Ethnic Distribution of ECG Predictors of Atrial Fibrillation and Its Impact on Understanding the Ethnic Distribution of Ischemic Stroke in the Atherosclerosis Risk in Communities (ARIC) Study

Elsayed Z. Soliman, MD, MSc, MS; Ronald J. Prineas, MD, PhD; L. Douglas Case, PhD; Zhu-ming Zhang, MD; David C. Goff, Jr, MD, PhD

Background and Purpose—The paradox of the reported low prevalence of atrial fibrillation (AF) in blacks compared with whites despite higher stroke rates in the former could be related to limitations in the current methods used to diagnose AF in population-based studies. Hence, this study aimed to use the ethnic distribution of ECG predictors of AF as measures of AF propensity in different ethnic groups.

Methods—The distribution of baseline measures of P-wave terminal force, P-wave duration, P-wave area, and PR duration (referred to as AF predictors) were compared by ethnicity in 15,429 participants (27% black) from the Atherosclerosis Risk in Communities (ARIC) study by unpaired t test, $\chi^2$, and logistic-regression analysis, as appropriate. Cox proportional-hazards analysis was used to separately examine the association of AF predictors with incident AF and ischemic stroke.

Results—Whereas AF was significantly less common in blacks compared with whites (0.24% vs 0.95%, $P<0.0001$), similar to what has been reported in previous studies, blacks had significantly higher and more abnormal values of AF predictors ($P<0.0001$ for all comparisons). Black ethnicity was significantly associated with abnormal AF predictors compared with whites; odds ratios for different AF predictors ranged from 2.1 to 3.1. AF predictors were significantly and independently associated with AF and ischemic stroke with no significant interaction between ethnicity and AF predictors, findings that further justify using AF predictors as an earlier indicator of future risk of AF and stroke.

Conclusions—There is a disconnect between the ethnic distribution of AF predictors and the ethnic distribution of AF, probably because the former, unlike the latter, do not suffer from low sensitivity. These results raise the possibility that blacks might actually have a higher prevalence of AF that might have been missed by previous studies owing to limited methodology, a difference that could partially explain the greater stroke risk in blacks. (Stroke. 2009;40:00-00.)

Key Words: atrial fibrillation ■ ischemic stroke ■ electrocardiogram ■ ethnicity

Black Americans have a disproportionate stroke burden, with a 2 to 5 times higher incidence rate and a 2 to 4 times higher mortality rate compared with whites.1,2 Because of the strong association between atrial fibrillation (AF) and ischemic stroke,3–5 it was expected that the stroke disparity between blacks and whites could be partially explained by an increased prevalence of AF in blacks. However, all previous studies reported that AF (detected by self-report and/or short-term ECG recording) was less prevalent in blacks compared with whites.10–19 Nevertheless, self-report and short-term ECG are limited in their ability to account for all AF patterns, especially paroxysmal AF, which constitutes >30% of AF cases.20–23 which raises doubts about the conclusions made by those studies. Although longer-term ECG recording (≥24 hours) may yield better AF detection,24–26 the cost of such ECG modalities remains an obstacle to use in epidemiologic studies. Hence, in this study, we used ethnic differences in the distribution of variables derived from P-wave morphology (referred to as AF predictors) as measures of AF propensity in different ethnic groups. These AF predictors are readily measured from a standard 12-lead ECG and have shown good predictive accuracy for future AF, including paroxysmal AF.20–39 By avoiding the limitations of previous studies of ethnic differences in AF, this study has the potential to provide better insight regarding ethnic differences in AF with less detection bias and subsequently a better understanding of the role of AF in explaining the ethnic differences of stroke. To further justify using AF predictors as...
a surrogate for AF, this study also aimed to test the association between baseline abnormal AF predictors and future risk of AF and ischemic stroke. We hypothesized that black ethnicity is associated with more abnormal values of AF predictors (primary aim), and those AF predictors are associated with an increased risk of both incident AF and incident stroke in blacks and whites (secondary aim).

