass index (kg/m^2) was calculated using measured height and weight. Blood pressure measurements were obtained using a standardized approach. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Serum creatinine was measured by an enzymatic method from Ortho Clinical Diagnostics through October 2008 and by the Jaffe method from Beckman Coulter thereafter, and standardized to isotope dilution mass spectrometry-traceable values. Serum cystatin C was measured using a particle-enhanced immunonephelometric assay on the BN II System (Siemens, Munich, Germany). Glomerular filtration rate (GFR) was estimated at baseline and each annual visit using the serum creatinine and cystatin C-based equation developed in a subgroup of CRIC participants with measured iothalamate GFR.[10] Urinary total protein and creatinine were measured using standard assays. Diabetes mellitus was defined by a fasting glucose ≥126 mg/dl or use of insulin or oral hypoglycemic medications; hypertension was defined by a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications.

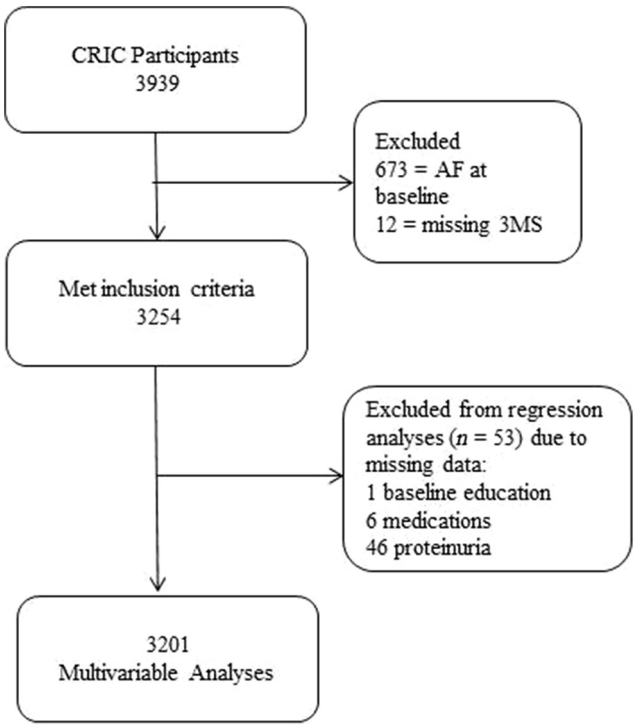

Figure 1. Flow chart for analytic cohort. AF, atrial fibrillation; CRIC, Chronic Renal Insufficiency Cohort.

Predictor Variable

Incident AF was the main predictor of interest. Incident AF was ascertained by ECG obtained at study visits and/or identification of hospitalizations with AF during study follow-up. Participants were asked twice yearly if they were hospitalized, and electronic health records from selected hospitals or health care systems were additionally 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 2 study physicians reviewed all possible AF events by manual review of relevant medical records and ECG. All discordances were discussed by the 2 reviewers and resolved. AF was confirmed when both reviewers agreed on the diagnosis of AF.

Assessment of Cognitive Function

Participants completed the Modified Mini-Mental State Exam (3MS) biennially except for individuals older

