

Usefulness of Atrial Premature Complexes on Routine Electrocardiogram to Determine the Risk of Atrial Fibrillation (from the REGARDS Study)



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Atrial premature complexes (APCs) serve as acute triggers for atrial fibrillation (AF), but it is currently unknown whether the association between APCs and AF varies by race or sex. We examined the association between APCs and AF in 13,840 (mean age = 63 ± 8.4 years; 56% women; 37% black) participants from the REasons for Geographic And Racial Differences in Stroke study. APCs were detected on baseline electrocardiograms (2003 to 2007). Incident AF was identified by study-scheduled electrocardiograms and self-reported history at a follow-up examination. Logistic regression was used to compute odds ratios (OR) and 95% confidence intervals for the association between APCs and incident AF. A total of 950 participants (6.9%) had APCs at the baseline visit. After a median follow-up of 9.4 years, 1015 incident AF cases (7.3%) were detected. APCs were associated with an increased risk of AF (odds ratios = 1.92, 95% confidence intervals = 1.57, 2.35). The relation between APCs and AF did not vary by race (interaction p value = 0.56) or sex (interaction p value = 0.66). In conclusion, APCs detected on a routine electrocardiogram are associated with an increased risk of AF development, and this association does not vary by race or sex. The findings of this analysis suggest that the risk of AF associated with atrial ectopy does not account for the differential risk of AF that is observed in whites compared with blacks, and in men compared with women. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;120:782–785)

Atrial premature complexes (APCs) serve as acute triggers for atrial fibrillation (AF).¹ This is supported by several reports that have linked APCs with AF development.^{2–4} However, it is currently unknown whether the association

between APCs and AF varies by race or sex. Blacks have a lower prevalence of AF compared with their white counterparts,^{5–8} and it has been suggested that a differential risk factor profile exists between races.^{9,10} Similarly, women are less likely to develop AF compared with men.^{5,11} An examination of the risk of AF associated with APCs may provide insight into why these race and sex differences exist in AF susceptibility. Possibly, whites and men are more susceptible to acute triggers, such as APCs, implicating atrial remodeling as a more important AF risk factor in blacks and women. Therefore, the purpose of this study was to examine if race and sex differences exist in the association between APCs and incident AF in the REasons for Geographic And Ethnic Differences in Stroke (REGARDS) study, a large racially diverse prospective cohort study of men and women.

Methods

Details of the REGARDS study have been published previously.¹² Briefly, REGARDS is a prospective cohort study designed to identify causes of regional and black-white disparities in stroke mortality. The study oversampled blacks and persons residing in the Stroke Belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) between January 2003 and October 2007. A total of 30,239 participants aged 45 years and older were recruited through a commercially available list of residents using postal mailings and telephone data. Demographic information and medical histories were obtained using a computer-assisted telephone interview that was conducted by

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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, and a resting electrocardiogram (ECG).

Approximately 10 years after the baseline assessment, 15,517 REGARDS participants completed a follow-up examination similar to the baseline visit, including a 12-lead ECG. Participants were excluded if they had baseline AF (n = 1,048) or if baseline covariates were missing (n = 629), resulting in a final sample of 13,840. All participants provided written informed consent, and the study was approved by all participating institutional review boards.

APCs were detected on the baseline 12-lead ECG and defined by Minnesota code criteria (Minnesota codes 8.1.1, 8.1.3).¹³ APCs were classified as present or absent. All ECGs were centrally read at the Epidemiological Cardiology Research Center (Wake Forest School of Medicine, Winston-Salem, NC) by readers who were blinded to study outcomes.

Incident AF was identified during follow-up by a study-scheduled ECG and also from self-reported medical history of a physician diagnosis during the computer-assisted telephone interview. 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?", a question that has been shown to be a reliable predictor of incident stroke events.¹⁴

Age, sex, race, household income, and smoking status were self-reported. Income was dichotomized at \$20,000. Smoking was coded as ever (e.g., current and former) or never smoker. Fasting blood samples were obtained and assayed for total cholesterol, high-density lipoprotein cholesterol, and serum glucose. Diabetes was defined as a fasting glucose ≥ 126 mg/dl (or a nonfasting glucose ≥ 200 mg/dl in those failing to fast) or self-reported diabetes medication use. The current use of aspirin and antihypertensive medications was self-reported. 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 baseline ECG data, left ventricular hypertrophy was defined by the Sokolow-Lyon Criteria.¹⁵ Coronary heart disease was ascertained by self-reported history of myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, or if evidence of previous myocardial infarction was present on the baseline ECG. Previous stroke was ascertained by self-reported history. Cardiovascular disease was defined as the composite of coronary heart disease and stroke.