Subjects and Methods

Study Population
The Atherosclerosis Risk in Communities (ARIC) study is a prospective, population-based epidemiologic study conducted in 4 US communities: Forsyth County, North Carolina; Jackson, Miss; Minneapolis suburbs, Minn; and Washington County, Maryland. ARIC is designed to investigate the etiology and natural history of atherosclerosis; the etiology of clinical atherosclerotic diseases; and the variation in cardiovascular risk factors, medical care, and disease by ethnicity, sex, location, and date. ARIC includes 2 parts: the cohort component (1987–1998), which we used for this analysis, and the community surveillance component (currently ongoing). A detailed description of the study objectives and research questions as well as the methodology of recruiting, enrollment, examination, and follow-up have been described elsewhere.40–42 In brief, starting in 1987, each ARIC field center randomly selected and recruited a sample of ~4000 individuals. Potential eligible participants were selected by probability sampling from the noninstitutionalized residential population in the 4 communities. Considered eligible on each sampling frame were all individuals age 45 to 64 years at the time of enumeration who were permanent residents, had no definite plans to leave the area, were mentally and physically capable of participating in the clinical examination, and for whom there were no language barriers to participation. To ensure adequate representation, a greater proportion of black than white residents was sampled in Forsyth County, and black residents were exclusively sampled in Jackson. After enumeration, which involved identifying the age, sex, and ethnicity of all eligible household members, an interviewer conducted a detailed interview with each eligible participant. The interview, lasting ~30 minutes, was conducted in the respondent’s home and, whenever possible, was completed at the time of enumeration. After completing the home interview, eligible participants received a written and verbal description of the ARIC study and were invited to take part in the complete program. Appointments were made for those who agreed to attend the first clinical examination at designated study centers, which lasted 3 to 4 hours. Approximately 75% of age-eligible individuals (45 to 64 years) in each community completed the home interview. In 3 of the communities, 86% to 88% of those who took part in the home interview also completed the clinical examination, whereas only 63% did so in Jackson. General health status and recent hospitalization rates were almost identical in black respondents and nonrespondents. A total of 15,792 participants received an extensive examination, including medical, social, and demographic data. These participants were reexamined every 3 years, with the first screen (baseline) occurring in 1987 to 1989, the second in 1990 to 1992, the third in 1993 to 1995, and the fourth and last examination in 1996 to 1998. Retention rates were 93%, 87%, and 81% at the first, second, and third follow-up examinations, respectively. Follow-up occurred yearly by telephone to maintain contact with participants and to assess health status of the cohort. The follow-up period ranged from 3 to 13.75 years (mean ± SD, 6.97 ± 1.46 years; median, 7 years). Participants (n = 563) with poor-quality baseline ECG recordings, baseline ECG conditions affecting P-wave measurement, or a self-identified ethnicity other than black or white have been excluded from this analysis.

AF Predictors Measurement and AF Diagnosis
The study ECGs were recorded with MAC PC ECG machines (Marquette Electronics, Milwaukee, Wis) in all clinical centers. ECGs were initially processed in a central laboratory at the EPICORE Center (University of Alberta, Edmonton, Alberta, Canada) and during later phases of the study at the EPICARE Center (Wake Forest University, Winston-Salem, NC). All ECGs were visually inspected for technical errors and inadequate quality. Initial ECG processing was done by the Dalhousie ECG program, and processing was later repeated with the 2001 version of the GE Marquette 12-SL program (GE Marquette, Milwaukee, Wis). ARIC participants were scheduled to have 4 ECG recordings that were performed during the baseline and the every-3-year study examination. The baseline ECG recordings were used to create the AF predictors, whereas the follow-up ECG recordings were used to measure AF incidence. The ECG variables that we used as AF predictors included P-wave terminal force, P-wave duration, P-wave area, and PR duration, all measured automatically. Because of the automatic measurement, the repeatability of all ECG measures was 100%. P-wave terminal force was defined as the duration in seconds of the terminal part (negative) of the P wave in lead V1 multiplied by its depth in microvolts. P-wave duration (maximum, mean, and in lead II) was measured in milliseconds as the first “onset” and last “offset” deflection from the baseline. P-wave area (maximum and mean) was measured in microvolt · milliseconds2 as the area under the P wave in the 12 leads of the ECG. PR duration was measured in milliseconds as the mean P-wave duration plus the mean PR-segment duration in the 12-lead ECG. The ECG recordings that were automatically coded as AF were visually rechecked by a trained cardiologist to confirm diagnosis. The visually confirmed AF cases in any of the 3 follow-up visits were the ones used in our analysis.

