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Atrial fibrillation and Incident End-Stage Renal Disease: The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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Abstract

Background—Atrial fibrillation (AF) is an independent risk factor for end-stage renal disease (ESRD) among persons with chronic kidney disease (CKD), however, the association between AF and incident ESRD has not been examined in the general population.

Methods—A total of 24,953 participants (mean age 65 ± 9.0 years; 54% women; 40% blacks) from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study were included in this analysis. AF was identified at baseline (2003-2007) by electrocardiogram and self-reported history of a physician diagnosis. Incident cases of ESRD were identified through linkage of REGARDS participants with the United States Renal Data System. Cox proportional-hazards regression was used to generate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between ESRD and AF.

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Disclosures
None.

Results—A total of 2,155 (8.6%) participants had AF at baseline. Over a median follow-up of 7.4 years, 295 (1.2%) developed ESRD. In a model adjusted for demographics and potential confounders, AF was associated with an increased risk of incident ESRD (HR=1.51, 95%CI=1.08, 2.11). However, the association between AF and ESRD became non-significant after further adjustment for CKD markers (eGFR< 60 mL/min/1.73 m² and urine albumin-to-creatinine ratio 30 mg/dl) (HR=1.24, 95%CI=0.89, 1.73).

Conclusion—AF is associated with an increased risk of ESRD in the general population, however, this association potentially is explained by underlying CKD. Future studies should investigate whether underlying CKD is in the causal pathway between AF and ESRD.

INTRODUCTION

Atrial fibrillation (AF) has been estimated to affect 3 million individuals in the United States and its prevalence is projected to double by 2050.^{1,2} Similarly, chronic kidney disease (CKD) affects 13.1% of the United States population and its prevalence is expected to increase due to the aging population and the growing epidemics of diabetes and hypertension.³

It is well established that CKD is a risk factor for AF. Several population-based studies have shown an increased incidence and prevalence of AF among individuals with CKD, including those with end-stage renal disease (ESRD).⁴⁻⁸ Recent findings also suggest that AF leads to CKD, implicating a bidirectional relationship between AF and CKD, with each condition potentially influencing the development of the other. For example, data from the general Japanese population have shown that AF is associated with the development of kidney dysfunction and vice versa.⁹ Additionally, a recent study showed that incident AF was an independent predictor of the progression to ESRD among persons with CKD.¹⁰

The association between AF and incident ESRD has not been examined in the general population and whether such an association is similar in whites and blacks is unknown. The purpose of this study was to examine the association between AF and the risk of incident ESRD using data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national, general population sample including a large black population.

METHODS

Study Population and Design

Details of the REGARDS study and design have been published previously.¹¹ Briefly, this prospective cohort study was designed to identify causes of regional and racial disparities in stroke mortality. The study population over sampled blacks and residents of the southeastern stroke belt region (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Between January 2003 and October 2007, a total of 30,239 participants were recruited from a commercially available list of residents using a combination of postal mailings and telephone data. Demographic information and medical histories of study participants were obtained using a computer-assisted telephone interview (CATI) system that was conducted by trained interviewers. Additionally, a brief in-home

physical examination was performed 3 to 4 weeks after the telephone interview. During the in-home visit, trained staff collected information regarding medications, blood and urine samples were collected, and a resting electrocardiogram was recorded. For the purpose of this analysis, participants were excluded if they had ESRD at baseline, identified by a self-reported history of dialysis or a date indicating treatment for ESRD in the United States Renal Data System (USRDS) prior to the baseline REGARDS in-home exam date. Study participants who were missing baseline creatinine values or other baseline covariates also were excluded.

Atrial Fibrillation

AF was identified in study participants at baseline by the study-scheduled electrocardiogram recorded during the in home visit and also from a self-reported history of a physician diagnosis of AF during the CATI surveys. The electrocardiograms were read and coded at a central reading center by electrocardiographers blinded to the other REGARDS study data. Self-reported AF was defined as an affirmative response to the following question: “Has a physician or a health professional ever told you that you had atrial fibrillation?”¹²

End-Stage Renal Disease

Incident cases of ESRD among REGARDS participants were identified through linkage with the USRDS. Linkage of REGARDS participants with the USRDS has been described previously.¹³ Briefly, the USRDS provides a complete ascertainment of nearly all persons in the United States who are receiving treatment for ESRD. Matching was based on an algorithm that included social security number, date of birth, and first and last name. Different configurations of full and partial individual identifiers then were matched sequentially. For participants with a partial match to the USRDS, the nonmatching variables were visually inspected to confirm that a valid match could not be made. Data from the USRDS included all incident ESRD cases, regardless of treatment modality, through September 1, 2012.