Table 1. Baseline characteristics

	Overall $n = 3254$	No incident AF $n = 3158$	Incident AF $n = 96$
Age, y	57.0 (11.2)	56.9 (11.2)	61.1 (9.130)[b]
Female	1461 (44.9)	1421 (45.0)	40 (41.7)
Non-Hispanic White	1363 (41.9)	1320 (41.8)	43 (44.8)
Non-Hispanic Black	1317 (40.5)	1280 (40.5)	37 (38.5)
Hispanic	441 (13.6)	429 (13.6)	12 (12.5)
Other	133 (4.1)	129 (4.1)	4 (4.2)
Education <High school	659 (20.3)	636 (20.2)	23 (24.0)
Income <$20,000	992 (30.5)	960 (30.4)	32 (33.3)[a]
Cardiovascular disease	918 (28.2)	875 (27.7)	43 (44.8)[b]
Myocardial infarction or prior coronary revascularization	582 (17.9)	554 (17.5)	28 (29.2)[b]
Peripheral arterial disease	196 (6.0)	188 (6.0)	8 (8.3)
Stroke	288 (8.9)	277 (8.8)	11 (11.5)
Hypertension	2791 (85.8)	2702 (85.6)	89 (92.7)[a]
Diabetes mellitus	1555 (47.8)	1500 (47.5)	55 (57.3)
Current smoker	425 (13.1)	414 (13.1)	11 (11.5)
Current of former alcohol use	2084 (64.0)	2028 (64.2)	56 (58.3)
Body mass index, kg/m^2	31.9 (7.7)	31.9 (7.7)	33.1 (7.6)
Systolic blood pressure, mm Hg	129 (22)	128 (22)	131 (23)
Diastolic blood pressure, mm Hg	72 (13)	72 (13)	69 (11)[a]
Modified Mini-Mental State Exam	91.38 (9.06)	91.41 (9.07)	90.28 (8.67)
Beck Depression Inventory	7.8 (7.9)	7.8 (7.9)	7.0 (6.6)
KDQOL-36, Mental Component Summary	50.5 (10.4)	50.4 (10.4)	52.9 (9.2)[a]
KDQOL-36, Physical Component Summary	42.1 (11.4)	42.1 (11.4)	40.6 (10.8)
ACE inhibitor or angiotensin receptor blocker	2205 (68.2)	2132 (68.0)	73 (76.0)
Beta blocker	1479 (45.8)	1436 (45.8)	43 (44.8)
Antiplatelet	1449 (44.8)	1395 (44.5)	54 (56.3)[a]
Warfarin	82 (2.5)	75 (2.4)	7 (7.3)[b]
Statin	1737 (53.8)	1677 (53.493)	60 (62.5)
eGFR, ml/min per 1.73m^2, CRIC Study equation[10]	45.4 (17.0)	45.6 (17.0)	38.9 (14.5)[b]
Urine protein/creatinine ratio, median (IQR)	0.15 (0.06–0.81)	0.15 (0.06–0.81)	0.29 (0.08–1.26)[a]
Low-density lipoprotein, mg/dL	103.7 (35.5)	103.8 (35.7)	99.5 (28.7)
Potassium, mEq/l	4.3 (0.5)	4.3 (0.5)	4.4 (0.6)
Hemoglobin, g/dl	12.6 (1.8)	12.7 (1.8)	12.0 (1.9)
High-sensitivity C-reactive protein, mg/l	5.5 (9.9)	5.5 (10.0)	5.7 (6.8)

ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KDQOL-36, Kidney Disease Quality of Life-36.
[a]$P < 0.05$.
[b]$P < 0.01$.
Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± SD or median (IQR).

than 65 who completed it annually after 2013. The 3MS is a test of global cognitive function with components for concentration, orientation, language, praxis, and memory.[11] Higher scores on the 3MS indicate higher cognitive function. The smaller subset of participants who participated in the ancillary study also received the following tests on an annual basis: Trail Making Test (Trails) A (measures attention, visuospatial scanning, and motor speed); Trails B (executive function),[12] Category Fluency (verbal production, semantic memory and language),[13] Buschke Selective Reminding Test (verbal memory with delayed components),[14] and Boston Naming Test (language function).[13]

Statistical Analysis

Continuous variables were expressed as means ± SDs and were compared using *t*-tests. Categorical variables were expressed as proportions and compared using the χ^2 test.

We determined the association between incident AF as a time-dependent predictor, and annualized visit-to-visit changes in cognitive scores on each test, using mixed effects models with a random intercept-slope and an unstructured covariance to account for within-subject correlation of the repeated changes. Follow-up for each subject started on the date of the first cognitive function test between 2006 and 2008 and continued until loss to follow-up, death, or end of study period (September 2015). If a participant 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, individuals contributed person-time to the incident AF exposure group. For each outcome of interest, we fitted a series of nested regression models that adjusted for sociodemographic and clinical factors at baseline, which were chosen a priori based on prior literature.[15] Model 1 adjusted for study

site, age, sex, race/ethnicity, and education. Model 2 adjusted for the same variables in Model 1 plus systolic blood pressure, diabetes, peripheral artery disease, stroke, alcohol use, antiplatelet agents, anticoagulant drugs, statin use, estimated GFR, and proteinuria. The following variables were time-updated: systolic blood pressure, antiplatelet agents, and anticoagulant drugs. We evaluated age as a potential effect modifier in the association between incident AF and the outcome by adding an interaction term to the fully adjusted model. For multivariable regression analysis, 53 participants were excluded due to missing covariate data (including 24-hour urine protein [$n = 46$], medications [$n = 6$], and education [$n = 1$]) (Figure 1). Follow-up was censored at the time of death ($n = 852$), lost to follow-up ($n = 224$), or the end of the follow-up period, whichever occurred first. Patients' data before the censoring still contributed to the mixed effects models. End-stage renal disease, defined as receipt of chronic dialysis or kidney transplant, was identified through participant self-report, medical records review, and data from the U.S. Renal Data System. Deaths were ascertained from next of kin, death certificates, obituaries, reviews of hospital records, and the Social Security Death Master File.

