The Association Between Trait Anger and Incident Stroke Risk
The Atherosclerosis Risk in Communities (ARIC) Study

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Background and Purpose—This study examined the relation between trait anger and incident stroke risk among participants without a history of stroke at the first follow-up examination of the Atherosclerosis Risk in Communities (ARIC) study.

Methods—The study sample included 13 851 black and white men and women, aged 48 to 67 years, who completed the Spielberger Trait Anger Scale. Median follow-up time was 77.3 months.

Results—In the full cohort, Cox proportional hazards regression analyses showed a modest increase in the risk for stroke among individuals with high trait anger, though the association did not remain statistically significant after multivariate adjustment. Participants ≤60 years of age who reported having high trait anger had a 2.82 (95% CI, 1.65 to 4.80) times greater risk for hemorrhagic and ischemic strokes combined (any) and a 2.93 (95% CI, 1.64 to 5.22) times greater risk for ischemic strokes alone than their counterparts who reported having low trait anger (hazard rate ratios adjusted for sex and race/ethnicity). Similarly, among participants with HDL cholesterol levels >47, the risk for any stroke was 2.86 (95% CI, 1.56 to 5.25) times greater for those who reported having high trait anger, whereas the risk for ischemic strokes alone was 2.98 (95% CI, 1.58 to 5.61) times greater (hazard rate ratios adjusted for age, sex, and race/ethnicity). These associations remained strong and statistically significant after further adjustment for several established biological and sociodemographic risk factors for stroke and were absent among older participants and those with lower HDL cholesterol values.

Conclusions—Trait anger was associated with an increased risk for incident stroke in the ARIC study among younger participants and those with higher HDL cholesterol levels. (Stroke. 2002;33:13-20.)

Key Words: anger ■ prospective studies ■ risk factors ■ stroke, ischemic ■ survival analysis

Anger/hostility can have deleterious consequences for physical health, most notably coronary heart disease (CHD) and cerebrovascular disease or stroke. Although a considerable body of epidemiologic and clinical research data supports a positive association between anger and CHD, fewer data are available for stroke. The extant research literature on anger and stroke consists of only a handful of studies. Adler et al, in a retrospective case study, reported that among men in their sample, stroke was most often preceded by negative affective states, primarily hopelessness and anger. Similarly, Gianturco et al reported that compared with hospitalized control subjects, a greater proportion of stroke patients had anger just before their stroke. Although the full report from the Framingham Heart Study is unavailable, in an abstract summarizing its findings, Eaker and Feinleib reported that the 10-year incidence of stroke was significantly associated with anger among women and marginally associated with anger among men; however, the association was no longer statistically significant after risk factor adjustment. The most recent published work in this area is a prospective study by Everson et al based on results from the Kuopio Ischemic Heart Disease Study. After examining the association between different anger expression styles and the incidence of stroke among middle-aged Finnish men, these investigators found that men who were most prone to frequent outward expressions of anger had twice the risk for stroke as those who were least prone to such expressions. Furthermore, among men with prevalent CHD, they found those who were most prone to outwardly expressed anger had almost six times the risk for stroke as those who were least prone.

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In the literature, anger is conceptualized in terms of the degree to which people have this emotion and the characteristic means by which they express it. The predisposition for frequent, intense, long-lasting anger is a relatively enduring and stable personality attribute known as trait anger. Anger expression, on the other hand, refers to how anger is managed, that is, whether it is expressed outwardly, held in, or controlled. In the current study, we examined the relation of trait anger to incident stroke risk in a large bi-ethnic US population of middle-aged men and women enrolled in the Atherosclerosis Risk in Communities (ARIC) study. Analyses of ARIC data and results of other studies have shown the relation between anger/hostility and cardiovascular disease (CVD) risk to be modified by hypertensive status, and age. Taken together, these findings suggest that anger/hostility may confer a greater CVD risk among people who otherwise are at low risk for the disease. The aims of this study were (1) to assess the relation between trait anger and stroke incidence and (2) to test whether this relation differed by levels of selected risk factors.