Baseline characteristics were compared between those with and without APCs. Categorical variables were reported as frequency and percentage, whereas continuous variables were reported as mean \pm standard deviation. Statistical significance for categorical variables was tested using the chi-square method and the Student's *t* test for continuous variables. Since the exact date of AF onset was unknown, odds ratios (ORs) as the measure of association were computed using unconditional logistic regression to examine the association between APCs and AF. Normal theory approximation was used to determine the 95% confidence intervals (CIs) for the OR estimates (hereafter called 'risk'). Multivariable models included the following covariates: model 1 adjusted for age,

Table 1
Baseline characteristics (N = 13,840)

Characteristic	APCs		p Value*
	Yes (n = 950)	No (n = 12,890)	
Age, mean \pm SD (y)	67 \pm 8.9	63 \pm 8.4	<0.001
Men	479 (50%)	5585 (43%)	<0.001
Black	387 (41%)	4736 (37%)	0.014
Region			
Stroke belt	295 (31%)	4375 (34%)	
Stroke buckle	215 (23%)	2753 (21%)	
Nonbelt	440 (46%)	5762 (45%)	0.19
Education (high school or less)	332 (35%)	4031 (31%)	0.019
Ever smoker	495 (52%)	6528 (51%)	0.38
Income (<\$20,000)	131 (14%)	1615 (13%)	0.26
Diabetes mellitus	183 (19%)	2102 (16%)	0.018
Systolic blood pressure, mean \pm SD (mm Hg)	128 \pm 16	126 \pm 16	<0.001
Body mass index, mean \pm SD (kg/m ²)	29 \pm 6.3	29 \pm 5.9	0.92
Total cholesterol, mean \pm SD (mg/dl)	189 \pm 38	193 \pm 39	0.0010
HDL cholesterol, mean \pm SD (mg/dl)	52 \pm 16	53 \pm 16	0.37
Aspirin	434 (46%)	5345 (41%)	0.011
Antihypertensive medications	494 (52%)	5961 (46%)	<0.001
Left ventricular hypertrophy	99 (10%)	1039 (8%)	0.011
Cardiovascular disease	165 (17%)	1891 (15%)	0.024

* Statistical significance for categorical variables was tested using the chi-square method, and for continuous variables, the Student's *t* test was used.

APC = atrial premature complex; HDL = high-density lipoprotein; SD = standard deviation.

sex, race, education, income, and geographic region; model 2 included covariates in model 1 with the addition of systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, left ventricular hypertrophy, and previous cardiovascular disease. We evaluated for effect modification by race and sex, using a stratification technique, and compared models with and without interaction terms. The Wald-type test was used to determine statistical significance for interaction effects. Statistical significance for all comparisons including interactions was defined as $p < 0.05$. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

A total of 13,840 (mean age = 63 \pm 8.4 years; 56% women; 37% black) participants were included in the final analytical sample. A total of 950 participants (6.9%) had evidence of APCs on the baseline ECG. Baseline characteristics stratified by the presence of APCs are shown in Table 1.

After a median follow-up of 9.4 years, 1,015 (7.3%; 43% women; 22% black) AF cases were detected. Of these, 227 cases (22%) were detected on the ECG and 788 cases (28%) were self-reported. AF was more frequent in those with baseline APCs (n = 139, 15%) compared with participants who did not have APCs (n = 876, 6.8%; $p < 0.001$). An increased risk of AF was observed for participants who had baseline APCs (OR = 1.92, 95% CI = 1.57, 2.35) (Table 2). This relation did not vary by race (whites: OR = 1.98, 95% CI = 1.57, 2.50; blacks: OR = 1.78, 95% CI = 1.19, 2.67; interaction p value = 0.56) or sex (women: OR = 1.95, 95% CI = 1.42, 2.68;

Table 2
Risk of atrial fibrillation (n = 13,840)

	Events/No. at risk	Model 1* OR (95% CI)	p Value	Model 2† OR (95% CI)	p Value	P-interaction‡
APC						
No	876/12,890	Ref	—	Ref	—	—
Yes	139/950	1.94 (1.58, 2.36)	<0.001	1.92 (1.57, 2.35)	<0.001	
Race						
Black	221/5,123	1.84 (1.23, 2.74)	0.0027	1.78 (1.19, 2.67)	0.0051	0.56
White	794/8,717	1.98 (1.57, 2.50)	<0.001	1.98 (1.57, 2.50)	<0.001	
Sex						
Female	436/7,776	1.91 (1.39, 2.61)	<0.001	1.95 (1.42, 2.68)	<0.001	0.66
Male	579/6,064	1.99 (1.54, 2.58)	<0.001	1.93 (1.49, 2.51)	<0.001	

* Adjusted for age, sex, race, education, income, and geographic region.