RESULTS

Baseline Characteristics

Among 3254 eligible participants, the mean age was 57.0 ± 11.2 years, 44.9% were women, 41.9% were non-Hispanic White, 40.5% were non-Hispanic Black, 13.7% were Hispanic, and 4.1% belonged to other racial/ethnic groups (Table 1). The mean estimated GFR was 45.4 ± 17.0 ml/min per 1.73 m^2, and the median 24-hour urine protein was 0.15 (0.06–0.81) g/24 hours at entry. Compared with those without incident AF, individuals with incident AF were older, more likely to be non-Hispanic White, and have income <$20,000 and a prior history of myocardial infarction. In addition, individuals with incident AF had lower estimated GFR, higher proteinuria, and were more likely to report anticoagulant use. Mean baseline scores on the 3MS were similar for those with and without incident AF (Table 1).

Outcomes

The median overall follow-up was 6.8 (2.3–9.2) years. For the AF group, the median follow-up after the development of AF was 2.1 (0.7–4.0) years. The median number of cognitive function assessments for the no-AF group was 4.0 (2–6). For the AF group, participants had an average of 3.4 3MS measurements before the development of AF and 2.0 measurements after the development of AF. For those who developed AF during follow-up, the median (interquartile range) number of days between the development of AF and the cognitive function measure before AF was 389 (224–591) days. The median (interquartile range) number of days between the development of AF and the following cognitive function measurement was 271 (163–520) days. Median 3MS scores by AF status over time are depicted in Figure 2.

In multivariable analyses, after adjustment for sociodemographic factors and site, individuals without and with incident AF each experienced an increase in 3MS score but the increase was larger in the AF group (ß [95% confidence interval], 0.101 [0.064–0.138] for no-AF vs. 0.409 [0.125–0.690] for AF, Table 2). However,

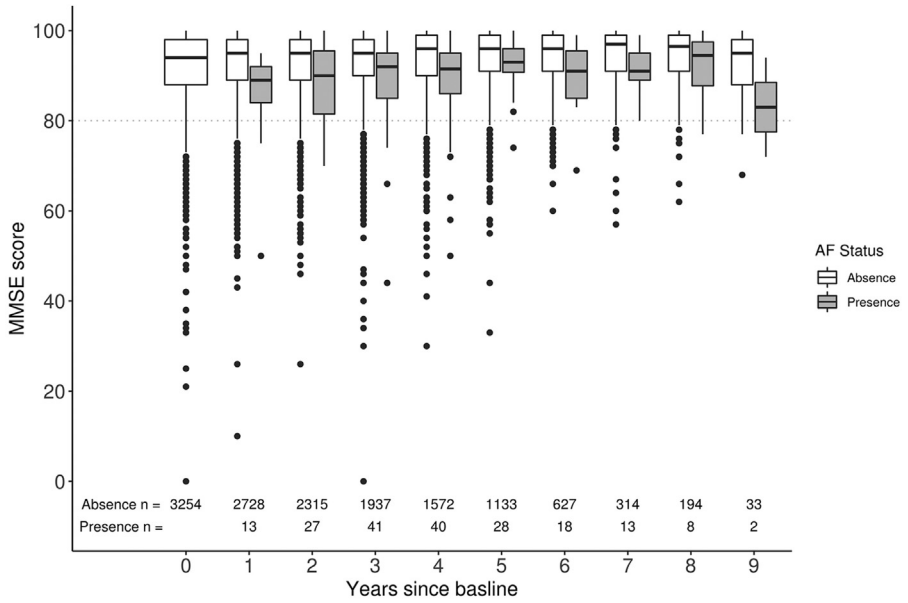

Figure 2. Median (interquartile range) 3MS scores over time by AF status. AF, atrial fibrillation; MMSE, Mini-Mental State Exam; 3MS, Modified Mini-Mental State Exam.