Covariates

Participant characteristics collected during the initial REGARDS study visit were used in this analysis. Age, sex, race/ethnicity, income, education, and smoking status were self-reported. Annual household income was categorized into 5 levels (<\$20,000, \$20,000-\$34,999, \$35,000-\$74,999, \$75,000, and “refused”). Similarly, education was categorized into “high school or less,” “some college,” and “college or more.” Smoking was defined as ever (e.g., current and former) or never smoker. Serum samples were obtained and measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, fasting glucose, high-sensitivity C-reactive protein (hs-CRP), and serum creatinine were used in this analysis. Diabetes was classified as present if one of the following was detected: fasting glucose level was ≥ 126 mg/dL, non-fasting glucose, ≥ 200 mg/dL, self-reported diabetes medication use, or self-reported diagnosis of diabetes. Regular aspirin use was self-reported. Statin, antihypertensive, and lipid-lowering medication use were assessed through pill-bottle review. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. After the participant rested for 5 minutes in a seated position, blood pressure was measured using a sphygmomanometer. Two values were obtained following a

standardized protocol and averaged. Using serum creatinine measurements from the baseline study visit, eGFR was estimated using the CKD-EPI equation.¹⁴ Participants with ESRD were excluded from inclusion in REGARDS and were not present in the study at baseline. Additionally, urine albumin-to-creatinine ratio (ACR) was computed for study participants. Albuminuria was defined as ACR ≥ 30 mg/g.¹⁵

Statistical Analysis

For participants with and without AF, categorical variables were reported as frequency and percentage while continuous variables were reported as mean $\pm$ standard deviation. Statistical significance of differences across baseline AF status for categorical variables was tested using the Fisher's exact method and the Wilcoxon rank-sum procedure for continuous variables. Incidence rates per 1000 person-years were calculated for ESRD by AF status. Kaplan-Meier estimates were used to compute the cumulative incidence of ESRD by AF and the difference in estimates were compared using the log-rank procedure.¹⁶ Follow-up time was defined as the time between the initial study visit until the first of the following events: diagnosis of ESRD, death, or end of follow-up (September 30, 2012). Cox proportional-hazards regression was used to generate hazard ratios (HR) and 95% confidence intervals (95%CI) for the association between AF and ESRD. Multivariable Cox regression models were used to examine the association between AF and incident ESRD. The models were as follows: Model 1 adjusted for age, sex, race/ethnicity, and region of residence; Model 2 adjusted for covariates in Model 1 with the addition of systolic blood pressure, HDL-cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, statins, and aspirin. Additionally, sub-analyses were performed to evaluate effect modification by age (dichotomized at 65 years), sex, and race/ethnicity comparing models with and without interaction terms.

We did not adjust for baseline eGFR in our main analysis due to its potential to be in the causal pathway between AF and ESRD.¹³ Instead, we performed several sensitivity analyses. We computed multivariable-adjusted HRs for ESRD stratified by baseline eGFR (>60 mL/min per 1.73 m² and eGFR 15-60 mL/min per 1.73 m²) and ACR (≥ 30 mg/g and <30 mg/g). We also adjusted for markers of CKD (eGFR 15-60 mL/min per 1.73 m² and ACR ≥ 30 mg/g) with the aforementioned covariates of Model 2.

The proportional hazards assumption was not violated in our analysis. Statistical significance was defined as $p < 0.05$. SAS Version 9.3 (Cary, NC) was used for all analyses.

RESULTS

Of the 30,183 (30,239) participants from the original REGARDS cohort, 352 participants had a diagnosis of ESRD before enrolment. Of those that remained, 513 participants with missing follow-up data, 676 missing AF data, and 3,689 participants with either missing baseline characteristics or missing medication data also were excluded. A total of 24,953 study participants (mean age: 65 ± 9.0 years; 54% women; 40% blacks) were included in the final analysis.

