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The Sensitivity of the Methods of Detection of Atrial Fibrillation in Population Studies Affects Group-Specific Prevalence Estimates: Ethnic and Regional Distribution of Atrial Fibrillation in REGARDS Study

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Abstract

Background—The paradox of reported low atrial fibrillation (AF) prevalence in blacks and in Southern U.S. states despite having high rates of stroke warrants investigation. We hypothesized that the ethnic and regional distribution of AF has been affected by the sensitivity of methods used to diagnose AF in prior reports.

Methods—18,833 black and white participants from the U.S. national study REasons For Geographic And Racial Differences In Stroke (REGARDS) study were included in this analysis. Levels of sensitivity to detect AF, from the least to the most sensitive, were created with graded combinations of self-report (SR) and ECG methods as follows: (a) Both SR and ECG, (b) ECG alone, (c) SR alone and (d) SR or ECG. Geographic regions were dichotomized as Stroke-Belt (the Southern U.S. states) and non Stroke-Belt. Logistic regression analysis estimated the odd ratios of AF associated with Stroke-Belt and black ethnicity across each diagnostic combination.

Results—Stroke-Belt was significantly associated with AF detected by “Both SR and ECG” (Multivariable adjusted OR (95% CI): 0.66 (0.47, 0.92)), an association that was no longer significant when AF was diagnosed with a more sensitive method, “SR or ECG”, (OR (95% CI): (0.95 (0.85, 1.06)). Similarly, the association between black ethnicity and AF was sequentially attenuated as measured across the 4 increasingly sensitive AF detection methods (OR: 0.20, 0.40, 0.70, 0.71 respectively).

Conclusions—The association between AF and Stroke-Belt or black ethnicity has an inverse relationship with the sensitivity to detect AF; as the sensitivity increases, the association attenuates

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(or even reverses), a finding that may partially explain the reported lower prevalence of AF in populations with higher stroke rates.

Keywords

Atrial fibrillation; Race/ethnicity; REGARDS study

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, currently affecting 2.3 million Americans.[1] AF is associated with more than a 5-fold increase in stroke incidence, a relative risk that is the greatest of the "traditional" risk factors for incident stroke.[2] Because of such a strong association between AF and the risk of stroke, it has been suggested that the ethnic and regional differences in stroke burden might be explained in part by the ethnic and regional difference in the prevalence of AF. However, despite the increased stroke burden in blacks[3] and in the Southern U.S. (Stroke-Belt)[4, 5], it has been reported that blacks have less AF compared to whites[1, 6-12] and that there is no difference in AF prevalence between the Stroke-Belt and the rest of the U.S. regions.[13] Such a paradox warrants examination of the methods by which these studies reached such a conclusion regarding ethnic and regional differences in AF prevalence. Despite acknowledging the limitations of the current methods, 12-lead electrocardiogram (ECG) and self-report (SR), to diagnose all AF cases, especially paroxysmal AF which represents over 30% of cases[14-16], previous studies assume that such limitations in AF diagnosis should not affect the proportionate distribution of AF prevalence between different ethnicities or regions. This is based upon the assumption that the ability or inability (sensitivity) to detect AF equally affects AF prevalence in all groups and that subsequently the proportionate distribution of AF among groups would be preserved. This assumption is examined in the present analyses by estimating the prevalence of AF across different levels of sensitivity of the diagnostic methods used to detect AF.

METHODS

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is a U.S. national, population-based, longitudinal study of black and white adults aged ≥45 years. The study was designed to oversample African Americans to represent 42% of the cohort, and to provide approximate equal representation of men and women (45%/55%). By design, 50% from the 8 Southern US states referred to as stroke belt states (North Carolina, South Carolina, and Georgia plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and 50% from the other 40 contiguous states. Individuals were recruited from commercially available lists of residents using a combination of mail and telephone contact. For those who agreed to participate, demographic information, medical history, and measures of cognitive function and quality of life were obtained by computer-assisted telephone interview. Standardized physical measures were collected at an in-home physical examination that included height and weight to calculate body mass index (BMI) in Kg/m^2, blood pressure, and resting ECG. The study methods were reviewed and approved by the Institutional Review Boards at the participating centers. Additional methodological details are provided elsewhere.[17] The in-home exam was conducted in person 3−4 weeks after the telephone interview, by a health care professional from Examination Management Services, Inc. (EMSI). The ECGs were sent to a central ECG reading center at Wake Forest University where they were read and coded by electrocardiographers blinded to clinical data.