Subjects and Methods

Study Population

The study population consisted of participants in ARIC, a large, prospective study of cardiovascular disease and its risk factors carried out in the US communities of Washington County, Maryland; suburban Minneapolis, Minnesota; Forsyth County, North Carolina; and Jackson, Mississippi. ARIC study participants were recruited from random probability samples enumerated in these communities. Written informed consent to participate in the ARIC study was obtained from each participant at the baseline clinical examination (visit 1) and updated at each follow-up examination (visits 2, 3, and 4). The study was approved triennially by the institutional review board at each participating university, as were the study protocols by the ARIC Steering Committee, the ARIC Policy Board, and the National, Heart, Lung, and Blood Institute. Blacks were oversampled in Forsyth County, North Carolina, and only blacks were sampled in Jackson, Mississippi. The ARIC study was designed with two distinct research arms: (1) community surveillance of residents 35 to 74 years of age and (2) cohorts of volunteers who were 45 to 64 years of age at recruitment. The baseline cohort evaluations were conducted in 1987 to 1989 and were followed by 3 triennial clinical examinations and ongoing morbidity and mortality surveillance. At the second clinical examination (visit 2), conducted between 1990 and 1992, the Spielberger Trait Anger Scale was administered to 14,348 returning cohort members, 92.9% of the cohort members enrolled at baseline. Of these, 148 with incomplete responses to the anger questionnaire and 42 with a racial/ethnic identity other than black or white were excluded from analyses. An additional 307 were excluded because of a history of stroke at visit 2. After these sequential exclusions were made, a total of 13,851 participants remained for the current analyses.

Assessment of Trait Anger

The Spielberger Trait Anger Scale was used to assess the frequency and degree to which each participant had anger (see Appendix). This scale was a component of the Health-Life Profile that participants completed at visit 2. The Spielberger scale consists of 10 items endorsed on a 4-point anchor, including almost never = 1, sometimes = 2, often = 3, and almost always = 4. The sum of the response category for each of the individual items comprised the overall trait anger score, which ranged from 10 to 40. High trait anger was defined by scores of 22 to 40, moderate anger by scores of 15 to 21, and low anger by scores of 10 to 14. The chosen cut-points were comparable with those used in previously published work with the Spielberger scale. Adequate internal consistency has been reported for the Spielberger scale. Correlations with the Buss-Durkee Hostility Inventory have been reported as ranging from 0.66 to 0.73 and 0.43 to 0.59 with the Cook-Medley Hostility Scale. A study in ARIC has been planned to determine the internal consistency and stability of the Spielberger scale in this cohort.

Assessment of Stroke Risk Factors

Technicians who were trained and certified in the use of standardized protocols made the physiological measurements and laboratory assessments during the clinical examination at visit 2. Three consecutive blood pressure measurements, assessed with a random zero sphygmomanometer, were taken after participants were seated for a 5-minute rest period. The blood pressure levels reported were the average of the second and third readings. Waist-to-hip ratio was the ratio of waist girth (abdominal circumference measured at the umbilicus) to hip girth (circumference measured at the maximal gluteal protrusion). Diabetes was defined as a fasting serum glucose level \( \geq 126 \text{ mg/dL} \), a nonfasting serum glucose level \( \geq 200 \text{ mg/dL} \), and/or a history of diabetes, insulin therapy, or oral hypoglycemic medication use. Data on alcohol consumption, cigarette smoking, and education were based on self-reports by participants. Von Willebrand factor antigen was measured by the enzyme-linked immunosorbent assay method. Left ventricular hypertrophy was determined by the Cornell voltage electrocardiographic criteria. HDL cholesterol (HDL-C) levels were measured enzymatically after precipitation of LDL-containing lipoproteins with dextran-magnesium. LDL cholesterol (LDL-C) levels were calculated by means of the Friedewald formula. Prevalent CHD was defined as a history of myocardial infarction or cardiac revascularization procedures (eg, coronary artery bypass graft surgery or percutaneous transluminal angioplasty).