Ischemic Stroke
ARIC participants were contacted annually by phone, and all hospitalizations and deaths during the previous year were identified. In addition, local hospitals provided lists of cardiovascular disease discharges, which were examined for participants’ hospitalizations. Appropriate sections of the medical record of eligible hospitalizations were then copied and sent to a central location (University of Minnesota) for abstraction by a single trained nurse. At Minneapolis, strokes were classified by computer algorithm as either hemorrhagic (subarachnoid hemorrhage and intracerebral hemorrhage) or ischemic (thrombotic and embolic) strokes; each was further categorized into “definite stroke,” “possible stroke,” “out-of-hospital fatal stroke—based on an underlying cause of death from the death certificate only,” and “no stroke.” In addition to the computer-determined diagnosis, cases were independently reviewed by a physician. The final diagnosis was determined by agreement of computer and physician-reviewer classification. Disagreements were adjudicated by a second physician-reviewer. Our analysis included all cases of definite or possible ischemic (thromboembolic) stroke.

Other Clinical Variables
Data on blood pressure, diabetes, lipid profile, body mass index (BMI), and smoking status were obtained from the ARIC baseline examination. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level >126 mg/dL, nonfasting glucose level of ≥200 mg/dL, and/or a history of or treatment for diabetes. BMI was measured in kg/m2 from the formula: [weight (lbs)/2.20/[^height(cm/100)]^2].

Statistical Analysis
Frequency distributions of all variables were first inspected to identify anomalies and outliers possibly caused by measurement artifacts. Differences in characteristics and AF predictors by ethnicity were assessed by χ² and nonpaired t tests. General linear models were used to compare the age- and sex-adjusted means of AF predictors between blacks and whites, whereas logistic-regression analysis was used to estimate age- and sex-adjusted odds ratios (ORs) for abnormal AF predictors for comparing blacks with whites, with the 95th percentile as a cutpoint to define abnormality.
Regarding comparison of AF predictors in blacks and whites (the primary aim), there was ≥95% statistical power to detect a 0.2-μV·s difference in P-wave terminal force, a 5-ms difference in maximum and mean P-wave duration, a 10-μV·ms² difference in maximum and minimum P-wave area, and a 5-ms difference in PR interval, with the assumption of standard deviations of 1.85 μV·s, 12.4 ms, 12.9 ms, 109.2 μV·ms², 49.7 μV·ms², and 25.4 ms, respectively, at α=0.05.

Cox proportional-hazards (CPH) analysis was used to assess the effect of individual AF predictors on the risk of AF and ischemic stroke (secondary aims), after adjusting for demographic characteristics [age, sex, and ethnicity (model 1)] and further adjusting for clinical characteristics [hypertension, systolic blood pressure, diabetes, LDL, HDL, triglycerides, smoking status, and BMI (model 2)]. Each AF predictor was initially included as a continuous variable, and relative risk was calculated to show the incremental risk per 1-SD change in each measure. Then, in the AF analysis, each AF predictor was dichotomized at defined cutoff points to establish prognostic indexes with practical clinical utility. We categorized each AF predictor as abnormal (>95th percentile) or normal (≤95th percentile). Other analyses included examining the interaction between ethnicity and AF predictors, examining the correlation between the AF predictors, and examining the differences in the effect of ethnicity on the risk of stroke with and without including selected AF predictors as covariates in a CPH analysis. SAS, version 9.1 (SAS Institute, Inc, Cary, NC) was used in all analyses.