Hypertension was defined as systolic blood pressure greater than or equal to 140 mmHg, or diastolic blood pressure greater than or equal to 90 mmHg, or use of antihypertensive drugs. Diabetes was defined as fasting blood glucose >126 mg/dL, or a non-fasting blood glucose

>200 mg/dL, or use of insulin or oral diabetic medication. In addition to ECG diagnosis of AF, history of AF by SR was also collected. AF by SR was defined as a positive response to the question: "Has a physician or a health professional ever told you that you had atrial fibrillation? AF by ECG and/or SR was further classified into 4 groups: a) AF by SR and ECG *(Both SR and ECG)*, b) AF by ECG alone *(ECG AF)*, c) AF by SR alone *(SR AF)*, and d) AF by SR or ECG *(SR or ECG)*. This classification is proposed to provide different degrees of sensitivity to detect AF with AF by "both SR and ECG" being the least sensitive and AF by "SR or ECG" being the most sensitive.

Between January 25, 2003, and November 30, 2005, 191,028 telephone numbers called to recruit participants had a final disposition. Defined according to standards recommended by Morton et al [18] the response rate (percentage agreeing to be interviewed among known eligible candidates contacted plus an adjustment for estimate of likely eligible participants among unknown eligible participants) was 40.7% (31 556/77 526).[19] As of December 1, 2005, there were 20,677 participants with completed in-home baseline data. After exclusion of those with ECG evidence of an implanted pacemaker, or those with poor quality ECG recordings, there were 18,833 participants included in the present analysis.

Statistical Analysis

Frequency distributions of all variables were first inspected to identify anomalies and outliers possibly caused by measurement artifacts. Descriptive statistics included mean, SD, and percentiles for continuous variables, and frequency and percentage for categorical variables. Logistic regression models were used to estimate the associations, expressed as odds ratios, between AF (as measured using different detection methods) and either ethnicity (blacks vs. whites) or geographic region (Stroke-Belt vs. non-Stroke-Belt). Three models were fitted: model 1) unadjusted, model 2) age, gender and ethnicity (for region analysis) or region (for ethnicity analysis) adjusted, and model 3) age, gender and ethnicity (for region analysis) or region (for ethnicity analysis) hypertension, diabetes and BMI adjusted.

RESULTS

Table 1 shows the characteristics of the study population (N= 18,833) as well as the unadjusted prevalence of AF stratified by ethnicity and geographic region. The average age of the study population was 65.9 years, 41% were blacks, 51.5% were females, 57.5% had hypertension and 21.2% were diabetics. Unadjusted AF prevalence in all subgroups varied markedly across different levels of sensitivity created by the different combinations of the SR and ECG-diagnosed AF. AF detected by "SR or ECG" was the most sensitive, followed by "SR" alone and "ECG" alone, and the least sensitive method was by "both SR and ECG". In general, AF by "SR or ECG" was more than 7 times as prevalent as AF by "both SR and ECG": AF prevalence in the total population by "SR or ECG" was 7.8% compared to only 0.8 % when AF was diagnosed by "both SR and ECG". Regardless of the variations in the sensitivity, the unadjusted prevalence of AF was not different in the Stroke-Belt compared to the rest of the U.S. while it was more prevalent in whites compared to blacks.

Table 2 shows unadjusted and multivariable adjusted associations between ethnicity and region with AF as detected by the 4 different levels of sensitivity. In all models, the association, expressed as odds ratios, between region (Stroke-Belt vs. non-Stroke-Belt) or ethnicity (blacks vs. whites) and AF showed an inverse relationship with the sensitivity to diagnose AF - the higher the sensitivity, the less the effect of ethnicity or region. The effect of the region on the prevalence of AF reversed from being statistically significant when AF was diagnosed using less sensitive methods, "Both SR and ECG" or "ECG" [OR (95% CI) for model 3 : 0.66 (0.47, 0.92) and 0.71 (0.55, 0.92), respectively] to a statistically non-significant effect when AF was diagnosed by more sensitive methods, "SR" or "SR or ECG" [OR (95% CI) for model 3: 0.96

(0.85, 1.08) and 0.95 (0.85, 1.06), respectively]. Similarly, the association of ethnicity with AF was attenuated as measured across different sensitivities [OR (95% CI) for the full models: 0.20 (0.12, 0.33), 0.40 (0.29, 0.54), 0.70 (0.62, 0.79), 0.71 (0.63, 0.80) when the AF was measured by successively more sensitive detection methods..

