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Chronic Kidney Disease and Prevalent Atrial Fibrillation: The Chronic Renal Insufficiency Cohort (CRIC)

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Abstract

Background—The epidemiology of atrial fibrillation (AF) has been mainly investigated in patients with end-stage renal disease (ESRD), with limited data on less advanced chronic kidney disease (CKD) stages.

Methods—A total of 3267 adult participants (50% non-Hispanic blacks, 46% females) with CKD from the Chronic Renal Insufficiency Cohort (CRIC) were included in this study. None of the study participants had been on dialysis. Those with self-identified race/ethnicity other than non-Hispanic black or white (N=323) or those without ECG data (N=22) were excluded. AF was ascertained by a 12-lead electrocardiogram (ECG) and self-report. Age- sex- race/ethnicity-specific prevalence rates of AF were estimated and compared between subgroups. Cross sectional associations and correlates with prevalent AF were examined using unadjusted and multivariable adjusted logistic regression analysis.

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Results—The mean estimated glomerular filtration rate (GFR) was 43.6 (±13.0) ml/min/1.73 m^2. AF was present in 18% of the study population and in more than 25% of those 70 years or older. In multivariable adjusted models, 1-SD increase in age (11 years) [odds ratio (OR) and CI 95%: 1.27 (1.13, 1.43), P<0.0001], female sex [0.80 (0.65, 0.98), P=0.0303], smoking (former vs. never) [1.34 (1.08, 1.66), P= 0.0081], history of heart failure [3.28 (2.47, 4.36), P<0.001], and history of cardiovascular disease [1.94 (1.56, 2.43), P<0.0001] were significantly associated with AF. Race/ethnicity, hypertension, diabetes, body mass index, physical activity, education, high sensitivity C-reactive protein, total cholesterol, and alcohol intake were not significantly associated with AF. An estimated GFR <45 ml/min/1.73 m^2 was associated with AF in an unadjusted model [1.35 (1.13–1.62)); P=0.0010)], but not after multivariable adjustment [1.12 (0.92– 1.35), P=0.2710].

Conclusions—Nearly one in five participants in CRIC, a national study of CKD, had evidence for AF at study entry, a prevalence similar to that reported among patients with ESRD and 2–3 times of that reported in the general population. Risk factors for AF in this CKD population do not mirror those reported in the general population.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population. Over 2.3 million Americans have AF, and the number of cases is expected to rise to 5.6 million by 2050 (1). AF is one of the strongest risk factors for ischemic stroke and an independent predictor of death (2–6). While AF prevalence in the general population ranges from 1% to 8% (7,8,9) depending on age and method of AF detection, the estimated prevalence of AF among patients with end-stage renal disease (ESRD) has been reported to be between 13% and 23% (10,11,12,13). Because more than 26 million US adults have chronic kidney disease (CKD) (14), understanding the prevalence and correlates of AF has important public health, epidemiologic and clinical implications. AF and CKD share several common risk factors (e.g. hypertension, diabetes, pre-existing cardiovascular disease, obesity, metabolic syndrome) (6, 10,12,15–20). While a high prevalence of AF has been demonstrated in ESRD, there are limited data on the prevalence and correlates of AF in less severe CKD, which is substantially more common than ESRD (14). Therefore, we examined the prevalence and correlates of AF in a large, diverse cohort of adults with CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study, a multi-racial national US prospective study examining risk factors for the progression of kidney disease and cardiovascular disease in CKD patients.

METHODS

Study population

The Chronic Renal Insufficiency Cohort (CRIC) study is a prospective cohort of 3612 participants with CKD. The study design and methods (21) as well as the baseline cohort characteristics (22) have been described elsewhere. Briefly, seven clinical centers recruited adults who were aged 21 to 74 years and had CKD (but were not on dialysis) using age-based eGFR inclusion criteria (eGFR of 20 to 70, 60 or 50 ml/min/1.73 m^2 for age ranges 21–44, 45–64 and 65–74 years, respectively). Informed consent was obtained from all participants. Participants with self-identified race/ethnicity other than non-Hispanic black or non-Hispanic white (169 Hispanics and 154 others) or those without ECG data (N=22) were excluded from this analysis. After all exclusions, the final analytic sample included 3267 non-Hispanic black and non-Hispanic white participants.

