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ORIGINAL RESEARCH

Atrial Fibrillation and Stroke Symptoms in the REGARDS Study

Meghan Reading Turchioe, PhD, MPH, RN; Elsayed Z. Soliman, MD, MS; Parag Goyal, MD, MSc; Alexander E. Merkler, MD; Hooman Kamel, MD; Mary Cushman, MD, MSc; Orysya Soroka, MS; Ruth Masterson Creber, PhD, MSc, RN; Monika M. Safford, MD

BACKGROUND: It is unknown if stroke symptoms in the absence of a stroke diagnosis are a sign of subtle cardioembolic phenomena. The objective of this study was to examine associations between atrial fibrillation (AF) and stroke symptoms among adults with no clinical history of stroke or transient ischemic attack (TIA).

METHODS AND RESULTS: We evaluated associations between AF and self-reported stroke symptoms in the national, prospective REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort. We conducted cross-sectional (n=27 135) and longitudinal (n=21 932) analyses over 8 years of follow-up of REGARDS participants without stroke/transient ischemic attack and stratified by anticoagulant or antiplatelet agent use. The mean age was 64.4 (SD±9.4) years, 55.3% were women, and 40.8% were Black participants; 28.6% of participants with AF reported stroke symptoms. In the cross-sectional analysis, comparing participants with and without AF, the risk of stroke symptoms was elevated for adults with AF taking neither anticoagulants nor antiplatelet agents (odds ratio [OR], 2.22; 95% CI, 1.89–2.59) or antiplatelet agents only (OR, 1.92; 95% CI, 1.61–2.29) but not for adults with AF taking anticoagulants (OR, 1.08; 95% CI, 0.71–1.65). In the longitudinal analysis, the risk of stroke symptoms was also elevated for adults with AF taking neither anticoagulants nor antiplatelet agents (hazard ratio [HR], 1.41; 95% CI, 1.21–1.66) or antiplatelet agents only (HR, 1.23; 95% CI, 1.04–1.46) but not for adults with AF taking anticoagulants (HR, 0.86; 95% CI, 0.62–1.18).

CONCLUSIONS: Stroke symptoms in the absence of a stroke diagnosis may represent subclinical cardioembolic phenomena or "whispering strokes." Future studies examining the benefit of stroke symptom screening may be warranted.

Key Words: atrial fibrillation ■ embolic stroke ■ stroke ■ symptom assessment

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a lifetime incidence of 1 in 4 for adults over 40 years of age[1] and an associated 4- to 5-fold increased risk of stroke.[2] A relatively unexplored dimension of AF-related strokes is the relationship between AF and "whispering strokes," or strokes that are not clinically recognized.[3,4] Stroke symptoms may resolve quickly enough that a patient does not always seek medical attention.[5] The prevalence of stroke symptoms among adults without a prior history of stroke or transient ischemic attack (TIA) may be as high as 18%.[6] Stroke symptom screening has been identified as a potentially clinically effective and cost-efficient intervention to target primary stroke prevention,[7–9] with a possible greater benefit for AF patients given their high risk of stroke.

We aimed to identify associations between AF and self-reported stroke symptoms in the large, prospective, national REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort. We hypothesized that baseline AF would be significantly associated with the presence, number, and type of stroke symptoms at baseline and incident stroke symptoms over 8 years of follow-up. We conducted analyses

Correspondence to: Meghan Reading Turchioe, PhD, MPH, RN, Department of Population Health Sciences, Weill Cornell Medicine, 425 East 61st Street, Suite 301, New York, NY10065. E-mail: mjr2011@med.cornell.edu

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CLINICAL PERSPECTIVE

What Is New?

- In the large, prospective, national REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort, nearly 1 in 3 adults with atrial fibrillation who had no documented history of stroke or transient ischemic attack nonetheless reported stroke symptoms.

What Are the Clinical Implications?

- This study demonstrates that stroke symptoms may represent subclinical cardioembolic events, or "whispering strokes," among individuals who have atrial fibrillation, no documented history of stroke or transient ischemic attack, and are not taking anticoagulants.
- Stroke symptom screening as an adjunct to other stroke risk scores such as CHA_2DS_2-VASc could be an important prevention strategy for patients with atrial fibrillation who are not receiving anticoagulant therapy, as well as for other high-risk populations, in whom a positive screen may warrant a thorough stroke workup to prevent subsequent stroke.

Nonstandard Abbreviations and Acronyms

BRFSS	Behavioral Risk Factor Surveillance Study
FSRS	Framingham Stroke Risk Score
QVSFS	Questionnaire for Verifying Stroke-Free Status
REGARDS	Reasons for Geographic and Racial Differences in Stroke

stratified by use of anticoagulants, antiplatelet agents alone, and neither because of past evidence that anticoagulation with these medications reduces risk of stroke in the setting of AF.[10,11] Among individuals with no history of stroke or TIA, differences in the risk of stroke symptoms by these medications would suggest that they represent clinically unrecognized cardioembolic events.

METHODS

The REGARDS study database includes identifying participant information and cannot be made publicly available because of ethical/legal restrictions. Deidentified data sets and statistical code specific to this article are available to researchers meeting criteria for access to confidential data.

REGARDS Study Design

The REGARDS study is a national longitudinal cohort study that recruited 30 239 English-speaking Black and White adults residing in the continental United States between 2003 and 2007. Full details of the REGARDS study have been published elsewhere.[12,13] Recruitment methods were similar to those used by the National Center for Health Statistics BRFSS (Behavioral Risk Factor Surveillance Study); a letter containing information about the study was mailed to potential participants and followed up with a telephone call. Individuals who agreed to participate completed a baseline telephone interview to provide demographic information, medical history, and stroke history. Consent was obtained verbally and later in writing.

Following this call, trained examiners visited all participants in their homes to obtain blood pressure, height, weight, resting ECG, blood samples, urine samples, and current medications. The trained examiners were unaware of participants' stroke/TIA history. Participants were followed by telephone every 6 months for study end points. Study methods were reviewed and approved by the institutional review boards at collaborating institutions.