Baseline characteristics for study participants by AF status are shown in Table 1. Persons with AF were more likely to be older, white, and to have lower levels of education and income compared with those without AF. Additionally, persons with AF were more likely to smoke, have diabetes, and to use anti-hypertensive medications, statins, aspirin, and lipid-lowering medications than non-AF persons. Increased values of systolic blood pressure, hs-CRP, serum creatinine, and ACR were observed among participants with AF compared with those without AF. Persons without AF had higher values for total cholesterol and HDL cholesterol than those with AF.

Over a median follow-up of 7.4 years, 295 (1.2%) participants developed ESRD. The cumulative incidence for ESRD by AF is shown in Figure 1 (log-rank $p < 0.001$). The incidence of ESRD in participants with AF was 1.72 (95% CI=1.23, 2.40) times the incidence in those without AF (Table 2). In a multivariable Cox regression model, AF was associated with an increased risk of incident ESRD (HR=1.51, 95% CI=1.08, 2.11) (Table 3). The association between AF and ESRD became non-significant after further adjustment for eGFR < 60 mL/min/1.73 m² and ACR ≥ 30 mg/dl (HR=1.24, 95% CI=0.89, 1.73) (Table 3). The results were consistent in subgroup analyses stratified by age, sex, race/ethnicity, eGFR, and ACR (Table 4).

DISCUSSION

In this analysis from REGARDS, a population-based study, AF was associated with an increased risk of ESRD after adjustment for sociodemographics and cardiovascular risk factors. However, this association was attenuated and became non-significant after adjustment for CKD markers. These findings suggest that although AF is associated with ESRD in the general population, similar to what has been reported in persons with CKD,¹⁰ this association potentially is explained by underlying kidney dysfunction.

Although several reports have shown that CKD is associated with an increased prevalence of AF,⁴⁻⁸ few have examined the association of AF with incident CKD outcomes such as ESRD. Data from a voluntary annual health check-up program in Japan reported that AF was associated with the development of kidney dysfunction (e.g., eGFR < 60 mL/min/1.73 m²) and proteinuria (e.g., urine stick result $\geq 1+$).⁹ Additionally, an examination of data from the Kaiser Permanente Health System in Northern California showed that among 206,229 persons with CKD (e.g., 2 eGFR measurements < 60 mL/min/1.73 m²) incident AF was associated with an increased risk of ESRD (HR=1.67, 95% CI=1.46, 1.91).¹⁰ Our results support the claim that AF is associated with CKD and extend this hypothesis to the general population.

There are several explanations for the increased risk of ESRD among persons with AF. Persons with AF and ESRD share several common comorbid conditions (e.g., hypertension, diabetes, obesity, and cardiovascular disease).^{17,18} However, the association of AF with ESRD remained significant after adjustment for these common conditions, suggesting that that these factors do not fully explain the observed association. Persons with AF have an increased level of inflammation and potentially increased oxidative stress and acute-phase inflammation promote the development of ESRD.^{19,20} Additionally, the irregular rhythm of

AF is associated with decreased cardiac output that may decrease perfusion to the kidneys that predisposes to repeated injury.²¹ Also, multiple renal emboli in the setting of AF may compromise renal perfusion and promote renal dysfunction and progression to ESRD. Rate-control (e.g., diltiazem) and rhythm-control (e.g., amiodarone) therapies for AF may increase the risk of renal dysfunction as well.^{22,23}