Ascertainment of atrial fibrillation (AF)

AF was identified in CRIC study from two sources; 1) electrocardiograms (ECGs) recorded during the study's baseline visit and 2) participants' responses to a question about history of AF: "Have you ever been diagnosed with or has a doctor or other health professional ever told

you that you have atrial fibrillation?" Standard 12-lead ECGs were recorded in all participants by strictly standardized procedures using identical electrocardiographic equipment (GE MAC 1200, GE Medical Systems, Milwaukee, WI). The digitally recorded ECGs stored in the electrocardiographic machines were transmitted regularly over analogue phone lines to the CRIC ECG Reading Center located at Wake Forest University, Winston-Salem, NC for analysis using Minnesota ECG classification (23). In this analysis, we defined AF as either presence of AF in the study baseline ECGs or an affirmative response to the AF question.

Other clinical variables

At the baseline visit, data on socio-demographic characteristics, medical history, lifestyle behaviors, current medications, and anthropometric measures (e.g. height and weight) were obtained. Levels of physical activity were measured based on survey questions regarding different types of activity. Minutes of activity were summed for each discrete activity type, converted to hours for ease of presentation, and multiplied by metabolic equivalent (MET) level (24,25). Participants who report drinking alcohol more than once a month during the 12 months preceding the baseline visit were classified as alcohol drinkers. History of chronic heart failure and history of cardiovascular disease (angina, myocardial infarction, or coronary revascularization) were collected from the medical history questionnaire completed at the baseline visit. Standardized blood pressure measurements were obtained using a previously validated protocol (26) and calibrated sphygmomanometers (27). Hypertension was defined as either systolic blood pressure >=140 mmHg, diastolic blood pressure >=90 mmHg, or self-reported use of antihypertensive medications (28). Diabetes was defined as either a fasting glucose >=126 mg/dl, random glucose >=200 mg/dl or use of insulin or other anti-diabetic medication (29). Serum creatinine was measured at the University of Pennsylvania laboratory and calibrated based on standard measurements made from the Cleveland Clinic Foundation laboratory in Cleveland, OH (30). Estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation (31). Other blood assays such as cholesterol, serum uric acid, and high sensitivity C-reactive protein (hs-CRP) were conducted in the CRIC Study's central laboratory.

Statistical analysis

Frequency distributions of all variables were first inspected to identify anomalies and outliers possibly caused by measurement artifacts. Continuous data were described by their mean and standard deviation (SD), and categorical data as proportions (%). The prevalence of AF at the study baseline was examined by eGFR (dichotomized using 45 ml/min/1.73 m^2 as a cutoff point), age, sex and race/ethnicity. A series of logistic regression analysis was used to identify correlates of AF. Our approach was first to examine unadjusted associations between individual sociodemographic and clinical variables with AF. Next, we examined the same variables after adjustment for age, sex, race/ethnicity, and study center. Finally, we conducted a final multivariable model that included all the variables that were significantly associated with AF after adjustment for the demographic variables. Age, sex race/ethnicity and study center were forced into the final model. A two-tailed $P<0.05$ was considered significant at alpha level of 0.05. SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina) was used in all analyses.

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RESULTS

Among the 3267 participants included in this analysis, 1627 were non-Hispanic white and 1640 were non-Hispanic black (Table 1). Mean age was 58.6 years and 46% were women. More than 86% were hypertensive, 45% were diabetic, and 34% had a self-reported history of cardiovascular disease. The mean eGFR was 43.6 +13.4 ml/min/1.73m^2; approximately 55% of the study population had an eGFR<45 ml/min/1.73m^2.

AF was present in 602 (18%) participants (Table 2). Most AF cases were detected by self report. ECG-detected AF was present in only 40 participants. Participants with eGFR <45 ml/min/1.73 m^2 had a higher prevalence of AF compared with participants with eGFR >=45 ml/min/1.73 m^2 (20.4% vs. 16.0%; P=0.001). When age was categorized into decades (<40, 40–49, 50–59, 60–69, >=70 years), the prevalence of AF across decades were significantly greater with higher age (7.9%, 12.3%, 16.9%, 21.0% and 25.5%, respectively, P<0.0001). There was no statistically significant difference in the prevalence of AF between women and men (18.6% vs. 18.3%; P=0.78). Blacks had a significantly higher prevalence of AF compared with whites (20.1% vs. 16.8%; P=0.02).