Ascertainment of Incident Stroke

Incident strokes were hospitalized events among members of the ARIC study cohort captured from the time of their second clinical examination (1990 to 1992) through December 31, 1997. In this study, strokes were classified as ischemic or hemorrhagic. Potential strokes were identified through annual telephone interviews with cohort members and through ongoing morbidity and mortality surveillance in local hospitals. Hospital records (eg, medical records and hospital discharge summaries) were reviewed for the presence of a diagnosis consistent with cerebrovascular disease (eg, International Classification of Diseases, ninth revision, Clinical Modification codes 430–438, a CT or MRI image diagnostic of cerebrovascular disease, or a patient history of hospitalization on the neurological intensive care unit). Potentially eligible cases were subjected to classification and validation through the use of a computerized algorithm and physician review. Relevant data from hospital records used in the classification scheme included the type and duration of patients’ initial neurological symptoms, their medical history, results of medical procedures, medications, reports from imaging (CT or MRI), autopsy findings, and other supportive clinical evidence. The inclusion criterion for a diagnosis of stroke was evidence of sudden or rapid onset of neurological symptoms (eg, paralysis, numbness/weakness, aphasia, headache, vertigo, convulsions) lasting for \( >24 \) hours. Disagreements between computer-generated diagnoses and those derived by physician review were adjudicated by a second physician reviewer. Classification of stroke was conducted without knowledge of the participant’s status on the trait anger scale. A more detailed description of the procedures and definition for classification of stroke events in the ARIC cohort have been previously reported.

Statistical Analyses

Anger classes (low, middle, high) were entered into Cox proportional hazards regression models as dummy variables in the main analyses. Anger was entered into the models as a continuous variable when assessing the presence of a linear trend in stroke risk. The association between trait anger and incident stroke risk was examined for effect...
RESULTS

The distribution of trait anger was as follows: among persons 60 years of age and younger, mean trait anger scores were 15.6 (SD=3.9) for black men, 16.1 (SD=3.9) for black women, 16.5 (SD=3.8) for white men, and 16.1 (SD=3.5) for white women. Correspondingly, among those >60 years of age, mean trait anger scores were 15.7 (SD=4.6) for black men, 15.8 (SD=4.2) for black women, 6.1 (SD=3.7) for white men, and 15.5 (SD=3.3) for white women.

Selected characteristics of the study population at the first follow-up examination, shown in Table 1, indicate that participants who scored in the high trait anger range were slightly younger, more likely to be male, and more likely to have fewer years of formal education than those who scored in the moderate- or low-anger range. High trait anger scorers also had higher von Willebrand factor values, lower HDL-C levels, and higher waist-to-hip ratios than moderate- or low-anger scorers. Furthermore, participants who scored in the high trait anger range smoked more cigarettes, consumed more alcohol, and were more likely than their counterparts to have a history of CHD.

Of the 257 participants who had strokes in the study’s 96.2-month follow-up period (median period, 77.3 months), 31 scored in the high anger range, 136 in the moderate anger range, and 90 in the low anger range. Of these strokes, 31 were ischemic and 31 hemorrhagic. In the full cohort, there was a modest association between trait anger and incident stroke (any) risk, though the multivariate-adjusted hazard rate ratio (HRR) was not statistically significant. The crude association between trait anger (high versus low) and any stroke was 1.60 (95% CI, 1.07 to 2.41).

In the fully adjusted model again not reaching statistical significance.
trend = 0.004). After adjustment for sex and race/ethnicity, the risk was 2.82 times greater (P value for linear trend = 0.001). Furthermore, the HRRs for ischemic stroke in the crude model (2.78) and in the model adjusted for sex and race/ethnicity (2.93) were both higher than those for any stroke when the high trait anger group was compared with the low (Table 2). These associations remained strong and statistically significant after multivariate adjustment; they were absent among the older participants (age > 60 years). Crude Kaplan-Meier probability curves for the two age groups are displayed in the Figure (Panels 1 and 2).

The pattern of risk among participants in the two HDL-C strata was similar to that observed in the two age strata, as described above. Among participants with HDL-C values above the median (>47), the risk for any stroke increased monotonically with levels of trait anger (Table 3). However, these associations were not observed among participants with HDL-C levels at or below the median (≤47). Additionally, among participants with higher HDL-C levels (>47), each HRR for ischemic strokes alone was higher than that for any stroke. Crude Kaplan-Meier probability curves for the two HDL-C groups are displayed in the Figure (Panels 3 and 4).