REGARDS Participants

Individuals were eligible to participate in REGARDS if they were community-dwelling adults ≥45 years of age and self-identified as non-Hispanic Black or White; the race criteria was specified because the largest stroke-related racial disparities existed between these 2 groups at the time the study was designed.[14] Individuals were excluded if they self-reported medical conditions that would prevent long-term participation (such as cancer) or were on a waiting list for a nursing home.

Over half (56%) of participants were recruited from the stroke belt, as this is an area in the southeastern United States with high stroke mortality. The "buckle" of the stroke belt refers to the coastal plains of North Carolina, South Carolina, and Georgia (21% of the total sample), while the remainder of stroke belt includes other areas in North Carolina, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana (35%); the remaining 44% of the sample were recruited from the other 40 continental US states.

In the cross-sectional analysis of this study, we excluded participants who reported physician-verified stroke or TIA at baseline on the Questionnaire for Verifying Stroke-Free Status (QVSFS).[15] In the longitudinal analysis, we excluded participants who reported stroke symptoms or physician-verified stroke or TIA at baseline on the QVSFS.

Main Exposure: AF

The primary exposure was AF at baseline, defined by either self-reported history of AF on the telephone interview or study ECG evidence. A prior REGARDS study demonstrated that self-reported AF is a strong independent predictor of stroke and is essentially equivalent to ECG-detected AF in stroke risk prediction models, validating the use of the self-report variable in combination with ECG-detected AF in predictive models.[16] AF from ECG was based on central readings of the study ECGs by analysts who were blind to other REGARDS 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?"

Outcomes: Stroke Symptoms

The QVSFS contains 8 items and has been validated in verifying stroke-free status in multiple prior studies (positive predictive value=0.71).[15,17–19] The first 2 items ask whether a participant has ever been told by a physician that they had a stroke or mini-stroke/TIA. If participants responded "no" to both questions, they were asked if they had ever experienced 6 stroke symptoms in nonmedical terms: sudden painless weakness on 1 side of your body, numbness or a dead feeling on one side of your body, painless loss of vision in one or both eyes, painless loss of one-half of your vision, loss of the ability to understand what people were saying, and loss of the ability to express yourself verbally or in writing. At the semiannual follow-up calls, participants were asked if they had any of these symptoms "since the last time we talked with you." A positive response to ≥1 of these questions was considered a positive stroke symptom history. The QVSFS was collected at baseline and every 6 months thereafter. Stroke symptom data through December 31, 2017, were used.

Covariates

Vascular risk factors were selected from the Framingham Stroke Risk Score (FSRS)[20,21] and the list of factors associated with the prevalence of stroke symptoms in prior REGARDS studies.[22] Age, race, sex, region of residence, smoking status, education, and income were collected during the baseline telephone interview. Region of residence (stroke belt, stroke buckle, or other) was included to control for the oversampling of participants in the stroke belt and buckle in REGARDS. In addition, history of hypertension, diabetes, dyslipidemia, and heart disease were obtained using a combination of self-report, objective measurements, and medication information collected during the in-home visit. Hypertension was defined as self-reported physician or nurse diagnosis or self-reported use of antihypertensive medications, or blood pressure of at least 140/90 mm Hg during the in-home visit. Blood pressure was assessed after a 5-minute rest with both feet flat on the floor in a chair supporting the back; the mean of 2 measurements was used for analysis. Diabetes was defined as a fasting glucose ≥126 mL/dL, nonfasting glucose ≥200 mL/dL, or self-reported use of diabetes medications. Dyslipidemia was defined as triglycerides ≥240 mg/dL, low-density lipoproteins ≥160 mg/dL, or high-density lipoproteins ≤40 mg/dL. History of heart disease was defined as self-reported history of myocardial infarction, coronary artery bypass surgery, coronary artery angioplasty or stenting, or evidence of old myocardial infarction on the study ECG. Finally, left ventricular hypertrophy was defined by Sokolow-Lyon criteria from the study baseline ECGs.

Censoring Variables: Stroke, TIA, and Death

Strokes, TIAs, and death were censoring events in the longitudinal analysis. Strokes and TIAs were determined by adjudication of medical records from hospitalizations or outpatient visits for participants or proxies who reported possible stroke events during semiannual telephone interviews. The World Health Organization definition of stroke and clinical evidence were used as criteria guiding event adjudication. The World Health Organization defines stroke as "rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin."[23] Clinical strokes were defined as events not meeting the World Health Organization definition but with neuroimaging consistent with acute ischemic or hemorrhagic strokes. Using these criteria, a trained neurological nurse first reviewed medical records to verify record completeness and rule out clear nonstroke cases. A team of stroke experts then used the same criteria to review all remaining records and confirm presence of a stroke or TIA.

Vital status was determined using the Social Security Death Index death master file, National Death Index, and proxy report through the mail, during semiannual telephone interviews, or using a toll-free number for REGARDS participants.

For this analysis, strokes, TIAs, and deaths through December 31, 2017, were used.

Statistical Analysis

Descriptive statistics, including proportions and measures of central tendency, were calculated for demographic, socioeconomic, vascular risk factors, geographic, and medication variables at baseline by AF status using the χ^2 test for categorical variables and ANOVA for continuous variables.

Cross-Sectional Analysis

The outcomes include presence, type, and number of prior stroke symptoms reported at baseline among participants without a prior history of stroke or TIA. Logistic regression was used to examine associations between baseline AF and the presence and type of prior stroke symptoms reported at baseline among participants without a prior history of stroke or TIA. Multinomial logistic regression was used to examine associations between baseline AF and the number of stroke symptoms. To assess the independent influence of AF on the report of a history of stroke symptoms, we constructed a set of models including only AF, and then another set adjusted for covariates including demographic factors (age, race, sex), socioeconomic factors (income, education), vascular risk factors (hypertension, diabetes, current smoking, left ventricular hypertrophy, history of heart disease, and hyperlipidemia), and region of residence (stroke belt, stroke buckle, or other). All analyses were stratified by medication usage: (1) anticoagulants (eg, warfarin) with or without antiplatelet agents, (2) antiplatelet agents only (eg, aspirin, clopidogrel, aggrenox, cilostazol, dipyridamole, and/or ticlopidine, but not warfarin), or (3) none of these medications.