In univariate analyses, older age, eGFR<45 ml/min/1.73 m^2, black race, higher levels of total cholesterol, higher body mass index, lack of physical activity, smoking, drinking, diabetes, history of heart failure and history of cardiovascular disease were significantly associated with a higher odds of prevalent AF. On the other hand, sex, uric acid, hs-CRP, and hypertension were not significantly associated with AF in the sample. Compared with having high school education, less than high school education was associated with a higher prevalence of AF while postgraduate education was associated with a lower prevalence of AF. After adjustment for age, sex, race and study centers, the strength of associations between AF with eGFR level, diabetes, educational attainment, body mass index and drinking status became attenuated (Table 3).

In the final multivariable model, only older age (per 1-SD increase) [odds ratio (OR) 95% CI: 1.27 (1.13, 1.43)], female sex [(OR 0.80 (0.65, 0.98),], smoking (former vs. never) [OR 1.34 (1.08, 1.66)], history of heart failure [OR 3.28 (2.47, 4.36)], and history of cardiovascular disease [OR 1.94 (1.56, 2.43)] were significantly associated with AF (Table 4).

DISCUSSION

This study addressed the prevalence and correlates of prevalent AF in a well-defined multi-racial cohort of US individuals with CKD who are not receiving chronic dialysis treatments. Most of the previous studies that examined associations between AF and CKD were conducted either in ESRD patients on dialysis or in a general population sample, or were restricted to a single racial/ethnic group (10–13,32,33). Our study revealed three main findings. First, the prevalence of AF was high in this sample of participants with mild-moderate CKD; affecting nearly one in five persons overall and more than one in four participants aged 70 years or older. This prevalence estimate is 2-to-3-fold higher than estimates from the general population using AF ascertainment methods similar to those used in our study (8). In the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national US cohort study with over 30,000 participants, the prevalence of AF was only 7.8% despite the fact that REGARDS participants were approximately seven years older than CRIC Study participants.

Second, the high prevalence of AF observed in our study sample is similar to estimates among patients with ESRD receiving chronic dialysis, which ranges from 13%–23% (10–13). This finding suggests that processes influencing the development of AF likely occur early in the course of CKD. Interestingly, when examining eGFR level and prevalent AF, the graded association with lower eGFR was no longer significant after adjustment for age, sex, race/

ethnicity, and study center. Similar results were obtained when eGFR was modeled as a continuous variable (1-SD increase) or categorized into different strata (data not shown). Since CKD is substantially more common than ESRD in the US, these findings are of particular significance from a clinical and public health perspective.

Third, risk factors for AF in this CKD population do not mirror those reported in the general population. In our multivariable logistic regression analysis, while selected risk factors for AF in the general population were independent correlates in our sample (i.e. older age, heart failure, other cardiovascular disease), others were not (i.e. race/ethnicity, hypertension, diabetes, body mass index, physical activity, education, hs-CRP, total cholesterol, and alcohol intake). These findings suggest the need for further investigation of the risk factors for AF in the setting of CKD as various AF risk prediction models developed in the general population (34) may not apply.

Of interest, we found that black race was significantly associated with a higher prevalence of AF in crude analyses, but was no longer a significant correlate after adjustment for other covariates. Although this observation contrasts the reported higher prevalence of AF among whites in the general population (1,9,35,36,37), our finding is consistent with the high rate of stroke among blacks (38), the high prevalence of AF and stroke risk factors among blacks, and the strong association between AF and stroke (39–42). The observed prevalence of ethnic/racial distribution of AF in CRIC is consistent with the possibility that studies of the general population may have disproportionately under-diagnosed AF in non-white populations (7,8, 43). Under-diagnosis of AF in blacks might be a result of black having a higher prevalence of paroxysmal or asymptomatic AF, the difficult-to-detect patterns of AF (7,8). Future longitudinal evaluation of incident AF is needed among large, diverse populations with CKD to provide further clarification of the racial/ethnic epidemiology of AF in the setting of CKD. The strong and unique association of AF with CKD could be explained by the fact that AF and CKD share a number of risk factors (6,10,12,15–20,32). Although mechanical stress on atria due to volume overload could be the mediating factor that leads to development of AF in patients with ESRD, this may not be the case in less advanced stages. One possible mechanism for a higher prevalence of AF in early stages of CKD could be related to inflammation (36). Elevated levels of inflammatory markers have been reported in CKD even in its early stages (44,45), inflammatory markers predict progression of kidney dysfunction (46,47), and inflammation plays a significant role in the pathogenesis of AF (48,49). Nevertheless, the negative association between high hs-CRP (an inflammatory marker) with AF in our study is not concordant with such an explanation. It is not clear, however, whether other inflammatory markers other than hs-CRP have stronger associations with AF or not, a possibility that needs testing.