**Discussion**

In the full cohort, trait anger was associated with only a modest increased stroke risk. This personality trait, however, was associated with a significant increase in the risk for stroke, especially ischemic stroke, among younger men and women and those with higher HDL-C levels. Younger participants (≤60 years) who reported having high trait anger

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**TABLE 2. Hazard Rate Ratios (95% CI) for Association Between Trait Anger and Incident Stroke by Age: ARIC Study, 1990 to 1997**

<table>
<thead>
<tr>
<th>Spielberger Trait Anger Scores</th>
<th>Age ≤60 y</th>
<th></th>
<th>Age &gt;60 y</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low, 10–14</td>
<td>Moderate, 15–21</td>
<td>High, 22–40</td>
<td>P*</td>
</tr>
<tr>
<td>Population, n</td>
<td>362</td>
<td>735</td>
<td>796</td>
<td></td>
</tr>
<tr>
<td>Individuals with any stroke, † n</td>
<td>35</td>
<td>63</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.00</td>
<td>1.12 (0.74–1.69)</td>
<td>2.67 (1.57–4.55)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex- and race/ethnicity-adjusted</td>
<td>1.00</td>
<td>1.24 (0.82–1.87)</td>
<td>2.82 (1.65–4.80)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted‡</td>
<td>1.00</td>
<td>1.35 (0.85–2.12)</td>
<td>1.96 (1.06–3.62)</td>
<td>0.06</td>
</tr>
<tr>
<td>Individuals with ischemic stroke, n</td>
<td>29</td>
<td>51</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.00</td>
<td>1.09 (0.69–1.72)</td>
<td>2.78 (1.56–4.96)</td>
<td>0.009</td>
</tr>
<tr>
<td>Sex- and race/ethnicity-adjusted</td>
<td>1.00</td>
<td>1.21 (0.77–1.91)</td>
<td>2.93 (1.64–5.22)</td>
<td>0.004</td>
</tr>
<tr>
<td>Multivariate-adjusted‡</td>
<td>1.00</td>
<td>1.37 (0.82–2.29)</td>
<td>2.28 (1.18–4.41)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Value for linear trend.
†Hemorrhagic and ischemic strokes combined.
‡Adjusted for race/ethnicity, level of educational attainment, sex, waist-to-hip ratio, cigarette years of smoking, plasma LDL and HDL cholesterol levels, diabetes, hypertensive status, von Willebrand factor, prevalent CHD, and left ventricular hypertrophy.
were at nearly 3 times greater risk for ischemic stroke than those who reported having low trait anger. Among participants with higher HDL-C levels (>47) and high trait anger, the magnitude of risk was similar. These associations remained strong and statistically significant after further adjustment for several established biological and sociodemographic risk factors for stroke and were absent among older persons and participants with lower HDL-C levels.

The mechanism by which trait anger increases ischemic stroke risk is unknown. The research on anger and CHD may help explain the association, since both ischemic stroke and the acute coronary syndromes (eg, myocardial infarction, sudden death, angina pectoris) result from an occlusive arterial process. In the anger-CHD literature, anger is viewed as a trigger of hemodynamic (eg, increased arterial pressure), vasoconstrictive, and hemostatic (eg, increased platelet adhesion) forces that are key in the pathogenesis of the acute coronary syndromes. They contribute to the atherosclerotic process by disrupting vulnerable atherosclerotic plaques in the artery wall, leading to the formation of lesions and to occlusive thrombosis. The triggering hypothesis may be a useful conceptual framework from which to understand the link between trait anger and incident stroke; that is, anger may trigger similar physiological changes in the vessels supplying the brain with blood, causing occlusive thrombosis, blockage, and a resulting stroke.