Longitudinal Analysis

Cox proportional hazards models were used to examine the association between baseline AF and time to incident self-reported stroke symptoms among participants without a prior history of stroke, TIA, or stroke symptoms at baseline. The time metric was years since study entry, with participants censored at the date of a reported of a stroke symptom; date of an adjudicated stroke/TIA; date of withdrawal from the study; date of death; or December 31, 2017, whichever came first. Time to any stroke symptom and time to each individual stroke symptom were modeled separately. We again fit adjusted models using the same sets of covariates used in the cross-sectional analysis described above, stratified on anticoagulants and antiplatelet agents as described above. We used Kaplan-Meier plots to visually inspect the cumulative risk of developing stroke symptoms for each of AF groups (no AF and AF) overall and for each medication group. Finally, we tested the assumption of proportionality of all Cox models, and visually inspected Kaplan-Meier curves and log(–log[survival]) plots when assumptions were violated.

RESULTS

Cross-Sectional Analysis

The participant exclusion cascade for the REGARDS participants used in the cross-sectional analysis is shown in Figure S1. The final analytic sample included 27 135 (89.7%) of the 30 239 REGARDS participants, after excluding participants with missing baseline forms (0.2%), stroke or TIA reported at baseline (10.1%), and missing AF or stroke symptoms data at baseline (0.01%).

Demographic characteristics of participants with AF (n=2124) and without AF (n=25 011) at baseline are compared in Table 1. Participants with AF were older,

Table 1. Baseline Characteristics of REGARDS Study Participants Stratified by History or Presence of AF (n=27 135)

Characteristic	No AF (n=25 011)	AF (n=2124)	*P* value
Demographic factors			
Age, y, mean (±SD)	64.21 (9.3)	67.12 (9.7)	<0.001
Black, n (%)	10 310 (41.2)	757 (35.6)	<0.001
Male, n (%)	11 136 (44.5)	994 (46.8)	0.04
Measures of socioeconomic status			
Income, n (%)			
<$20 K	4202 (16.8)	451 (21.2)	<0.001
$20–$34 K	5900 (23.6)	547 (25.8)	
$35–$74 K	7674 (30.7)	579 (27.3)	
$75K+	4242 (17.0)	271 (12.8)	
Refused	2993 (12.0)	276 (13.0)	
Education category, n (%)			
<High school	2885 (11.5)	268 (12.6)	0.03
High school graduate	6396 (25.6)	586 (27.6)	
Some college	6735 (26.9)	558 (26.3)	
College graduate	8981 (35.9)	709 (33.4)	
Stroke risk factors, n (%)			
Hypertension	14 056 (56.3)	1415 (66.9)	<0.001
Diabetes	4878 (20.3)	500 (24.4)	<0.001
Current smoking	3576 (14.4)	276 (13.0)	0.10
Left ventricular hypertrophy	2336 (9.5)	204 (9.8)	0.64
Hyperlipidemia	13 861 (57.6)	1331 (64.9)	<0.001
History of heart disease	3621 (14.7)	717 (34.5)	<0.001
Systolic blood pressure, mean (±SD)	127.14 (16.43)	127.84 (17.16)	0.06
Geographic factors, n (%)			
Region of residence			
Belt region	8677 (34.7)	747 (35.2)	0.08
Buckle region	5219 (20.9)	480 (22.6)	
Non–belt region	11 115 (44.4)	897 (42.2)	
Medications, n (%)			
Warfarin (with or without antiplatelet agents)	325 (1.3)	443 (20.9)	<0.001
Antiplatelet agents	8176 (32.8)	768 (36.2)	
None of these	16 447 (66.1)	913 (43.0)	

AF indicates atrial fibrillation; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

more likely to be men, less likely to be Black, and had lower income (<$34 000 annually), lower education level (high school diploma or less), and a higher prevalence of most vascular risk factors. They were also slightly more likely to live in the stroke belt or buckle regions. As expected, participants with AF had a higher prevalence of warfarin use (20.9% versus 1.3% among those without AF) and were slightly more likely to be taking antiplatelet agents (36.2% versus 32.8% among those without AF).

The type and number of stroke symptoms reported by participants at baseline are depicted in Figure 1. Among those with AF, 28.6% reported ever having a stroke symptom, 9.0% reported 2 symptoms, and 6.2% reported ≥3 symptoms. Among those without AF, 16.6% reported ever having a stroke symptom, 4.3% reported 2 symptoms, and 2.1% reported ≥3 symptoms. Among those with AF, the most commonly reported type of symptom was sudden numbness (15.8%) followed by sudden painless weakness (11.6%). Similarly, among those without AF, the most commonly reported type of symptom sudden numbness (7.9%) followed by sudden painless weakness (5.3%). Complete data for baseline stroke symptoms are reported in Table S1.

Table 2 presents the crude and fully adjusted odds ratios (ORs) for the association between AF and reporting a history of stroke symptoms at baseline, stratified by antiplatelet and anticoagulant use. Among participants not taking an anticoagulant or antiplatelet agents, AF was strongly associated with any stroke symptoms in fully adjusted models (OR, 2.22; 95% CI, 1.89–2.59). Among those taking antiplatelet agents but not anticoagulants, the association between AF and stroke symptoms was slightly weaker in fully adjusted models (OR, 1.92; 95% CI, 1.61–2.29). Among those taking anticoagulants, there was no association between AF and stroke symptoms (OR, 1.08; 95% CI,