† Adjusted for model 1 covariates plus systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, left ventricular hypertrophy, and previous cardiovascular disease.

‡ Interactions tested using model 2.

APC = atrial premature complex; CI = confidence interval; OR = odds ratio.

men: OR = 1.93, 95% CI = 1.49, 2.51; interaction p value = 0.66) (Table 2).

Discussion

In this analysis from the REGARDS study, APCs detected on a routine 12-lead ECG were associated with an increased risk of AF. The results were consistent in subgroups stratified by race and sex. Overall, the findings of this analysis suggest that the risk of AF associated with atrial ectopy does not account for the differential risk of AF that is observed in whites compared with blacks, and in men compared with women.

Several reports have examined the association of APCs with AF. An examination of 42,751 patients (90% men; 94% whites) from the Palo Alto Veterans Health Care System demonstrated that APCs automatically detected on 12-lead ECGs are predictive of incident AF.² A report of 428 patients who underwent elective 24-hour electrocardiographic monitoring has also shown that frequent atrial ectopic beats (>100 APCs/day) increases one's risk of AF development.³ Additionally, a study of 1,260 participants (95% whites) from the Cardiovascular Health Study who underwent 24-hour ambulatory electrocardiographic monitoring demonstrated that the risk of AF increases with APC count.⁴

The aforementioned studies clearly demonstrated that APCs, whether detected on the 12-lead ECG² or 24-hour electrocardiographic monitoring,^{3,4} are associated with an increased risk of AF. However, these reports were limited regarding their inclusion of black participants and women. The findings of the current analysis support this conclusion and provide another example of the value of the resting ECG to identify patients who are likely to develop AF. Additionally, due to the diverse population of the REGARDS study, we were able to determine if the risk of AF associated with atrial ectopy varied by race or sex. Overall, previous reports and the findings of the present analysis suggest that APCs identify at-risk patients in whom intense risk factor modification strategies are warranted to prevent AF occurrence.¹⁶ This is further supported because participants with APCs were more likely to have well-known risk factors for AF (e.g., cardiovascular disease).

The present analysis provides important information regarding the risk of AF associated with atrial ectopy. Numerous reports have demonstrated that an increased risk of AF exists for whites compared with blacks,⁵⁻⁸ and for men compared with women.^{5,11} Explanations for these differences have been proposed, and suggest that a differential impact of AF risk factors exists by race^{9,10} and sex.^{17,18} Other explanations are related to differences in anatomic and electrophysiologic properties, suggesting that the necessary substrate for AF propagation is less likely to develop in blacks compared with whites, and in women compared with men. This is supported by studies which have demonstrated that smaller left atrial diameters exist in blacks compared with whites,¹⁹ and in women compared with men.²⁰ Similar findings have been reported for ECG phenotypes of AF.²¹ Lastly, it is possible that differences in sex hormones explain the differential risk of AF between men and women,²² and further studies are needed to explore this hypothesis.

Although these previous reports have demonstrated that adverse atrial remodeling varies by race and sex, the results of this study suggest that the risk of AF associated with APCs, a trigger for AF,¹ does not vary by race or sex. This implies that the race and sex differences in AF susceptibility probably are more related to variation in atrial remodeling than susceptibility to atrial ectopy. Therefore, a better characterization of risk factors for adverse atrial remodeling is needed to understand differences in AF susceptibility by race and sex.

The findings of the current analysis should be interpreted in the context of certain limitations. Our analysis was subjected to recall bias, as several baseline characteristics were self-reported. APCs were detected on a single ECG recording, and it is possible that more APCs would have been detected with longer electrocardiographic monitoring. However, the detection of more APCs would have merely strengthened our effect estimates rather than reducing the observed association toward the null. AF events were also ascertained nearly 10 years after the initial ECG tracing, and this outcome was subjected to recall bias, as some of the cases were ascertained by self-reported history of a physician diagnosis. Similarly, in most patients, AF is paroxysmal, and

certain events possibly were missed on the follow-up ECG tracing. It is likely that more cases would be detected with ambulatory electrocardiographic monitoring. Nonetheless, the significant association between APCs on the ECG and AF suggests that this method of APC ascertainment was sufficient to assess the risk of AF. Furthermore, we adjusted for several AF risk factors but acknowledge that other unmeasured factors possibly influenced our results.

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Disclosures

The authors have no conflicts of interest to disclose.

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