**Results**

The average age of the study population at baseline was 54.2±5.8 years, 27% were blacks, 55% were females, 35% had hypertension, 12% had diabetes, and 29% had never smoked. Table 1 shows the baseline characteristics of the study population stratified by ethnicity. As shown in Table 1, blacks were slightly younger (53.6±5.8 vs 54.4±5.8 years, P<0.0001) with more females (62% vs 53% P<0.0001) compared with whites. The established risk factors for AF/stroke, such as hypertension, diabetes, and increased BMI, were more manifest in blacks compared with whites (P<0.0001 for all comparisons). Whereas the proportion of current smokers was significantly higher in blacks (45% vs 37%), the proportion of former smokers in whites was significantly higher (35% vs 23%, P<0.0001). In blacks, the levels of HDL were significantly higher and the levels of triglycerides were significantly lower (P<0.0001), whereas LDL was not significantly different compared with whites (P<0.487).

During the follow-up period (6.97±1.46 years), 117 participants developed ECG-diagnosed AF, and 599 developed ischemic stroke. Despite having more strokes (6.27%, n=258 vs 3.03%, n=342; P<0.0001), blacks had less AF (0.24%, n=10 vs 0.95%, n=107; P<0.0001) compared with whites, similar to what has been reported in previous studies. However, all AF predictors (P-wave terminal force, maximum P-wave duration, mean P-wave duration, mean P-wave duration in lead II, maximum P-wave area, mean P-wave area, and PR duration) showed significantly higher values in blacks compared with whites (Table 2). These findings were consistent whether the AF predictors were compared as continuous variables or as categorical variables with the 95th percentile as a cutpoint, in unadjusted analysis or in multivariable

**Table 1. Baseline Characteristics of the Study Population Stratified by Ethnicity**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>All</th>
<th>Blacks</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>15429</td>
<td>4114 (27)</td>
<td>11315 (73)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>15429</td>
<td>54.2±5.8</td>
<td>53.6±5.8</td>
<td>54.4±5.8</td>
</tr>
<tr>
<td>Females</td>
<td>15429</td>
<td>8542 (55)</td>
<td>2564 (62)</td>
<td>5978 (53)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15359</td>
<td>5347 (35)</td>
<td>2282 (56)</td>
<td>3065 (27)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>15399</td>
<td>121.2</td>
<td>128.8</td>
<td>118.5</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>15358</td>
<td>73.8</td>
<td>79.7</td>
<td>71.6</td>
</tr>
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<td>Diabetes</td>
<td>15300</td>
<td>1815 (12)</td>
<td>792 (20)</td>
<td>1023 (9)</td>
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<tr>
<td>Smoking status</td>
<td>15408</td>
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</tr>
<tr>
<td>Current</td>
<td>6058 (39)</td>
<td>1849 (45)</td>
<td>4209 (37)</td>
<td></td>
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<tr>
<td>Former</td>
<td>4955 (32)</td>
<td>960 (23)</td>
<td>3995 (35)</td>
<td></td>
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<tr>
<td>Never</td>
<td>4395 (29)</td>
<td>1293 (32)</td>
<td>3102 (27)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>15417</td>
<td>27.7±5.4</td>
<td>29.6±6.2</td>
<td>27.01±4.9</td>
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<tr>
<td>HDL, mg/dL</td>
<td>14979</td>
<td>51.6±16.9</td>
<td>54.9±17.0</td>
<td>50.5±16.6</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>14929</td>
<td>137.8±38.6</td>
<td>138.2±42.3</td>
<td>137.7±37.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>14973</td>
<td>124.9±64.4</td>
<td>109.2±54.8</td>
<td>130.3±66.6</td>
</tr>
</tbody>
</table>

Values are expressed as No. of participants (%) or mean±SD.

*P<0.0001 for all comparisons except for LDL, where P=0.487.