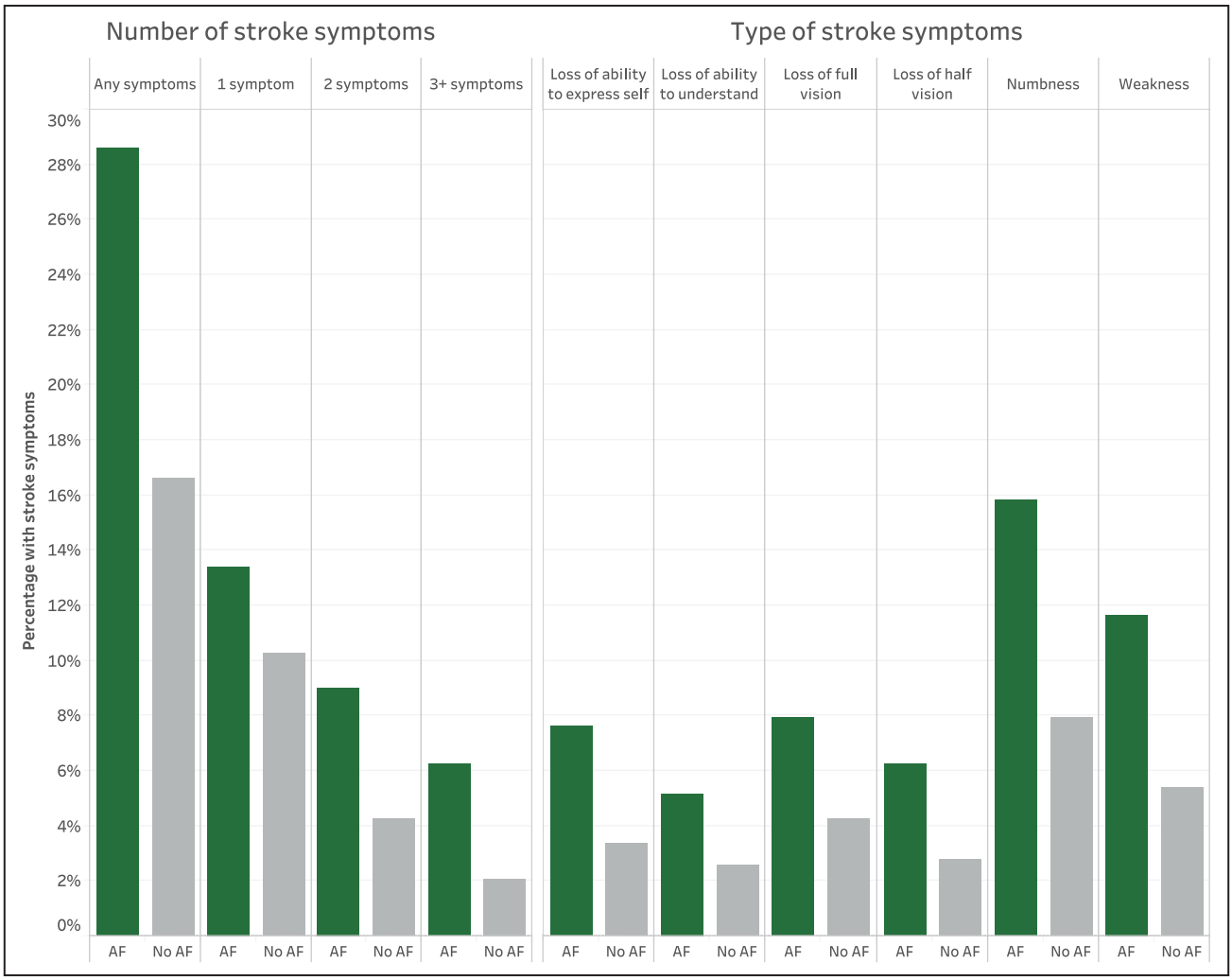

Figure 1. Percentage of individuals reporting each type and number of stroke symptoms among those with AF (n=2124) and without AF (n=25 011) in the baseline REGARDS Analysis Cohort.
AF indicates atrial fibrillation.

Table 2. Crude and Fully Adjusted Odds Ratios and 95% CIs for Reporting a History of Stroke Symptoms Associated with AF in the REGARDS Cross-Sectional Study Cohort, Stratified by Antiplatelet/Anticoagulant Use (n=27 135)

	No medication		Antiplatelets only (no warfarin)		Warfarin (with/without antiplatelets)	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Any stroke symptom*†	2.38 (2.06–2.75)	2.22 (1.89–2.59)	2.11 (1.79–2.48)	1.92 (1.61–2.29)	0.78 (0.55–1.11)	1.08 (0.71–1.65)
Type of stroke symptom						
Full vision loss*†	2.56 (2.02–3.23)	2.29 (1.78–2.94)	1.66 (1.25–2.20)	1.47 (1.09–2.00)	0.80 (0.42–1.52)	0.93 (0.44–1.95)
Half vision loss*†	2.97 (2.27–3.89)	2.73 (2.05–3.63)	1.85 (1.33–2.57)	1.61 (1.13–2.29)	1.13 (0.58–2.21)	1.57 (0.74–3.34)
Loss of ability to communicate*†	3.11 (2.46–3.93)	2.78 (2.17–3.57)	2.29 (1.70–3.07)	2.10 (1.54–2.87)	0.68 (0.34–1.36)	0.77 (0.34–1.74)
Loss of ability to understand†	2.78 (2.11–3.67)	2.33 (1.73–3.14)	2.11 (1.49–2.98)	1.63 (1.11–2.39)	0.41 (0.17–0.99)	0.63 (0.24–1.69)
Numbness*†	2.61 (2.19–3.12)	2.41 (1.98–2.92)	2.46 (2.02–3.01)	2.23 (1.79–2.78)	0.65 (0.40–1.06)	0.94 (0.52–1.71)
Weakness*†	2.78 (2.27–3.40)	2.52 (2.02–3.13)	2.62 (2.08–3.30)	2.23 (1.73–2.87)	0.59 (0.33–1.02)	0.89 (0.46–1.73)
Number of stroke symptoms*†						
1	1.67 (1.37–2.04)	1.59 (1.28–1.96)	1.60 (1.29–1.99)	1.52 (1.21–1.91)	0.84 (0.53–1.32)	1.08 (0.63–1.85)
2	2.70 (2.12–3.44)	2.54 (1.97–3.29)	2.62 (2.02–3.40)	2.48 (1.88–3.26)	0.97 (0.55–1.70)	1.48 (0.76–2.88)
3–6	5.10 (3.94–6.59)	4.50 (3.40–5.95)	3.68 (2.64–5.13)	2.75 (1.88–4.01)	0.27 (0.09–0.76)	0.39 (0.11–1.33)

Fully adjusted model accounts for (1) sociodemographic factors (age, race, sex), (2) socioeconomic factors (income, education), (3) stroke risk factors (hypertension, diabetes, current smoking, left ventricular hypertrophy, history of heart disease, and hyperlipidemia), and (4) geographic factors (region of residence).

