Self-Reported Stroke Symptoms Without a Prior Diagnosis of Stroke or Transient Ischemic Attack
A Powerful New Risk Factor for Stroke

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Background and Purpose—Previously in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort, we found 18% of the stroke/transient ischemic attack-free study population reported ≥1 stroke symptom at baseline. We sought to evaluate the additional impact of these stroke symptoms on risk for subsequent stroke.

Methods—REGARDS recruited 30,239 US blacks and whites, aged 45+ years in 2003 to 2007 who are being followed every 6 months for events. All stroke events are physician-verified; those with prior diagnosed stroke or transient ischemic attack are excluded from this analysis. At baseline, participants were asked 6 questions regarding stroke symptoms. Measured stroke risk factors were components of the Framingham Stroke Risk Score.

Results—After excluding those with prior stroke or missing data, there were 24,412 participants in this analysis with a median follow-up of 4.4 years. Participants were 39% black, 55% female, and had median age of 64 years. There were 381 physician-verified stroke events. The Framingham Stroke Risk Score explained 72.0% of stroke risk; individual components explained between 0.2% (left ventricular hypertrophy) and 5.7% (age + race) of stroke risk. After adjustment for Framingham Stroke Risk Score factors, stroke symptoms were significantly related to stroke risk: for each stroke symptom reported, the risk of stroke increased by 21% per symptom.

Conclusions—Among participants without self-reported stroke or transient ischemic attack, prior stroke symptoms are highly predictive of future stroke events. Compared with Framingham Stroke Risk Score factors, the impact of stroke symptom on the prediction of future stroke was almost as large as the impact of smoking and hypertension and larger than the impact of diabetes and heart disease. (Stroke. 2011;42:00-00.)

Key Words: acute stroke ■ aphasia ■ ischemia ■ risk factors ■ TIA ■ transient ischemic attack

The increased risk of stroke, myocardial infarction, or vascular death has been well established among patients who present to medical attention with either a stroke or transient ischemic attack (TIA).1–3 However, many of these studies have been among clinical trial participants, which are not necessarily representative of the patients with stroke and TIA within a population.4,5 Even within population-based studies, the ascertainment methods assume that patients with stroke or TIA seek medical care, either in the inpatient or out-of-hospital setting.3,6,7

It is also well established that those portions of the population at highest risk for stroke such as minorities, those with low income or individuals with lower educational levels, or those with comorbid mental disorders such as depression have significantly different and lower rates of accessing medical care, even for serious medical conditions.8 Therefore, there is a high likelihood that the highest risk patients are significantly underrepresented in the current stroke risk literature.

Previously, we have reported that 18% of 18,462 participants within the large national cohort of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study without a history of diagnosed stroke or TIA responded that they had experienced stroke-like symptoms.9 These symptoms correlated with the presence of vascular risk factors,9 an increased risk of cognitive impairment,10 and a lower health-related quality of life.11 suggesting that these events were likely in part undiagnosed events of cerebrovascular disease, including stroke and TIA. We sought to examine the impact of these self-reported stroke symptoms on the risk of stroke after adjustment for traditional stroke risk factors.

Methods

Design

The REGARDS study is a national longitudinal cohort study that recruited 30,239 US blacks and whites, aged 45+ years in 2003 to 2007.
2007, who are followed every 6 months for vascular events and/or death. REGARDS recruited 56% of participants from the Stroke Belt, an area of excess stroke mortality in the southeastern United States that has existed since at least 1940. Approximately 21% of the sample is from the “buckle” of the Stroke Belt (coastal plains of North Carolina, South Carolina, and Georgia); 35% from the remainder of the Stroke Belt (Alabama, Mississippi, Tennessee, Arkansas, Louisiana, and the rest of North Carolina, South Carolina, and Georgia); and the remaining 44% from the other 40 contiguous United States. Approximately 42% of the sample is black and 58% is white; the average age of the cohort at enrollment was 65.3 years. Because the largest stroke-related racial disparities are between blacks and whites, REGARDS only enrolled those reporting race as either non-Hispanic black or white. Within each region, individuals were initially contacted with mailings followed by telephone interview. For those agreeing to participate, telephone interviewers obtained demographic information, medical history, and stroke history by asking “has a healthcare professional ever told you that you’ve had a stroke or TIA?” Trained examiners then visited all participants at their homes to measure blood pressure, height, and weight; obtained an electrocardiogram, blood and urine samples; and recorded medications. The examiners were unaware of the participants’ stroke/TIA history. Study methods were reviewed and approved by the Institutional Review Boards at collaborating institutions. Additional details of the REGARDS study have been previously published.13,14