Table 2. Adjusted mean annual change in 3MS scores[a] ß coefficient (SE) with and without incident AF

	Mean annual change no-AF	Mean annual change incident AF	Incident AF vs. no-AF	*P* value
Model 1	0.101 (0.064, 0.138)	0.409 (0.125, 0.694)	0.308 (0.025, 0.592)	0.03
Model 2	0.121 (0.084, 0.159)	0.344 (0.013, 0.676)	0.222 (−0.108, 0.553)	0.19

AF, atrial fibrillation; 3MS, Modified Mini-Mental State Exam.
[a]Higher score indicates higher cognitive function.
Model 1: Adjusted for site, age, sex, race/ethnicity, education.
Model 2: Model 1 plus time-updated systolic blood pressure, diabetes, peripheral arterial disease, stroke, alcohol use, antiplatelet agents, anticoagulants, statin, baseline estimated glomerular filtration rate, and proteinuria.

after adjustment for clinic factors, the parameter estimate of incident AF versus no incident AF on change in 3MS was no longer significant (ß [95% confidence interval], 0.222 [−0.108 to 0.553], $P = 0.19$). No significant interaction between incident AF and sex for change in 3MS was observed.

In exploratory analyses of the smaller subset of participants in the CRIC cognitive ancillary study, only 21 participants experienced incident AF events (Supplementary Table S1). In multivariable analyses, after adjustment for sociodemographic factors and site, individuals with incident AF experienced worsening cognitive function as assessed by the Buschke and Trails A scores (Supplementary Table S2). These associations were attenuated but were of borderline significance after adjustment for clinical factors. There was no significant association between incident AF and change in the other cognitive function test scores (i.e., Category Fluency, Boston Naming, and Trails Test B).

DISCUSSION

In this cohort of adults with mild-to-moderate CKD, incident AF was not associated with cognitive function decline. Our findings are in contrast to studies in non-CKD populations, which have reported that AF is associated with increased risk for cognitive decline.[3,4] There are several potential reasons for our finding. First, it is possible that pathways linking AF to cognitive decline (i.e., hypoperfusion, thrombosis, inflammation) may already be activated in CKD, thus blunting the effect of incident AF on cognitive function. Second, it is possible that individuals with incident AF may have received more intensive medical care and control of vascular risk factors for cognitive decline. Specifically, whereas the mean age at study entry in CRIC was 57.0 years, the mean age was 66.5 years in a study by Marzona et al.[3] and 73.0 years in a study by Thacker et al.[4] Consequently, our study may have lacked sufficient precision and sufficient age-related cognitive decline to test whether AF was associated with decline in cognitive function. It is possible that additional follow-up time will allow us to better to assess this association.

In contrast to our primary findings, sensitivity analyses in a smaller subset of individuals revealed a significant association between incident AF and worsening of cognitive function as assessed by Buschke delayed recall and Trails A, suggesting the possibility of domain-specific cognitive vulnerability with incident AF. Specifically, it is possible that incident AF may negatively impact attention and information processing and may result in additional delayed memory alterations. However, these findings need to be interpreted with caution given the smaller sample size for the sensitivity analyses.

Despite our overall negative findings, AF still represents a high-risk state for patients with CKD. A recent large population study from Sweden reported increased risk for stroke in individuals with AF and CKD.[16] Furthermore, AF may lead to other adverse outcomes, as seen in a recent analysis of CRIC data that reported that it was associated with increased risk for progression to end-stage renal disease.[17]

Strengths of this study include the multicenter prospective design with a large and diverse sample of patients with CKD, rigorous processes for the capture and adjudication of incident AF, the annual administration of a comprehensive battery of cognitive tests, and time-updating of potential confounders. However, the study has limitations. As an observational study, our findings are subject to residual confounding and bias. In addition, because AF was determined by ECG at study visits and from hospital records, we were not able to assess the impact of undiagnosed paroxysmal AF and may have missed AF documented only in the outpatient setting. Therefore, we may have an incomplete ascertainment of AF. Furthermore, it is important to note that individuals in the CRIC cohort were younger than individuals in previously published studies that reported a significant association between AF and cognitive decline.[3,4] It is also possible that informative attrition may have made it more difficult to detect an association between incident AF and change in cognitive function. Finally, practice effects of serial assessment of cognitive function may have been a significant confounder.[18]

In this cohort of individuals with mild-to-moderate CKD, incident AF was not associated with cognitive

decline. Future work is needed to evaluate this association in other CKD populations.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Cognitive ancillary study: baseline characteristics CRIC.

Table S2. CRIC cognitive ancillary study: adjusted mean annual change in cognitive function tests ß coefficient (SE) with and without incident AF.

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