Statistically significant ($P<0.05$) associations between interaction of AF and medication category (no medication, antiplatelet agents only, and warfarin) and stroke symptoms are denoted for crude models (*) and fully adjusted models (†). AF indicates atrial fibrillation; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

0.71–1.65). The strengths of the associations by medication category persisted by each type and the cumulative number of stroke symptoms.

Longitudinal Analysis

The participant exclusion cascade for the REGARDS participants used in the longitudinal analysis is shown in Figure S2. The final analytic sample for the longitudinal analysis included 21 932 (72.5%) of the 30 239 REGARDS participants, after excluding participants with missing baseline forms (0.2%); those reporting stroke, TIA, or stroke symptoms at baseline (25.8%); and those who had no stroke symptom data during follow-up (1.5%). Characteristics of participants included in the longitudinal analysis are presented in Table S2.

In the overall sample, 24.6% reported new stroke symptoms over the mean follow-up of 8.3 years (maximum, 14.9 years). Among those with baseline AF, 29.8% reported any incident stroke symptoms during follow-up, 5.1% reported 2 symptoms, and 1.0% reported ≥3 symptoms. Among those without baseline AF, 24.2% reported incident stroke symptoms, 3.7% reported 2 symptoms, and 0.7% reported ≥ symptoms. Among those with baseline AF, the most commonly reported types of symptoms were loss of ability to understand (8.2%) and sudden numbness (8.2%). Among those without baseline AF, the most commonly reported types of symptoms were also loss of ability to understand (7.3%) and sudden numbness (6.2%). Complete data for follow-up stroke symptoms are reported in Table S3.

The Kaplan-Meier curves for overall associations and for each medication category are shown in Figure 2. There was evidence of violation of the proportional hazards assumption when examining the association between weighted Schoenfeld residuals and time. However, examination of log(–log[survival plots]) and Kaplan-Meier curves did not indicate any clinically meaningful differences in the association between AF and stroke symptoms over time.

Table 3 presents the crude and fully adjusted hazard ratios (HRs) for incident stroke symptoms associated with baseline AF over the follow-up period, stratified by anticoagulant and antiplatelet agent use. Among participants not taking anticoagulants or antiplatelet agents, AF was associated with any incident stroke symptoms in fully adjusted models (adjusted HR, 1.41; 95% CI, 1.21–1.66). Among those taking antiplatelet agents only, the association between AF and stroke symptoms was attenuated but remained significant in fully adjusted models (HR, 1.23; 95% CI, 1.04–1.46). Among those taking anticoagulants, there was no association between AF and stroke symptoms (adjusted HR, 0.86; 95% CI, 0.62–1.18).

Associations between AF and stroke symptoms varied by each type of stroke symptom over the follow-up

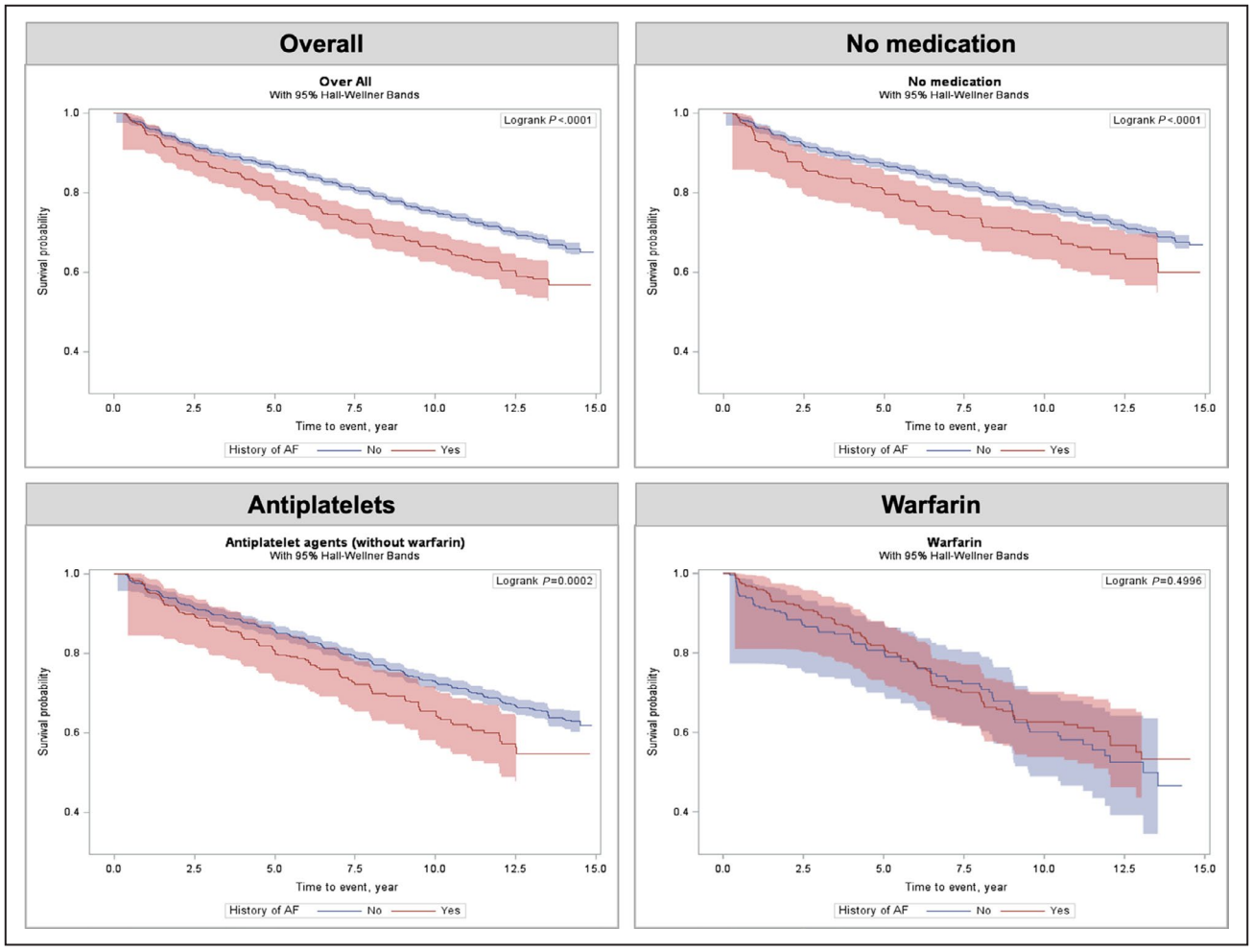

Figure 2. Kaplan-Meier curves for incident stroke symptoms during follow-up (2003–2017) by atrial fibrillation group, overall and by anticoagulant medications, n=21 932.
AF indicates atrial fibrillation.