Stroke Symptoms: Questionnaire for Verifying Stroke-Free Status
The Questionnaire for Verifying Stroke-Free Status contains 8 items. The first 2 items elicit history of physician-verified stroke and/or mini-stroke/TIA; a positive response on either of these items excluded people from the current analyses. The remaining 6 items were asked regarding stroke-like symptoms only if no history of stroke or TIA was reported. Participants were asked about ever having a sudden onset of: painless hemibody numbness, painless hemibody numbness, loss of vision in 1 or both eyes, loss of vision in 1 or both eyes, loss of hemifield vision, or inability to speak or understand: A positive response on 1 or more of these 6 stroke symptoms indicates a positive stroke symptom history. This scale has been validated in verifying stroke-free status by several authors.15–18

Vascular Risk Factors
Traditional vascular risk factors were defined as published in the Framingham Stroke Risk Score (FSRS).19 These definitions included: diabetes—fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or self-reported use of diabetes medications; systolic blood pressure—average of 2 blood pressures after 5 minutes seated; use of antihypertensive medications—by self-report; atrial fibrillation—history of atrial fibrillation diagnosis or atrial fibrillation on electrocardiogram; left ventricular hypertrophy—on electrocardiogram; heart disease—self-reported myocardial infarction, coronary artery bypass grafting, bypass, angioplasty or stenting, or electrocardiographic evidence of myocardial infarction; and current smoking by self-report. More detailed definitions of these variables have been previously published.20

Incident Stroke Determination
Incident stroke was determined by adjudication of medical records from suspected stroke events that were self- or proxy-reported on semianual telephone contacts. Suspected strokes were considered from hospitalizations and/or physician visits since the last time REGARDS staff spoke with the participant. Reasons for these medical encounters were asked and medical records were sought for stroke, TIA, death, unknown reason for hospitalization, or if the participant was hospitalized for sudden weakness, numbness, trouble speaking, sudden loss of vision, headache, or other stroke symptoms. For proxy-reported deaths, an interview was conducted with an informed proxy.

Once a potential event was identified, the medical records were retrieved and reviewed by at least 2 members of the REGARDS Stroke Adjudication Committee; all events were physician-verified. The World Health Organization definition of stroke was 1 of our case criteria for the definition of stroke, which is: “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.”21 We also included events defined as “clinical strokes,” which were events not meeting this definition but characterized by symptoms lasting >24 hours with neuroimaging consistent with acute ischemic or hemorrhage and consistent with stroke as per the physician adjudicator. For this analysis, we used a combination of World Health Organization-defined or clinical strokes.14

Analysis
Proportional hazards analysis was used to assess the association of risk factors (including stroke symptoms) with the risk of stroke. Multiple imputation techniques were used to reduce potential bias attributable to missing records on suspected stroke outcomes.22 The focus of the analysis was to assess whether stroke symptoms are an independent risk factor for incident stroke after adjustment for the risk factors included in the FSRS and to assess the relative contribution of stroke symptoms compared with these traditional risk factors in the prediction of incident stroke events. This was implemented by first fitting a proportional hazards model predicting incident stroke events using the risk factors in the FSRS. The 6 individual stroke symptoms were considered as predictors added to proportional hazards model after adjustment for the FSRS factors. In addition, the presence of ≥1 symptoms as well as the number of symptoms present was considered a predictor after adjustment for the FSRS factors. To examine improvement in model discrimination, each factor was then removed 1 at a time and change in the concordance statistic (C-statistic) between the full model and the model with a predictor variable calculated.23 We then calculated the integrated discrimination improvement using the methods described by Pencina et al to compare risk prediction between models with and without stroke symptoms.24 We layman’s terms, the integrated discrimination improvement describes how well a new risk factor improves the sensitivity of predicting events without sacrificing specificity, whereas the C-statistic provides a measure for model discrimination.

Results
Follow-up was available on 29 648 (98%) of the 30 239 REGARDS participants. Of these, 2985 (10%) had prevalent stroke or TIA at baseline. 1926 (6%) were missing ≥1 of the Framingham stroke risk factors (primarily glucose level), and 325 (1%) were missing ≥1 responses for the stroke symptoms and were eliminated from the analysis, reducing the analysis cohort to 24 412 participants. There were 381 incident stroke events during a median follow-up of 4.4 years.

Demographics of the participants and vascular risk factor prevalence at baseline are presented in Table 1 stratified by incident stroke status. As expected, participants with incident strokes occurring during the study period were older, more likely to be male and black, and had a higher prevalence of vascular risk factors. Participants with a stroke during the study period also had a higher prevalence of stroke symptoms reported during the baseline interview (reported before the stroke event itself): 19% versus 14% for those without stroke. Also presented within Table 1 are the specific stroke-like symptoms reported by participants with and without a subsequent stroke event. The most commonly reported stroke symptom was “sudden painless numbness on 1 side of the
body”; the least common was the “sudden painless loss of vision in part or half of vision.”