Another pathway by which anger may be associated with ischemic stroke is through the impact of sympathetic arousal and neuroendocrine activation in the initiation and progression of atherosclerosis. There can be direct injury to the blood vessel walls in response to increased blood pressure and increased flow velocity and in response to an exaggerated discharge of catecholamines (eg, epinephrine and norepinephrine). Furthermore, catecholamines can initiate other vascular and prothrombotic events that are associated with atherosclerosis such as increased platelet adhesion and aggregation, vascular lipid uptake, and activation of macrophages. Parenthetically, in this study, the prevalence of hypertension was only slightly higher in persons in the high-anger group compared with that in the low- or moderate-anger groups. In view of the sympathetic arousal hypothesis, a much higher prevalence of hypertension in the high-anger group would have been expected. Future studies in this cohort are needed to assess the relation of anger to blood pressure levels as well as to the development and progression of hypertension.

A third hypothesis suggests that persons who have higher levels of anger/hostility, compared with those who have lower levels, may be more likely to engage in adverse health behaviors (eg, sedentary lifestyles, cigarette smoking, greater consumption of alcohol, and overeating) that place them at increased risk for CHD. These behaviors and the resulting risk factors are viewed as potential mediators on the causal pathway from anger/hostility to CHD. Given the similarities between CHD and stroke risk factors, this hypothesis may help explain the mechanism linking trait anger to stroke. If a biobehavioral mechanism is chiefly operative in the trait anger-stroke relation, then the multivariate estimates of risk reported in this study may underestimate the strength of the association.

We observed neither a statistically significant nor a consistently positive association between trait anger and incident stroke risk among older participants (age >60 years) in the cohort. This finding is consistent with research on hostility and CHD in which the investigators have observed heterogeneity of effect by age and explained the association from the perspective of selective survival. This finding is also consistent with that from the Framingham study, in which the influence of smoking on CHD risk decreased with age. Alternatively, the lack of a positive association between trait anger and incident stroke risk among participants over age 60

<table>
<thead>
<tr>
<th>Population, n</th>
<th>Low, 10–14</th>
<th>Moderate, 15–21</th>
<th>High, 22–40</th>
<th>P*</th>
<th>Low, 10–14</th>
<th>Moderate, 15–21</th>
<th>High, 22–40</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with any stroke, n</td>
<td>2490</td>
<td>3550</td>
<td>474</td>
<td>0.001</td>
<td>2601</td>
<td>4107</td>
<td>629</td>
<td>0.001</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>1.09 (0.69–1.74)</td>
<td>3.08 (1.68–5.67)</td>
<td>0.001</td>
<td>1.00</td>
<td>1.03 (0.74–1.42)</td>
<td>1.10 (0.63–1.94)</td>
<td>0.39</td>
</tr>
<tr>
<td>Age-, sex-, race/ethnicity-adjusted</td>
<td>1.00</td>
<td>1.16 (0.73–1.84)</td>
<td>2.86 (1.56–5.25)</td>
<td>0.004</td>
<td>1.00</td>
<td>1.10 (0.79–1.53)</td>
<td>1.15 (0.65–2.03)</td>
<td>0.26</td>
</tr>
<tr>
<td>Multivariate-adjusted‡</td>
<td>1.00</td>
<td>1.09 (0.66–1.81)</td>
<td>2.30 (1.18–4.46)</td>
<td>0.04</td>
<td>1.00</td>
<td>1.08 (0.76–1.54)</td>
<td>0.66 (0.33–1.32)</td>
<td>0.91</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>27</td>
<td>34</td>
<td>15</td>
<td></td>
<td>54</td>
<td>83</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age-, sex-, race/ethnicity-adjusted</td>
<td>1.00</td>
<td>0.94 (0.57–1.56)</td>
<td>3.22 (1.71–6.06)</td>
<td>0.001</td>
<td>1.00</td>
<td>1.04 (0.74–1.46)</td>
<td>1.07 (0.58–1.95)</td>
<td>0.61</td>
</tr>
<tr>
<td>Multivariate-adjusted‡</td>
<td>1.00</td>
<td>0.99 (0.59–1.64)</td>
<td>2.98 (1.58–5.61)</td>
<td>0.004</td>
<td>1.00</td>
<td>1.11 (0.78–1.56)</td>
<td>1.11 (0.60–2.03)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Value for linear trend.
†Hemorrhagic and ischemic strokes combined.
‡Adjusted for age, race/ethnicity, level of educational attainment, sex, waist-to-hip ratio, cigarette years of smoking, plasma LDL cholesterol levels, diabetes, hypertensive status, von Willebrand factor, prevalent CHD, and left ventricular hypertrophy.
years may be explained, at least in part, by the fact that as a group they were at 2.59 times greater risk for stroke, and any further risk attributable to anger was negligible.