period (Table 3). Among those not taking anticoagulants or antiplatelet agents, AF was associated with sudden weakness (HR, 2.26; 95% CI, 1.65–3.09) and numbness (HR, 1.53; 95% CI, 1.13–2.07), but was not associated with loss of ability to communicate, ability to understand, full vision, or half vision in fully adjusted models. Among those taking antiplatelet agents, AF was associated only with sudden weakness (HR, 1.94; 95% CI, 1.36–2.76), numbness (HR, 1.66; 95% CI, 1.19–2.32), and full vision loss (HR, 1.42; 95% CI, 1.01–1.98) in fully adjusted models. Among those taking anticoagulants, AF was not associated with any type of stroke symptom.

DISCUSSION

In the large, national REGARDS cohort, baseline diagnosis of AF was significantly associated with the presence, number, and type of stroke symptoms at baseline, and with incident stroke symptoms over a mean 8 years of follow-up. Moreover, the risk of stroke symptoms at baseline and during follow-up was highest among adults with AF not taking anticoagulants or antiplatelet agents, and high but attenuated among those taking antiplatelet agents only. There was no increased risk of stroke symptoms among those taking anticoagulants.

This study grows the body of evidence suggesting that stroke symptoms may in some cases represent undiagnosed cardioembolic events or "whispering strokes" versus other underlying etiologies. Several prior REGARDS studies showed that stroke symptoms[9,24] and other silent infarcts[25–27] are powerful predictors of future stroke in a stroke-free cohort. Furthermore, among individuals without a clinical history of cerebrovascular disease, stroke symptoms are associated with stroke risk biomarkers[7] and predict hospitalizations,[28] coronary heart disease,[8] cognitive impairment,[29]and depressive symptoms.[30] The hypothesized underlying mechanism across these

Table 3. Risk of Stroke Symptoms Associated With AF in the REGARDS Cohort During Follow-Up (2003–2017; Mean Follow-Up 8.3 Years); Crude Association and Adjusted for Demographic, Socioeconomic, Stroke Risk, and Geographic Factors; Stratified by Antiplatelet/Anticoagulant Use; Hazard Ratio (95% CI) (n=21 932)

	No medication		Antiplatelet agents only (no warfarin)		Warfarin (with/without antiplatelets)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Any stroke symptom*†	1.42 (1.22–1.66)	1.41 (1.21–1.66)	1.36 (1.16–1.61)	1.23 (1.04–1.46)	0.91 (0.68–1.21)	0.86 (0.62–1.18)
Type of stroke symptom						
Full vision loss	1.08 (0.76–1.55)	1.09 (0.75–1.59)	1.54 (1.12–2.12)	1.42 (1.01–1.98)	0.78 (0.42–1.43)	0.88 (0.43–1.81)
Half vision loss	1.43 (0.93–2.20)	1.45 (0.93–2.26)	1.65 (1.08–2.52)	1.44 (0.92–2.27)	0.85 (0.40–1.82)	1.04 (0.42–2.58)
Loss of ability to communicate	1.39 (0.97–1.99)	1.37 (0.94–1.98)	1.31 (0.89–1.93)	1.09 (0.73–1.65)	0.71 (0.38–1.31)	0.59 (0.29–1.18)
Loss of ability to understand	1.20 (0.87–1.65)	1.12 (0.80–1.57)	1.05 (0.75–1.48)	0.92 (0.64–1.31)	1.08 (0.63–1.83)	0.82 (0.46–1.45)
Numbness	1.47 (1.10–1.98)	1.53 (1.13–2.07)	1.73 (1.26–2.37)	1.66 (1.19–2.32)	0.68 (0.35–1.33)	0.75 (0.35–1.61)
Weakness*	2.30 (1.72–3.09)	2.26 (1.65–3.09)	1.90 (1.34–2.69)	1.94 (1.36–2.76)	0.91 (0.46–1.77)	1.14 (0.51–2.54)

Fully adjusted model accounts for (1) demographic factors (age, race, sex), (2) socio-economic factors (income, education), (3) stroke risk factors (hypertension, diabetes, current smoking, left ventricular hypertrophy, history of heart disease, and hyperlipidemia), and (4) geographic factors (region of residence).

Statistically significant (P<0.05) associations between interaction of AF and medication category (no medication, antiplatelet agents only, and warfarin) and stroke symptoms are denoted for crude models (*) and fully adjusted models (†). AF indicates atrial fibrillation; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

studies is that stroke symptoms may represent whispering strokes. Our study builds on this body of work by demonstrating that the risk of stroke symptoms in an at-risk, stroke-free cohort is eliminated by anticoagulant medications, which are known to reduce the risk and incidence of stroke over antiplatelet agents.[31–33] Moreover, we demonstrate biological gradient (or dose-response relationship) between AF and stroke symptoms based on medication exposure: anticoagulation (no association), antiplatelet (moderate association), or neither (strong association). Future studies confirming this phenomenon, for example, using brain imaging to confirm cardioembolic events, are needed to elucidate the associations between stroke symptoms, cardioembolic events, and risk factors such as AF.