**Table 2. Unadjusted AF Predictors (Mean±SD) and the Proportion of Participants With Abnormal AF Predictors in Blacks vs Whites†**

<table>
<thead>
<tr>
<th></th>
<th>Blacks N=4114</th>
<th>Whites N=11315</th>
<th>Proportion (%) of Participants With Abnormal AF Predictors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD of the AF Predictors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-wave terminal force, μV·s</td>
<td>2.2±2.1</td>
<td>1.6±1.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Maximum P-wave duration, ms</td>
<td>112.3±12.3</td>
<td>107.0±12.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Mean P-wave duration, ms</td>
<td>109.4±12.7</td>
<td>104.0±12.7</td>
<td>8.0</td>
</tr>
<tr>
<td>P-wave duration in lead II, ms</td>
<td>112.0±13.4</td>
<td>106.6±13.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Maximum P-wave area, μV·ms²</td>
<td>384.2±115.2</td>
<td>338.6±104.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Mean P-wave area, μV·ms²</td>
<td>206.9±52.4</td>
<td>185.3±47.4</td>
<td>9.0</td>
</tr>
<tr>
<td>PR duration, ms</td>
<td>172.2±27.8</td>
<td>161.2±23.8</td>
<td>8.5</td>
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</table>

*Abnormal AF predictor was an AF predictor with a value >95th percentile value in the entire study population.
†P<0.0001 for all comparisons.
Table 3. Age- and Sex-Adjusted AF Predictors (Least Mean Square±SE), ORs, and 95% CIs of Abnormal AF Predictors* in Blacks vs Whites†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Blacks (N=4114)</th>
<th>Whites (N=11315)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-wave terminal force, μV·s</td>
<td>2.2±0.03</td>
<td>2.1±0.03</td>
<td>1.8 (1.2, 2.4)</td>
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<tr>
<td>Maximum P-wave duration, ms</td>
<td>112.8±0.19</td>
<td>106.8±0.11</td>
<td>1.0 (2.3, 3.1)</td>
</tr>
<tr>
<td>Mean P-wave duration, ms</td>
<td>109.8±0.19</td>
<td>103.8±0.12</td>
<td>1.0 (2.3, 3.1)</td>
</tr>
<tr>
<td>Maximum P-wave area, μV·ms²</td>
<td>384.6±1.67</td>
<td>338.5±1.01</td>
<td>1.0 (2.3, 3.0)</td>
</tr>
<tr>
<td>Mean P-wave area, μV·ms²</td>
<td>207.7±0.76</td>
<td>185.0±0.46</td>
<td>1.0 (2.3, 3.3)</td>
</tr>
<tr>
<td>PR duration, ms</td>
<td>172.7±0.39</td>
<td>160.9±0.23</td>
<td>1.0 (2.6, 3.6)</td>
</tr>
</tbody>
</table>

*Abnormal AF predictor was an AF predictor with a value >95th percentile value in the entire study population.
†Model 1 adjusts for demographic variables (age, sex, and ethnicity).

Table 5. HRs and 95% CIs of AF Predictors for Incident Ischemic Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1†</th>
<th>Model 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-wave terminal force, μV·s</td>
<td>1.33 (1.25, 1.42)</td>
<td>1.22 (1.14, 1.31)</td>
</tr>
<tr>
<td>Maximum P-wave duration, ms</td>
<td>1.14 (1.05, 1.23)</td>
<td>1.06 (0.97, 1.15)</td>
</tr>
<tr>
<td>Mean P-wave duration, ms</td>
<td>1.14 (1.05, 1.24)</td>
<td>1.05 (0.97, 1.15)</td>
</tr>
<tr>
<td>P-wave duration in lead II, ms</td>
<td>1.11 (1.02, 1.21)</td>
<td>1.04 (0.95, 1.14)</td>
</tr>
<tr>
<td>Maximum P-wave area, μV·ms²</td>
<td>1.17 (1.09, 1.27)</td>
<td>1.13 (1.05, 1.23)</td>
</tr>
<tr>
<td>Mean P-wave area, μV·ms²</td>
<td>1.17 (1.08, 1.26)</td>
<td>1.11 (1.02, 1.20)</td>
</tr>
<tr>
<td>PR duration, ms</td>
<td>1.04 (0.93, 1.09)</td>
<td>1.00 (0.92, 1.08)</td>
</tr>
</tbody>
</table>

*HR for a 1-SD change.
†Model 1 adjusts for demographic variables (age, sex, and ethnicity).
‡Model 2 adjusts for demographic variables in model 1 + clinical variables: hypertension, systolic blood pressure, diabetes, blood lipids (HDL, LDL, and triglycerides), smoking status, and BMI.