Our results should be interpreted in the context of a number of limitations. As a cross sectional analysis, we can not establish a causal inference between CKD and AF or the temporal sequence of the two conditions. Also, residual confounding might have affected some of the associations in the multivariable models. However, we adjusted for many of the most common risk factors for AF. Further, we controlled for the geographic location of the study clinical centers (7 clinical centers) to adjust for possible differences in unmeasured characteristics of the participants related to the residence location of care.

Standard 12-lead ECG, which was one of the two AF ascertainment methods in our study, has a major limitation in detecting paroxysmal AF, which is common among CKD patients (51, 52). We supplemented ECG data with self-reported AF to increase the sensitivity of AF ascertainment. Defining AF cases as “the presence of AF by self report and/or ECG” has been shown as a more sensitive method to detect AF (8). Self-report is a common method for AF ascertainment in epidemiologic studies, and it is known that the associations of morbidity and

mortality with self-reported AF are similar to those with ECG-detected AF (37,52). Having said that, since we could not validate the self-reported AF, there could be some misclassification of AF using this method, which is another study limitation.

Although it would be interesting to stratify AF correlates by the method of AF detection (ECG vs. self-report), the small number of AF detected by ECG alone did not allow us to make appropriate inferences because of statistical power considerations. Despite these limitations, this analysis provided a number of significant findings that shed light on the epidemiology of AF in patients with pre-ESRD.

In conclusion, the prevalence of AF in patients with less advanced CKD is very high and is similar to that observed in patients with ESRD. Many known predictors of AF observed in the general population were not significantly correlated with AF in the setting of CKD. These findings emphasize the underappreciated clinical and public health burden of AF among individuals with CKD and the need to delineate additional predictors of developing AF in CKD in order to provide more robust AF risk prediction models for patients with kidney dysfunction.

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Table 1

Characteristics of the study population

	Mean (SD) or number (%). N= *3267*
Age (years)	58.55 (10.81)
Sex (male)	1775 (54%)
Race/ethnicity (non-Hispanic black)	1640 (50%)
Education	
Less than high school grad	523 (16%)
High school grad	649 (20%)
Post-high school education	1028 (31%)
College graduate	606 (19%)
Post-grad degree	461 (14%)
Smoker	
Current	470 (14%)
Former	1392 (43%)
Never	1405 (43%)
Alcohol use (drinkers)	1310 (40%)
Total physical activity (MET Hours/week)	204.6 (148.33)
Hypertension	2807 (86%)
Diabetes	1486 (45%)
Congestive heart failure	328 (10%)
Cardiovascular Disease	1125 (34%)
Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2)	43.6 (13.4)
Participants with eGFR less than 45 ml/min/1.73 m^2	1795 (55%)
Body mass index (kg/m^2)	32.31 (8.0)
Total cholesterol (mg/dl)	182.8 (43.8)
Uric acid (mg/dL)	7.4 (1.9)
High sensitivity C-reactive protein (mg/dL)	5.8 (10.2)

Table 2

Prevalence of atrial fibrillation by eGFR, age, sex and race/ethnicity

		N=3267	Atrial fibrillation N (%)	P-value
All population		3267	602 (18.4%)	
Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2)				0.0010
	< 45	1795	367 (20.4%)	
	>= 45	1472	235 (16.0%)	
Age (years)				<.0001
	< 40	239	19 (7.9%)	
	40–49	398	49 (12.3%)	
	50–59	958	162 (16.9%)	
	60–69	1217	256 (21.0%)	
	>= 70	455	116 (25.5%)	
Sex				0.7807
	Male	1775	324 (18.3%)	
	Female	1492	278 (18.6%)	
Race/Ethnicity				0.0156
	Non-Hispanic White	1627	273 (16.8%)	
	Non-Hispanic Black	1640	329 (20.1%)	

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Table 3

Unadjusted and demographic adjusted associations with atrial fibrillation in logistic regression analysis