Another main finding of the current study was the lack of a positive association between trait anger and incident stroke risk among participants with lower HDL-C levels. In this study, there was an inverse association between incident stroke risk and higher HDL-C values (relative risk, 0.59; 95% CI, 0.45 to 0.76). Therefore, the lack of a statistically significant or a consistently positive association between trait anger and incident stroke risk among participants with lower concentrations of HDL-C, a known antiatherogenic lipoprotein, may be explained by the fact that in this context, the addition of an anger-prone personality confers little or no additional risk for stroke.

We are aware of only one other published prospective study of anger and stroke and none involving a bi-ethnic sample of white and black men and women. Our study contained a relatively large number of strokes that were validated by standardized diagnostic criteria. Additionally, this study, like a study reported recently by Everson et al., was based on data gathered with a well-known, reliable, and valid anger assessment instrument. Thus, in both exposure and outcome assessment, we were able to overcome some of the methodological weaknesses that plagued the earliest studies in this area. However, even though the process of ascertaining and validating strokes was standardized, there could have been errors in the classification of disease resulting from the incompleteness or inaccuracy of data abstracted from medical records and discharge summaries.

Persons who have high levels of anger may benefit from interventions designed to help them better handle anger-provoking situations. There is some evidence that anger management is effective for lowering anger/hostility levels, improving CHD risk factor profiles, and forestalling the recurrence of CHD events. The efficacy of anger reduction for the prevention of stroke awaits evaluation.

In conclusion, for the entire ARIC study cohort, trait anger was modestly associated with the risk for incident stroke. However, among younger persons and those with higher HDL-C levels, these associations were stronger and statistically significant even after adjusting for potential confounders. These results provide additional epidemiologic evidence of a positive association between anger and stroke. Although there are tenable hypotheses linking anger and ischemic stroke, additional studies are needed to identify the operative biological and behavioral mechanisms and to explore the effect modification of this association by age and HDL-C level.

Appendix

Spielberger Trait Anger Scale

1. I am quick-tempered.
2. I have a fiery temper.
3. I am a hot-headed person.
4. I get angry when I am slowed down by others’ mistakes.
5. I feel annoyed when I am not given recognition for doing good work.
6. I feel infuriated when I do a good job and get a poor evaluation.
7. I fly off the handle.
8. When I get angry, I say nasty things.
9. It makes me furious when I am criticized in front of others.
10. When I get frustrated, I feel like hitting someone.

Acknowledgments

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References


Editorial Comment

Adjustment in the Anger-Stroke Relationship: How Far Should One Go?

The Atherosclerosis Risk in Communities (ARIC) Study Group continues to be productive with contributions on cerebrovascular disease for Stroke from a large multi-ethnic, population-based study. In this issue, Williams et al report on the relationship between trait anger and the risk of stroke. Trait anger was evaluated by means of the Spielberger Trait Anger Scale and subdivided into 3 categories: high (scores 22 to 40), moderate (15 to 21), and low (10 to 14). During a median follow-up of about 6.5 years, 31 strokes occurred among 1103 participants with high scores (2.8%) as compared with 90 strokes in 5091 participants with low scores (1.8%). Participants with moderate scores had a risk similar to that of participants with low scores. The crude (ie, unadjusted) hazard ratio of high versus low scores was 1.60 (95% CI 1.07 to 2.41), virtually identical to the cumulative incidence ratio of 1.59 (2.81%/1.77%). The hazard ratio differed according to 2 of 8 studied subgroup characteristics: age and HDL-C level. Among persons aged 60 and below, the crude hazard ratio was 2.67 as opposed to 0.94 in the older participants; in persons with HDL-C levels above the median (47 mmol/L), the age-adjusted hazard ratio was 3.08 versus 1.10 among those with HDL-C at or below the median. Such differences were not observed between subgroups by LDL-C level, gender, hypertensive status, diabetes, prevalent coronary heart disease, and cigarette-years of smoking. The hazard ratios tended to be slightly higher if the analyses were restricted to ischemic stroke.