The association between AF and ESRD was attenuated after further adjustment for markers of CKD (e.g., eGFR<60 mL/min/1.73 m² and ACR ≥30 mg/g), suggesting that the association of AF with ESRD is potentially explained by underlying CKD. In this context, CKD could be either of the following: 1) a mediating factor that falls in the causal pathway between AF and ESRD; 2) a confounding factor, given its association with AF and ESRD; or 3) an effect modifier where the strength of association between AF and ESRD depends on the level of underlying CKD. Since AF and eGFR were measured at the same time and both conditions lead to development of the other, it is not possible to separate between the potential mediating and confounding effects of CKD in this analysis. Similarly, given the low power to detect an interaction, excluding or confirming effect modification cannot be determined with certainty either. Nevertheless, although the interaction between AF and CKD is not statistically significant, the association between AF and ESRD is quantitatively stronger for people with eGFR<60 mL/min/1.73 m² (HR 1.34) vs. ≥60 mL/min/1.73 m² (HR 1.11) after multivariable adjustment. This may provide support to the prior studies where an association was present between AF and ESRD among people with CKD (10). Notably, the association between AF and ESRD became non-significant when we adjusted for CKD markers in the demographic and full models. This made it unlikely that the non-significant result in the full model was simply an issue of power. Further research is needed to examine how underlying CKD could impact the relationship between AF and ESRD.

Our results should be interpreted in the context of several limitations. AF was detected during the baseline study electrocardiogram and from a self-reported history of a physician diagnosis. Potentially, asymptomatic paroxysmal cases were missed. Baseline characteristics, including eGFR and ACR were collected during a single time period and results may vary with subsequent measurements. Our main outcome was ESRD captured by the USRDS. Participants included in this data system are required to undergo treatment for ESRD (e.g., hemodialysis and renal transplantation and it is possible that participants may have developed ESRD without being appropriately classified. Several subgroup analyses were performed and there were no significant interactions detected. However, likely this reflects a lack of power to detect such associations due to the small number of ESRD cases.

In conclusion, we found that AF was associated with an increased risk of ESRD in REGARDS, a population-based study. Our results suggest that AF is a risk factor for the development of ESRD. However, this association potentially is explained by underlying kidney dysfunction. Further research is needed to elucidate the pathophysiologic mechanisms of the relationship between AF and CKD. Potentially, targeted preventative therapies may decrease the incidence of ESRD in this at-risk population.

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Figure 1. Cumulative Incidence of ESRD by AF

Incidence curves were statistically different (log-rank $p < 0.0001$).

AF=atrial fibrillation; ESRD=end-stage renal disease.

Table 1

Baseline characteristics of participants with and without AF

Characteristic	No AF (n=22,798)	AF (n=2,155)	P-value*
Age, Mean (SD), y	64.7 (9.3)	67.7 (9.6)	<0.001
Male Sex (%)	45.9	46.7	0.498
Black (%)	40.2	35	<0.001
Region			
Stroke Buckle	20.9	22.7	0.049
Stroke Belt	34.7	34.2	0.664
Non-belt	44.4	43.1	0.229
Education			
High school or less (%)	37.2	41.2	<0.001
Some college (%)	26.9	26	0.391
College or more (%)	35.9	32.8	0.004
Annual income			
< \$20,000 (%)	16.6	21.5	<0.001
\$20,000 to \$34,999 (%)	24	26.1	0.034
\$35,000 to \$74,999 (%)	30.8	27.4	0.001
\$75,000 (%)	16.8	12.3	<0.001
Refused	11.8	12.7	0.194
Body mass index, mean (SD) kg/m ²	29.2 (6.1)	29.5 (6.5)	0.109
Current or former smoker (%)	54.2	58.8	<0.001
Diabetes (%)	20.2	25.3	<0.001
Systolic Blood Pressure, mean (SD), mm Hg	127.2(16.4)	128.3(17.7)	0.004
Antihypertensive medication use (%)	51.7	65.5	<0.001
Total cholesterol, mean (SD), mg/dL	192.4(39.7)	184.5(41.3)	<0.001
HDL-cholesterol, mean (SD), mg/dL	52.0 (16.2)	50.0 (16.3)	<0.001
Statin use (%)	31.1	39.5	<0.001
Aspirin use (%)	43.1	51.2	<0.001
Lipid-lowering medication use (%)	32.6	42.3	<0.001
hs-CRP, median (25 th , 75 th percentile), mg/L	2.2 (0.9, 4.9)	2.6 (1.1, 6.0)	<0.001
Serum Creatinine, mean (SD), mg/L	0.9 (0.3)	1.0 (0.4)	<0.001
eGFR <60 mL/min/1.73 m ² (%)	10.3	18.7	<0.001
Urine ACR, median (25 th , 75 th percentile), mg/g	7.1 (4.6, 14.9)	9.4 (5.3, 23.5)	<0.001

* Statistical significance for continuous data was tested using Wilcoxon rank-sum procedure and Fisher's exact test was used for categorical data.