Abnormal AF predictors were not only more common in blacks compared with whites but also significantly associated with the risk of incidence of AF and ischemic stroke in multivariable adjusted CPH analyses. The hazard ratios (HRs) for incident AF associated with AF predictors ranged from 2.1 to 3.1 with relatively narrow 95% CIs (Table 3). Analysis adjusted for age and sex (P<0.0001 for all comparisons, Table 3). In a logistic-regression analysis, black ethnicity was significantly associated with abnormal AF predictors compared with whites. Age- and sex-adjusted ORs with different AF predictors ranged from 2.1 to 3.1 with relatively narrow 95% CIs (Table 3).

Abnormal AF predictors were not only more common in blacks compared with whites but also significantly associated with the risk of incidence of AF and ischemic stroke in multivariable adjusted CPH analyses. The hazard ratios (HRs) for incident AF associated with AF predictors ranged from 1.08 to 5.23, depending on which AF predictor was in the models, the number of covariates in the models, and whether the AF predictor was examined as a continuous or a categorical variable. All HRs associated with all AF predictors, whether used as continuous variables or categorical variables in all models (model 1 adjusts for demographic variables, and model 2 adjusts further for clinical variables), were statistically significant except for the PR duration when used as a categorical variable (upper 5th percentile vs first 95th percentile) and maximum P-wave area when used as a continuous variable. Among all AF predictors, maximum P-wave duration (upper 5th percentile vs first 95th percentile) was the most strongly associated predictor with the risk of incident AF (HR=5.23, 95% CI=3.33 to 8.22 in model 1, and HR=4.07, 95% CI=2.55 to 6.51 in model 2; Table 4).

Table 5 shows the association between the baseline AF predictors and the risk of incident ischemic stroke in CPH analysis after adjusting for demographic variables (model 1) and further adjusting for clinical variables (model 2). In model 1, all AF predictors (except PR duration) were significantly associated with the risk of incident stroke (HR ranged from 1.04 to 1.33). After further adjusting for clinical variables (model 2), P-wave terminal force, maximum P-wave area, and mean P-wave area remained significantly associated with the risk of incident stroke. It was of interest to notice that there was a minimal difference in the HR associated with P-wave terminal force in the 2 models (HR=1.33, 95% CI=1.25 to 1.42 in model 1, and HR=1.22, 95% CI=1.14 to 1.31 in model 2). Furthermore, when AF predictors were used as categorical variables (upper 5th percentile vs first 95th percentile) in similar CPH models,
P-wave terminal force was the strongest predictor for the risk of incident ischemic stroke (HR = 2.60, 95% CI = 2.05 to 3.29 in model 1 and HR = 2.28, 95% CI = 1.79 to 2.90 in model 2). These findings suggest that P-wave terminal force may provide a strong independent predictor for incident stroke in clinical practice. Figure 1 shows Kaplan-Meier survival curve comparing event-free survival for stroke events in blacks and whites with or without abnormal P-wave terminal force with the 95th percentile as a cutpoint. To test whether the ethnic differences in P-wave terminal force, as an example of AF predictors, partially explains the ethnic differences of stroke, the effect of ethnicity on the risk of incident stroke was compared in models similar to those CPH models in Table 5 with and without P-wave terminal force in the models. By including P-wave terminal force in the models, there was an attenuation of the ethnicity effect by 25% and 8%, respectively, compared with the effect of ethnicity in those models without P-wave terminal force (HR = 2.56, 95% CI = 2.18 to 3.02 and HR = 1.63, 95% CI = 1.35 to 1.96 in models 1 and 2, respectively, when P-wave terminal force was not in the models, and HR = 2.31, 95% CI = 1.96 to 2.73 and HR = 1.55, 95% CI = 1.28 to 1.88 for models 1 and 2, respectively, when P-wave terminal force was in the models). To explore this further, the effect of ethnicity on the risk of stroke with and without P-wave terminal force was compared in models in which the covariates were selected from all demographic and clinical variables in this analysis according to the stepwise selection approach. Covariates that remained in the models were age, sex, ethnicity, hypertension, diabetes, HDL, LDL, and smoking status. Again, the HR of stroke associated with ethnicity decreased by 11% in the second model (with P-wave terminal force) compared with the first model (without P-wave terminal force) (HR = 1.76, 95% CI = 1.46 to 2.10 and HR = 1.65, 95% CI = 1.38 to 1.98, respectively).