Table 2 presents the risk of incident stroke associated with the various historical and physiological measurements from the FSRS. Almost every component of the FSRS was significantly associated with stroke risk with the exceptions of male sex and current use of antihypertensive medication. The largest increased risk for stroke was the category of age, race, and sex and current use of antihypertensive medication. The risk of stroke than white participants at young ages, whereas at older ages, the risk is roughly equivalent). \( \text{Hazard Ratio} \ (0.001, 0.05) \)

We also considered measures of model discrimination and reclassification to determine the prognostic significance of including stroke symptoms in the model. The relative change in the integrated discrimination improvement after adding the number of stroke symptoms was 0.4%. This was similar to the relative integrated discrimination improvement for diabetes (4.4%), atrial fibrillation (3.0%), and left ventricular hypertrophy (2.3%). In comparison, a history of smoking had a much larger relative improvement in integrated discrimination improvement (21%) as did age, race, and the age–race interaction improvement (20.1%) as did age, race, and the age–race interaction.
interaction (83.5%). The marginal change in the C-statistic was also similar for number of stroke symptoms compared with diabetes, atrial fibrillation, and left ventricular hypertrophy (data not shown).

Discussion
Among participants without a diagnosis of stroke or TIA, ≥1 self-reported prior stroke-like symptoms was significantly related to the incidence of future stroke events, increasing the risk of a future stroke by 36%. Previously we reported that the presence of stroke-like symptoms was associated with the presence of vascular risk factors. Therefore, we expected that participants reporting stroke symptoms would be at higher risk for stroke. What we did not expect, however, was the strength of the association of stroke symptoms with stroke risk even after controlling for the traditional risk factors. In fact, compared with the traditional Framingham stroke risk factors, the impact of stroke symptoms on the prediction of stroke was almost as large as the impact of hypertension and larger than the impact of diabetes and heart disease. This is the strongest evidence yet that these stroke symptoms are associated with an increased risk of stroke and may even represent “undiagnosed stroke or TIA.” However, these self-reported stroke symptoms may also represent other medical conditions such as migraine headaches, seizures, syncopal events, dementia, ocular diseases other than vascular occlusion, psychiatric diseases, and others. Therefore, one cannot assume that all of these self-reported events are actually stroke or TIA. Given the large proportion of self-reported stroke symptoms among the population, it is of critical public health importance to further characterize the risk of potentially disabling cerebrovascular events among this group.

Describing stroke risk has been extensively studied in the current literature. One of the best-known examples is the Framingham stroke risk score, which is able to describe this group. Framingham stroke risk score, is able to describe this group.

A history of problems with understanding or expressing one’s self were the 2 stroke symptoms with the largest increase in stroke risk, increasing risk 1.87 times and 1.75 times, respectively. These individual symptoms could be more powerfully associated with stroke risk because they tend to be more reliably reported or alternatively perhaps because they could indicate a pathology that is more closely associated with stroke risk. We have previously shown that participants were more likely to seek medical treatment for hemibody weakness than for communication and/or speaking problems. If participants sought care and received a diagnosis of TIA or stroke, they were excluded from this analysis. Therefore, many possible explanations could be hypothesized for the differences seen by specific types of stroke symptoms.

There are several limitations to our analysis. Due to the large volume of participants, the initial baseline interview had to be limited in scope. As a result, the duration, timing, and any associated symptoms with these stroke-like symptom events were not collected. These kinds of clinical data would be helpful in further characterizing these stroke-like events. Another limitation is sample size; although REGARDS is the largest prospective stroke cohort ever collected, at the time of this analysis (after 4.4 years of followup), there were only 381 stroke events. Despite this, we were still able to find quite strong associations in our analysis. Our findings can only be applied to blacks and whites in the United States, because this study was specifically designed to understand black–white differences. Finally, as is the limitation with any cohort study, the cohort is likely not entirely representative of the population in general, because participants had to have a home address, a telephone, and agree to an in-home visit. However, the strengths of our analysis are that this cohort is truly a nationwide sample without the inherent biases of regional analyses. REGARDS also has the largest number of blacks of any cohort ever assembled in the United States and so is well poised for these kinds of analyses.

In conclusion, stroke-like symptoms as assessed by the 6-item Questionnaire for Verifying Stroke-Free Status likely in part represent undiagnosed stroke events, and future studies of stroke risk should query not only stroke history, but also prior stroke symptoms. Future study of these self-reported stroke-like symptom events are needed to evaluate this high-risk segment of the population.

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