	Model 1: Unadjusted		***Model 2: demographic adjusted***	
	Odds Ratio (95% CI)*	**P-value**	***Odds Ratio (95% CI)*****	**P-value**
Age (years)***	1.03 (1.02– 1.04)	<.0001	1.46 (1.32– 1.62)	<.0001
Female sex	0.98 (0.82– 1.16)	0.7805	0.90 (0.75– 1.09)	0.2875
Race (Non-Hispanic black vs. Non-Hispanic white)	1.24 (1.04– 1.49)	0.0157	1.25 (1.03– 1.52)	0.0228
Education (Reference: post high school education)				0.0452
Less than high school graduate	1.40 (1.09– 1.80)	0.0086	1.13 (0.86– 1.47)	
High school graduate	0.86 (0.67– 1.12)	0.2673	0.78 (0.60– 1.01)	
College graduate	0.80 (0.61– 1.04)	0.0990	0.85 (0.65– 1.13)	
Post graduate degree	0.69 (0.51– 0.93)	0.0162	0.73 (0.53– 1.00)	
Total cholesterol (mg/dl)***	1.00 (0.99– 1.00)	0.0006	0.85 (0.77– 0.94)	0.0014
Uric acid (mg/dl)***	1.04 (1.00– 1.09)	0.0716	1.01 (0.92– 1.11)	0.8366
Estimated glomerular filtration rate (eGFR) ml/min/1.73 m^2 (eGFR<45 vs >= 45)	1.35 (1.13– 1.62)	0.0010	1.12 (0.92– 1.35)	0.2710
High sensitivity C-reactive protein (mg/dL)***	1.00 (1.00– 1.01)	0.2751	1.02 (0.94– 1.12)	0.5922
Body mass index (kg/m^2)***	1.01 (1.00– 1.02)	0.0398	1.09 (1.00– 1.20)	0.0599
Physical activity: Total MET/hours/week***	1.00 (1.00– 1.00)	<.0001	0.85 (0.76– 0.95)	0.0056
Smoking status (Reference Never)				0.0001
Current	1.38 (1.04– 1.82)	0.0237	1.30 (0.98– 1.73)	
Former	1.78 (1.46– 2.16)	<.0001	1.56 (1.27– 1.91)	
Alcohol use (drinker vs. nondrinkers)	0.75 (0.62– 0.90)	0.0022	0.87 (0.71– 1.06)	0.1678
Hypertension	1.18 (0.91– 1.54)	0.2201	0.83 (0.63– 1.11)	0.2036
Diabetes	1.25 (1.05– 1.49)	0.0139	1.11 (0.92– 1.33)	0.2828
Congestive heart failure	5.63 (4.43– 7.14)	<.0001	5.20 (4.06– 6.67)	<.0001
Any cardiovascular disease	3.48 (2.90– 4.17)	<.0001	3.06 (2.53– 3.71)	<.0001

* Odds ratios represent unadjusted association of individual variables in the first column with AF

** Odds ratios represent age, sex, race/ethnicity and clinical center adjusted associations of the individual variables in the first column with AF each variable

*** Odds ratios for continuous variables are for 1-SD increase

Table 4

Multivariable-adjusted associations with atrial fibrillation in logistic regression analysis*

	*Odds Ratio (95% CI)**	P-value
Age (years)	1.27 (1.13– 1.43)	<.0001
Female sex	0.80 (0.65– 0.98)	0.0303
Race (Non-Hispanic Black vs. Non-Hispanic White)	1.07 (0.86– 1.34)	0.5283
Education (Reference: post-high school education)		0.0662
Less than high school graduate	1.14 (0.86– 1.52)	
High school graduate	0.76 (0.58– 1.01)	
College graduate	1.03 (0.77– 1.37)	
Post graduate degree	0.84 (0.60– 1.17)	
Total cholesterol (mg/dl)	0.93 (0.84– 1.02)	0.1243
Body mass index (kg/m^2)	1.04 (0.94– 1.14)	0.4809
Physical activity: Total MET Hours/week	0.93 (0.83– 1.04)	0.1957
Smoking status (Reference: never)		0.0276
Current	1.15 (0.84– 1.56)	
Former	1.34 (1.08– 1.66)	
Congestive heart failure	3.28 (2.47– 4.36)	<.0001
Any cardiovascular disease	1.94 (1.56– 2.43)	<.0001

*Odds ratios represent the multivariable associations of the individual variables which were significant in the demographic-adjusted models. Study geographic center was also in the multivariable model but the ORs were omitted from the table.