These findings are clinically significant because stroke symptoms may be neglected by clinicians[22] and underreported by patients; <60% of individuals seek care after experiencing stroke symptoms.[5] The possibility that stroke symptoms among at-risk individuals with no prior history of stroke or TIA could be whispering strokes means that cardioembolic events may be going unrecognized, placing these individuals at higher future risk of stroke[9,24] and other negative sequelae associated with stroke symptoms.[8,28–30] Furthermore, nearly 30% of adults with AF reported stroke symptoms, compared with 17% of those without AF, suggesting that stroke symptoms are much more common than previously recognized, especially among adults with AF. Stroke symptom screening could be an important prevention strategy for patients with AF who are not receiving anticoagulant therapy, as well as for other high-risk populations, in whom a positive screen may warrant a thorough stroke workup to prevent subsequent stroke.[34] The 8-item QVSFS has been validated for stroke symptom screening,[19] and is low cost and feasible for use in routine primary care. Stroke symptom screening may be an appropriate adjunct to other stroke risk scores such as CHA_2DS_2-VASc.

Strengths of this study include the use of a large, national, longitudinal cohort of community-dwelling US adults. Data were rigorously collected using quality-controlled protocols, offering advantages over studies using clinical data generated during the course of clinical care. There are also several limitations. Importantly, the association between stroke symptoms and true strokes is unknown. In our cross-sectional analyses, reverse causation is possible: Stroke symptoms may have prompted screening that led to AF diagnosis. However, we found an association even in a longitudinal analysis. In addition, the episodic nature of AF makes diagnosis challenging; therefore, some participants classified as not having AF in REGARDS may have in fact had undiagnosed AF. Given the paroxysmal nature of AF, we opted to use self-report to identify AF rather than ECG-confirmed AF. Although underestimating the prevalence of AF is likely a bigger concern in our study, there is also the possibility that we included some patients who did not have AF. Stroke symptoms were self-reported, potentially introducing recall bias in the baseline stroke symptoms variable. REGARDS follow-up data (used in the longitudinal analysis) include stroke symptoms data that have been self-reported every 6 months, reducing recall bias. Several baseline covariates were also self-reported with similar limitations. Baseline data were used for the covariates and

exposure of interest because the REGARDS study design optimized sample size and representativeness by recruiting participants from nearly 60% of the counties in the continental United States,[13,35] which made frequent, ongoing monitoring of risk factors and medications across participants infeasible. Finally, the majority of participants enrolled in REGARDS before novel oral anticoagulants were approved for use in nonvalvular AF[36]; thus, we were unable to evaluate differences in stroke symptoms with warfarin and other anticoagulant use.

SUMMARY

We found strong cross-sectional and longitudinal associations between AF and stroke symptoms, but only for participants with AF who were not anticoagulated. These findings support the proposition that some stroke symptoms in the absence of a stroke diagnosis may represent subclinical or whispering strokes. While these findings require further validation, they nonetheless support the possibility that many cardioembolic events are not clinically recognized in individuals with AF. Routine stroke symptom screening may be a powerful tool to prompt stroke workups to prevent future strokes.

ARTICLE INFORMATION

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Affiliations

Weill Cornell Medicine, New York, NY (M.R.T., P.G., A.E.M., H.K., O.S., R.M.C., M.M.S.); Wake Forest School of Medicine, Winston-Salem, NC (E.Z.S.); and Larner College of Medicine at the University of Vermont, Burlington, VT (M.C.).

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Supplemental Material

Tables S1–S3
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Number (percentage) of stroke symptoms, overall and by history of AF, in the baseline REGARDS cohort (n=27,135)

	All	No AF (n=25,011)	AF (n=2,124)
Any stroke symptom	4,756 (17.5%)	4,149 (16.6%)	607 (28.6%)
Type of stroke symptom			
Full vision loss	1,235 (4.6%)	1,067 (4.3%)	168 (7.9%)
Half vision loss	822 (3.0%)	690 (2.8%)	132 (6.2%)
Loss of ability to communicate	1,008 (3.7%)	846 (3.4%)	162 (7.6%)
Loss of ability to understand	746 (2.8%)	637 (3.6%)	109 (5.1%)
Numbness	2,315 (8.5%)	1,979 (7.9%)	336 (15.8%)
Weakness	1,590 (5.9%)	1,343 (5.3%)	247 (11.6%)
Number of stroke symptoms			
One	2,849 (10.5%)	2,565 (10.3%)	284 (13.4%)
Two	1,255 (4.6%)	1,064 (4.3%)	191 (9.0%)
Three to six	652 (2.4%)	520 (2.1%)	132 (6.2%)

Abbreviations: REGARDS, Reasons for Geographic and Racial Differences in Stroke; AF, Atrial Fibrillation.

Stroke symptoms were measures using the Questionnaire for Verifying Stroke-Free Status (QVSFS).

Table S2. Baseline Characteristics of REGARDS Longitudinal Study Participants Stratified by History of AF (n=21,932; follow-up 2003-2017)

Characteristic			No AF (n=20,451)	AF (n=1,481)	*p value*
Demographic Factors	Age (mean ± SD)		64.21 (9.2)	67.77 (9.6)	*<0.001*
	Black		7979 (39.0%)	448 (30.2%)	*<0.001*
	Male		9172 (44.8%)	738 (49.8%)	*<0.001*
Measures of Socio-Economic Status	Income	<$20K	3017 (14.8%)	262 (17.7%)	*<0.001*
		$20K-$34K	4740 (23.2%)	372 (25.1%)	
		$35K-$74K	6561 (32.1%)	451 (30.5%)	
		$75K+	3745 (18.3%)	217 (14.7%)	
		Refused	2388 (11.7%)	179 (12.1%)	
	Education Category	< High School	2062 (10.1%)	139 (9.4%)	*0.50*
		H.S. Graduate	5124 (25.1%)	395 (26.7%)	
		Some College	5486 (26.8%)	396 (26.8%)	
		College Graduate	7771 (38.0%)	550 (37.2%)	
Stroke Risk Factors	Hypertension		11183 (54.8%)	943 (64.0%)	*<0.001*
	Diabetes		3716 (18.8%)	306 (21.5%)	*0.01*
	Current Smoking		2720 (13.4%)	157 (10.7%)	*0.003*
	Left ventricular hypertrophy		1807 (9.0%)	118 (8.1%)	*0.26*
	Hyperlipidemia		11199 (56.9%)	920 (64.2%)	*<0.001*
	History of heart disease		2751 (13.7%)	478 (32.9%)	*<0.001*
	Systolic blood pressure (mean ± SD)		126.82 (16.16)	127.86 (16.87)	*0.02*
Geographic Factors	Region of Residence	Belt Region	7049 (34.5%)	498 (33.6%)	*0.12*
		Buckle Region	4277 (20.9%)	343 (23.2%)	
		Non-belt Region	9125 (44.6%)	640 (43.2%)	
Medications	Warfarin (with or without antiplatelet agents)		247(1.2%)	351(23.7%)	*<0.001*
	Antiplatelet agents		6614 (32.3%)	516 (34.8%)	
	None		13533 (66.2%)	614 (41.5%)	

Abbreviations: REGARDS, Reasons for Geographic and Racial Differences in Stroke; AF, Atrial Fibrillation; SD, standard deviation.