There was no strong correlation between the 4 main AF predictors: P-wave terminal force, maximum P-wave duration, maximum P-wave area, and PR interval, a finding that suggests that those AF predictors might be representing different electrophysiologic characteristics and subsequently may offer different information regarding AF prediction.
Pearson correlation coefficients ($R$) for those AF predictors ranged from 0.08 to 0.46. P-wave terminal force showed the least correlation with all other variables ($R$ ranged from 0.08 to 0.29), followed by PR duration ($R$ ranged from 0.08 to 0.46). However, as expected, correlation between different mathematical expressions of the same AF predictor, such as maximum and mean P-wave duration, was high. The pattern of the correlation between AF predictors was similar in both blacks and whites (results not shown).

There was no statistically significant interaction between any of the AF predictors and ethnicity in a CPH analysis with an outcome of yes/no for AF and an interaction term (AF predictors and ethnicity) as a covariate. Similarly, there was no interaction between any of the AF predictors (except P-wave area) and ethnicity when stroke was used as an outcome in a similar CPH analysis.

**Discussion**

This study has 3 major strengths: (1) a community-based sample drawn by probability sampling, (2) a large sample size with long follow-up, and (3) uniform ascertainment of all of the study variables, including ECG variables, AF, stroke, and AF/stroke risk factors.

The key result of this study is that blacks have more abnormal values of AF predictors than do whites, and these predictors are strongly associated with the risk of incident AF. These findings were consistent when AF predictors were statistically examined as continuous variables, statistically examined as categorical variables, or mathematically expressed in different ways, such as mean and maximum values of the same predictor. Even with the strong association between AF predictors and the risk of incident AF in our study, the reported HR should be considered conservative. Because AF was diagnosed in the ARIC study on the basis of a standard 12-lead ECG every 3 years in a follow-up period of 10 years, many AF cases, especially those of paroxysmal AF, must have been missed and subsequently counted as non-AF cases. This is expected to dilute the effect of the explanatory variables, abnormal AF predictors, on the outcome, AF, and bias the results toward null. We used different measures and different categorizations for the same AF predictor to ensure consistency and/or feasibility of measuring that predictor in clinical practice.

The results of the interaction tests mentioned in the Results section denote that AF predictors are equally predictive for AF in blacks as well as whites. However, these interaction results should be read in the context of the small number of AF ($n=10$) in blacks and that blacks represented 27% of the study population, and the subsequently lack of statistical power to detect a significant interaction is a possibility. Nevertheless, prediction of AF on the basis of ECG AF predictors, which has been reported in previous studies,$^{30–39}$ was not the primary aim of this study; rather, it was a secondary aim to further justify using the ethnic distribution of AF predictors as a surrogate marker for the ethnic distribution of AF.

Given that ARIC participants underwent ECG recording every 3 years, the time to event (AF) in our CPH analysis was a crude estimate of the actual time. Hence, we repeated the analysis with the use of logistic-regression models similar to those CPH models that we used in this analysis. The strong association between AF predictors and AF persisted in those logistic-regression analyses whether AF predictors were used as continuous variables (change in 1-SD) or categorical variables (upper 5th percentile vs first 95th percentile; results not shown).