DISCUSSION

The main reason to conduct this study was to look for a possible explanation for the disconnect between the reported increase in stroke burden in blacks and in the Stroke-Belt on one hand, and the reported low prevalence of AF in blacks compared to whites and lack of difference in the prevalence of AF between the Stroke-Belt and the rest of the US regions on the other hand. Our hypothesis was that the reported association between ethnicity and region with AF is much affected by the sensitivity of the current methods used for AF diagnosis. The current assumption is that a method with a low sensitivity would under-diagnose AF in all groups equally, thus preserving the proportionate distribution of AF between groups, and subsequently the effect of the groups on the risk of AF should be the same, regardless of the methods used to diagnose AF. However, the difficulty of estimating the prevalence of AF in large cohorts or population samples relates mainly to the difficulty in diagnosis of paroxysmal AF (PAF), being intermittent in nature with normal rhythm and ECG patterns between episodes. Hence, the ability to estimate the prevalence of AF in any population is related to the proportion of individuals with PAF. If groups differ in the prevalence or self recognition of paroxysmal AF, the ability for detection of AF will differ across groups. There may well be a difference in the awareness of PAF symptoms, and of follow-up medical consultation as a result, between different subgroups of the population. At present, no data on ethnic or regional differences in the prevalence of PAF have been published. Long duration of ECG recording (24 − 48 hour Holter monitoring) would be a better way to reasonably estimate the prevalence of PAF, but the high cost for such recordings present a major obstacle in large epidemiologic studies.

The current study showed that there is an inverse relation between the sensitivity to diagnose AF and the association between ethnicity and region with AF; the more sensitive the method, the more attenuated the association between ethnicity and region with AF: the effect of geographic region on AF reversed from being a statistically significant to a statistically non-significant association, and the effect of ethnicity was attenuated as an effect of diagnosing AF by more sensitive methods. Therefore, it may be that if a more sensitive approach for AF detection, such as long-term Holter monitoring, were employed, it might result in an estimate showing a reversed distribution of AF with blacks having more or at least equal AF compared to whites. Unfortunately long term Holter monitoring data are not available, and subsequently, the true AF prevalence is still unknown. Such a hypothetical conclusion, despite being at odds with the results of less sensitive detection methods (SR and ECG) used by previous studies, is in concert with the fact of the high stroke burden in blacks and the strong association between AF and stroke.

Noteworthy, in our results, despite the trend towards more attenuation of the association between ethnicity and AF across different sensitivities, such attenuation did not reach a flipping point similar to that shown for the association between region and AF. This could be explained by the fact that the different levels of diagnostic sensitivity created in this analysis were based upon two methods that already have low sensitivity to detect AF, at least compared to 24-Hour Holter monitoring and hospital diagnosed AF. The observed attenuation of the effect of differences in ethnicities as an effect of using more sensitive methods for AF diagnosis could be partially explained by the possibility that blacks might have more paroxysmal AF than whites. Subsequently, by using a more sensitive method, more paroxysmal AF could be detected and, hence, the difference in AF prevalence between blacks and whites diminishes. There is some indirect evidence that supports the possibility that blacks might have an increased

prevalence of paroxysmal AF compared to whites. In a recent prospective study[20] metabolic syndrome was a significant risk factor for paroxysmal AF that was independent of left atrial diameter or age [OR (95% CI): 2.8 (1.3, 6.2) P<0.01]. Because blacks have a high prevalence of the metabolic syndrome[21], they could be more liable to develop paroxysmal AF. Further, in a more recent publication in which the ethnic distribution of electrocardiographic predictors of AF has been used to make inference about future ethnic distribution of AF, the propensity to develop AF in blacks was almost 3 times that of whites. The authors justified their findings in the context that using electrocardiographic predictors to make inferences about ethnic distribution of AF will have higher sensitivity and would not be affected by paroxysmal AF which might have been masked by using traditional AF diagnosis methods to address the ethnic distribution of AF.[22]

Limitations

Selection bias might have occurred due to exclusion of participants with history of stroke, and the possibility that participants who agreed to participate in this study could be more or less sick than those who refused to participate. However, given the reasonable participation rate (compared to studies with similar design) and the large sample size, it is unlikely that such a limitation has a major effect on the conclusions.