Table S3. Number (percentage) of stroke symptoms overall and by history of AF in the REGARDS cohort during the follow-up period, 2003-2017, (n=21,932)

	All	No AF (n=20,451)	AF (n=1,481)
Any stroke symptom	5,393 (24.6%)	4,951 (24.2%)	442 (29.8%)
Type of stroke symptom			
Full vision loss	1,357 (6.2%)	1,249 (6.1%)	108 (7.3%)
Half vision loss	751 (3.4%)	678 (3.3%)	73 (4.9%)
Loss of ability to communicate	1,146 (5.2%)	1,051 (5.1%)	95 (6.4%)
Loss of ability to understand	1,604 (7.3%)	1,483 (7.3%)	121 (8.2%)
Numbness	1,388 (6.3%)	1,267 (6.2%)	121 (8.2%)
Weakness	1,081 (4.9%)	962 (4.7%)	119 (8.0%)
Number of stroke symptoms			
One	4,398 (20.1%)	4,046 (19.8%)	352 (23.8%)
Two	832 (3.8%)	757 (3.7%)	75 (5.1%)
Three to six	163 (0.7%)	148 (0.7%)	15 (1.0%)

Abbreviations: REGARDS, Reasons for Geographic and Racial Differences in Stroke; AF, Atrial Fibrillation.

Stroke symptoms were measures using the Questionnaire for Verifying Stroke-Free Status (QVSFS).

Figure S1. Participant exclusion cascade for cross-sectional analyses from the REGARDS Baseline Analysis Cohort (n=27,135)

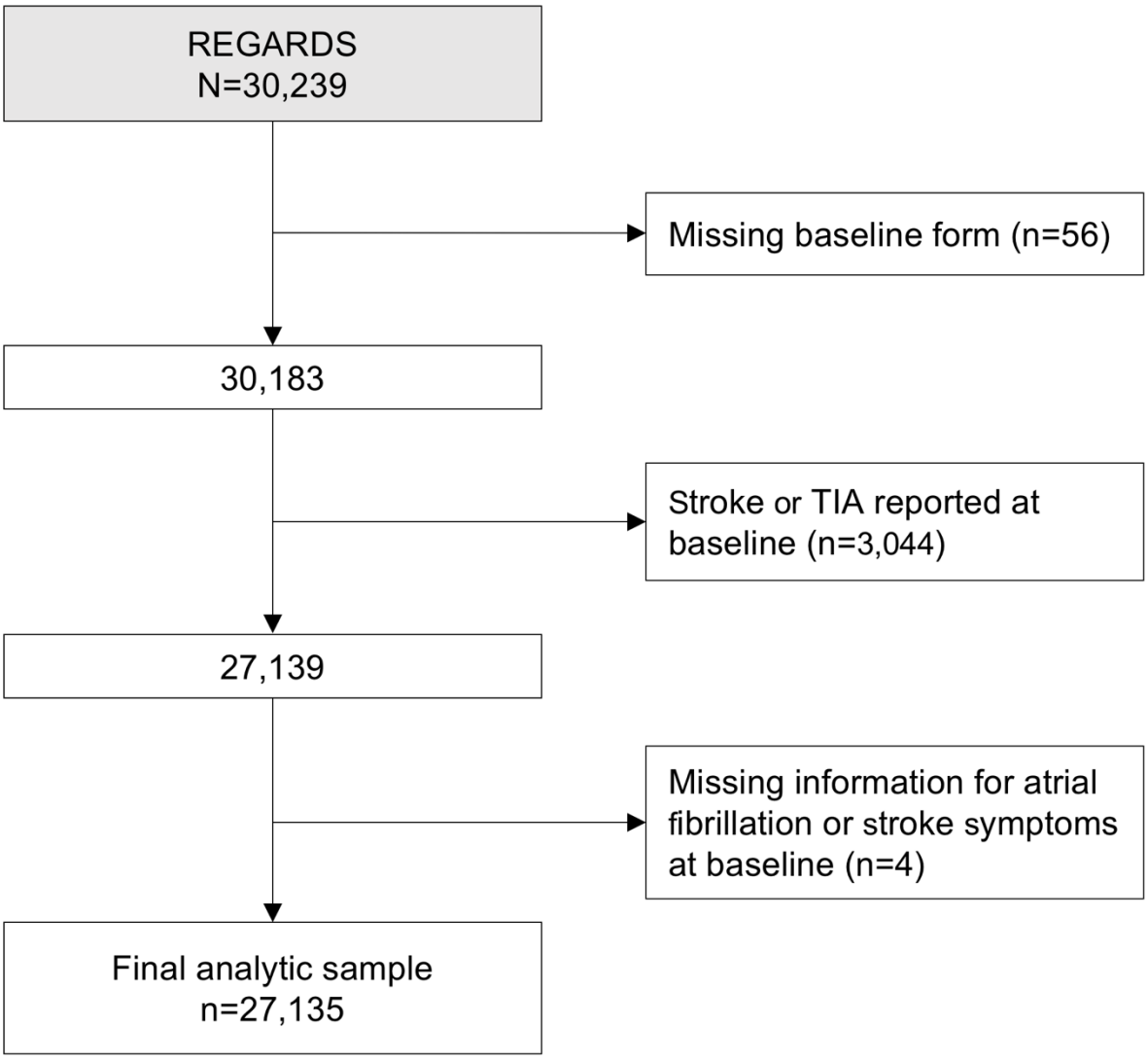

Figure S2. Participant exclusion cascade for longitudinal analyses using the REGARDS Analysis Cohort (n=21,932; follow-up 2003-2017)