The AF predictors were not only associated with the risk of incident AF but also with the risk of incident ischemic stroke. However, the association between AF predictors and the risk of stroke was less than that of the risk of AF, and the strength of the association decreased with further adjustment for clinical variables. This outcome is wholly consistent with the conceptual model illustrated in Figure 2, where the risk of stroke occurs further back in the disease pathway compared with AF. Additionally and from the same conceptual model, stroke risk factors (such as hypertension and diabetes, etc) could lead to stroke either through AF (ie, AF predictors are mediating factors) or through different pathways not necessarily related to AF or its predictors. Hence, adjusting for stroke risk factors is expected to lessen the association between AF predictors and risk of stroke. Despite this, it is important to emphasize that some predictors such as P-wave terminal force, maximum P-wave area, and mean P-wave area were independent predictors for stroke, even after adjusting for known stroke risk factors.

Attenuation of the effect of ethnicity on the risk of incident ischemic stroke when P-wave terminal force was included in the models raises the possibility that differences in AF predictors and subsequently ethnic differences in AF (including paroxysmal AF) could partially explain the ethnic difference of stroke incidence. Although we could not confirm that such attenuation is statistically significant, given the overlapping CIs of the HR in the models, the persistence of attenuation among different models is in favor of none by chance results.

Because we showed that ECG AF predictors were equally predictive for AF and that they are more prevalent in blacks than whites, it would be expected that an increased prevalence of AF in blacks compared with whites would result—just the reverse of findings reported by previous studies but in concert with the fact of high stroke burden in blacks and the strong association between AF and stroke. A potential explanation for this paradox comes from the notion that because all previous studies of ethnic distribution of AF used self-report, standard 12-lead ECG, or rarely, 24-hour Holter monitoring to diagnose AF,$^{10–19}$ all have major limitations of sensitivity for actual AF cases. Most AF cases are asymptomatic; up to 30% of patients with AF are unaware of their diagnosis,$^{20}$ 25% of those with AF-associated stroke have no
prior diagnosis of AF,24–25 and the fibrillation pattern is intermittent in 30% of patients with stroke and may not appear in a single ECG recording.24–26 Although the limited methodology in previous studies could have resulted in an overall underestimated AF prevalence, the reason why these methods might have disproportionately underdiagnosed AF in blacks more than whites is at the heart of the paradox. It is possible that the disproportionate ability of self-report or short-term ECG to detect AF might be related to different AF patterns in blacks compared with whites. Blacks might have more paroxysmal AF which is more likely to be missed by the conventional methods used to diagnose AF. Unfortunately, we were unable to test this hypothesis in this study because of the small number of paroxysmal AF cases, and to our knowledge, this possibility has never been tested before in a large population study powered to detect differences in the ethnic distribution of paroxysmal AF. However, there are some clues that support the possibility that blacks might have an increased prevalence of paroxysmal AF compared with whites. In a recent prospective study,43 the metabolic syndrome was a significant risk factor for paroxysmal AF that was independent of left atrial diameter or age (OR = 2.8, 95% CI 1.3 to 6.2; P<0.01). Among the components of the metabolic syndrome (hypertension, diabetes, lipid profile, obesity), increased BMI (≥25 kg/m²) was the strongest predictor for paroxysmal AF (OR = 3.0, 95% CI 1.2 to 7.4; P = 0.02). As noticed in our analysis, compared with whites, blacks have higher values of BMI as well as higher prevalences of most of the components of the metabolic syndrome, which might make them more liable to develop paroxysmal AF. The reported strong association between AF, whether paroxysmal or persistent, and the risk of ischemic stroke4,9,44 raises the possibility that excess paroxysmal AF in blacks compared with whites would contribute to the increased risk of ischemic stroke in blacks.

In conclusion, blacks have more abnormal values of AF predictors compared with whites, and these predictors are associated with the risk of AF and ischemic stroke. In contrast to what has been reported by previous studies, these results raise the possibility that blacks might actually have a higher prevalence of AF (possibly due to more paroxysmal AF) than whites, a finding that could partially explain the increased stroke risk in blacks.

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Disclosures

None.

References


Ethnic Distribution of ECG Predictors of Atrial Fibrillation and Its Impact on Understanding the Ethnic Distribution of Ischemic Stroke in the Atherosclerosis Risk in Communities (ARIC) Study

Elsayed Z. Soliman, Ronald J. Prineas, L. Douglas Case, Zhu-ming Zhang and David C. Goff, Jr

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