We did not test whether differences in the knowledge of what the term “Atrial Fibrillation” means, or whether inequities in access to proper healthcare might have played a role in less self-reported AF among blacks compared to whites. Nevertheless, AF diagnosis in this analysis included also ECG, an objective method of AF detection.

Conclusion

In conclusion, the current study showed that there is an inverse relation between the sensitivity of the method to diagnose AF and the association between ethnicity and region with AF; the higher the sensitivity to detect AF, the more attenuated the effect of ethnic and regional differences on prevalence estimates of AF. Given the known limitations of the sensitivity of the current methods to diagnose AF, this finding could partially explain the paradox of low prevalence of AF in populations known to have high rates of strokes.

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TABLE 1

Characteristics of the Study Population and Prevalence (%) of Atrial Fibrillation (AF) Stratified by Ethnicity and Geographic Region

Variable	All population	Region		Ethnicity	
		Stroke-Belt	Non Stroke-Belt	Blacks	Whites
	N=18,833	N = 9,786	N = 9032	N = 7722	N = 11,105
Age (years)	65.9±9.0	65.4 ± 8.9	66.5 ± 9.0	65.3 ± 8.9	66.3 ± 9.0
Females (%)	51.5	52.1	50.8	59.6	45.8
Blacks (%)	41.0	34.8	47.8	100.0	0.0
Body Mass Index (wt/ht^2)	29.2±6.1	29.1 ± 6.1	29.3 ± 6.1	30.6 ± 6.7	28.2 ± 5.5
Hypertension (%)	57.5	57.8	57.2	69.4	49.2
Diabetes (%)	21.2	21.8	20.7	29.6	15.5
AF (%)					
AF by both SR and ECG	0.8	0.7	0.9	0.2	1.2
ECG AF	1.4	1.3	1.5	0.7	1.8
SR AF	7.2	7.3	7.1	6.3	7.8
AF by SR or ECG	7.8	7.8	7.8	6.8	8.5

* SR= Self-reported; ECG= Electrocardiogram

TABLE 2

Unadjusted and Multivariable-Adjusted Logistic Regression Analysis for the Association Between Atrial Fibrillation (AF) and Ethnicity and Geographic Region Across Different levels of Sensitivity to Detect AF *

		Belt vs. non-belt OR (95%CI)	Black vs. white OR (95% CI)
AF by both SR and ECG	Model 1	0.80 (0.58 − 1.10)	0.19 (0.12 − 0.32)
	Model 2	0.69 (0.50 − 0.95)	0.20 (0.12 − 0.33)
	Model 3	0.66 (0.47 − 0.92)	0.20 (0.12 − 0.33)
ECG AF	Model 1	0.83 (0.65 − 1.06)	0.39 (0.29 − 0.52)
	Model 2	0.77 (0.60 − 0.98)	0.43 (0.31 − 0.57)
	Model 3	0.71 (0.55 − 0.92)	0.40 (0.29 − 0.54)
SR AF	Model 1	1.02 (0.91 − 1.14)	0.80 (0.71 − 0.90)
	Model 2	0.99 (0.88 − 1.10)	0.78 (0.70 − 0.88)
	Model 3	0.96 (0.85 − 1.08)	0.70 (0.62 − 0.79)
AF by SR or ECG	Model 1	1.01 (0.91 − 1.12)	0.80 (0.71 − 0.89)
	Model 2	0.98 (0.88 − 1.09)	0.79 (0.70 − 0.88)
	Model 3	0.95 (0.85 − 1.06)	0.71 (0.63 − 0.80)

* Model 1= Unadjusted; model 2= adjusted for age, sex and ethnicity (in the region analyses) or region (in the ethnicity analysis); model 3= adjusted for model 2+, hypertension, diabetes and BMI