ACR=albumin-to-creatinine ratio; AF=atrial fibrillation; eGFR=estimated glomerular filtration rate; HDL=high-density lipoprotein; hs-CRP= high sensitivity C-reactive protein; IQR=interquartile range; SD=standard deviation; y=years.

Table 2

Incidence rate and incidence rate ratio of ESRD by AF

	Events/No. at risk	Incidence Rate per 1000 person-years (95%CI)	Incidence Rate Ratio (95%CI) [†]
No AF	254 / 22,798	1.59 (1.40, 1.79)	1 (ref)
AF	41 / 2,155	2.91 (2.14, 3.96)	1.72 (1.23, 2.40)

[†] Incidence rate ratio calculated with no AF as the reference group.

AF=atrial fibrillation; CI=confidence interval; ESRD=end-stage renal disease.

Table 3

Hazard ratios for ESRD for participants with versus without AF.

	Events/No. at risk	Model 1 [*] HR (95%CI)	Model 1 plus CKD ^{*‡} HR (95%CI)	Model 2 [†] HR (95%CI)	Model 2 plus CKD ^{†‡} HR (95%CI)
No AF	254/22,798	1 (ref)	1 (ref)	1 (ref)	1 (ref)
AF	41/2,155	1.93(1.39, 2.69)	1.32(0.95, 1.84)	1.51(1.08, 2.11)	1.24(0.89, 1.73)

* Adjusted for age, sex, race/ethnicity, and region of residence.

† Adjusted for Model 1 covariates plus systolic blood pressure, HDL-cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, statins, and aspirin

‡ Adjusted further for eGFR<60 mL/min/1.73 m² and ACR ≥30 mg/dl.

ACR=urine albumin-to-creatinine ratio; AF=atrial fibrillation; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; HDL=high-density lipoprotein; HR=hazard ratio.

Table 4

Hazard ratios for ESRD associated with AF stratified by Age, Sex, Race/Ethnicity, eGFR, and Urine ACR

	Events/ No. at risk	Model 1* HR (95%CI)	Model 2† HR (95%CI)	Interaction P-value‡	Interaction P-value§
Age					
<65	124 / 12,582	1.84 (1.06, 3.22)	1.10(0.63, 1.94)	0.28	0.33
65	171 / 12,371	2.04 (1.35, 3.09)	1.78(1.18, 2.69)		
Sex					
Female	138 / 13,478	1.78(1.10, 2.89)	1.32 (0.81, 2.15)	0.50	0.63
Male	157 / 11,475	2.09 (1.33, 3.30)	1.67(1.06, 2.63)		
Race/Ethnicity					
Black	217 / 9,909	1.94 (1.30, 2.88)	1.53 (1.03, 2.28)	0.95	0.83
White	78 / 15,044	1.96 (1.08, 3.59)	1.43 (0.78, 2.61)		
eGFR					
60 mL/min per 1.73 m ²	74 / 22,202	1.46 (0.67, 3.19)	1.11(0.51, 2.43)	0.75	0.63
<60 mL/min per 1.73 m ²	221 / 2,751	1.41 (0.98, 2.03)	1.34(0.93, 1.94)		
Urine ACR					
<30 mg/g	54 / 21,297	2.03 (0.95, 4.31)	1.49 (0.70, 3.17)	0.42	0.47
30 mg/g	241 / 3,656	1.41 (0.97, 2.03)	1.33 (0.92, 1.93)		

* Adjusted for age, sex, race/ethnicity, and region of residence.

† Adjusted for covariates in Model 1 with the addition of systolic blood pressure, HDL-cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, statins, and aspirin

‡ Interactions tested using Model 2.

§ Interactions tested in Model 2 with eGFR<60 mL/min/1.73 m² and ACR ≥ 30 mg/dL.

ACR=albumin-to-creatinine ratio; AF=atrial fibrillation; CI=confidence interval; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; HR=hazard ratio.