In this comment I limit myself to 1 methodological issue and some suggestions for future research; aspects of behavioral attributes and cerebrovascular disease have been addressed recently in 2 other editorial comments.1–2 In the ARIC study, the authors tried to unravel the etiologic contribution of trait anger to stroke occurrence. This may be a difficult task at a time when only limited knowledge is available on the pathophysiologic mechanisms involved. Such knowledge is required to determine which other characteristics may be in the causal pathway between trait anger and stroke occurrence. These insights stipulate how one should proceed during data analysis. Characteristics extraneous to the causal path from trait anger to stroke might obscure the true relationship between the two. Such characteristics are potential confounders. Rothman, in his classic book on epidemiology, describes 3 conditions for a characteristic to be a confounder: (1) it should be related to the disease among the nonexposed; (2) it should be related to the exposure; and (3) the characteristic should not be an intermediary in the causal pathway between exposure and disease. The first 2 conditions may be investigated in one’s own database, but the third one requires a vision on the pertinent pathophysiologic processes. If data on the relevant characteristics are recorded, confounding may be resolved in the data analysis, basically by stratified analyses. In case the confounding effects of many characteristics need to be addressed simultaneously, multivariate regression analyses are employed. The resulting effect estimates are “adjusted” for the nuisance effect of the confounders and may be higher or lower than the crude value. Adjustment, however, for characteristics that are intermediate in the causal path from trait anger to stroke would lead to an underestimation of the “true” strength of the relationship. It is of note that the anger-stroke relationship might not be directly causal at all, eg, trait anger could be a proxy for another truly causal factor.

Williams et al adjusted the crude hazard ratio in several steps, first for age alone, then additionally for gender and race/ethnicity, and finally also for educational attainment, waist-to-hip ratio, cigarette-years of smoking, LDL-C, diabetes, hypertensive status, von Willebrand factor, prevalent coronary heart disease, and left ventricular hypertrophy. Thus, the readers get partial insight in the confounding effects of a dozen variables. A more detailed idea of such effects may be obtained in so-called bivariate analyses, ie, with trait anger and 1 potential confounder at a time. One may select those variables for multivariate adjustment that appeared to be of influence on the hazard ratio in the bivariate analyses. Thus, a parsimonious model would arise with sufficient statistical stability. So readers may fully evaluate for themselves which effect estimate they believe to be the most plausible one. For
example, should one adjust for hypertensive status? One might speculate that people with a high score of trait anger would have (more frequent episodes of) higher blood pressures, and that such blood pressure elevations would be responsible for an increased stroke incidence. In such a situation it would be inappropriate to adjust for hypertension. Although the ARIC data hardly point into this direction, the literature on this issue not yet conclusive, so one might argue both ways: adjust or do not adjust.

To try and understand the mechanisms operative in the trait anger-stroke relationship it would be of interest to study whether its strength differs according to stroke type. If the relationship is stronger with cardioembolic stroke, hemostasis might be involved in the causal route; a stronger relationship with cerebral ischemia of arterial origin would plead for atherosclerosis in the path. Another suggestion for future research would be to employ the case-crossover study design to determine whether fits of anger are directly related to stroke occurrence. In such an approach the stroke patient would serve as his or her own control. Mittleman et al applied this design to assess whether episodes of anger could trigger myocardial infarction.

In conclusion, epidemiological studies should go hand in hand with more fundamental ones to solve the difficult puzzles on causation. Insight in causal mechanisms helps to develop efficient preventive and therapeutic measures.

Dr. Algra is indebted to Dr. M.L. Bots for helpful remarks on an earlier version of this comment.

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Department of Neurology and the Julius Centre for General Practice and Patient Oriented Research
University Medical Centre Utrecht, the Netherlands

References
The Association Between Trait Anger and Incident Stroke Risk: The Atherosclerosis Risk in Communities (ARIC) Study
Janice E. Williams, F. Javier Nieto, Catherine P. Sanford, David J. Couper and Herman A. Tyrold

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