Prospective Study of Markers of Hemostatic Function With Risk of Ischemic Stroke

Aaron R. Folsom, MD; Wayne D. Rosamond, PhD; Eyal Shahar, MD; Lawton S. Cooper, MD; Nena Aleksic, PharmD, PhD; F. Javier Nieto, MD, PhD; Mandy L. Rasmussen, MPH; Kenneth K. Wu, MD; for the Atherosclerosis Risk in Communities (ARIC) Study Investigators

Background—Several markers of hemostatic function and inflammation have been associated with increased risk of coronary heart disease, but prospective evidence for their role in ischemic stroke is scant.

Methods and Results—The Atherosclerosis Risk in Communities (ARIC) Study measured several of these markers in more than 14 700 participants 45 to 64 years old who were free of cardiovascular disease and were followed up for 6 to 9 years for occurrence of ischemic stroke (n = 191). There was no apparent association between ischemic stroke incidence and factor VIIc, antithrombin III, platelet count, or activated partial thromboplastin time. After adjustment for multiple cardiovascular risk factors, von Willebrand factor, factor VIIIc, fibrinogen, and white blood cell count were positively associated and protein C was negatively but nonsignificantly associated with ischemic stroke incidence in regression analyses based on either continuous variables or fourths of the variable distributions. The adjusted relative risk (and 95% CI) for ischemic stroke in the highest versus lowest fourth were: von Willebrand factor, 1.71 (1.1 to 2.7); factor VIIIc, 1.93 (1.2 to 3.1); white blood cell count, 1.50 (0.9 to 2.4); fibrinogen, 1.26 (0.8 to 2.0); and protein C, 0.65 (0.4 to 1.0).

Conclusions—This study offers modest support for the hypothesis that some markers of hemostatic function and inflammation can identify groups of middle-aged adults at increased risk of stroke. These factors may play a role in the pathogenesis of ischemic stroke. (Circulation. 1999;100:736-742.)

Key Words: stroke ■ ischemia ■ hemostasis

Prospective studies have linked hemostatic factors (eg, fibrinogen,1-5 factor VII,1 and von Willebrand factor6-9) or markers of inflammation (eg, white blood cell [WBC] count4,5,7 and C-reactive protein8-10) with risk of coronary heart disease (CHD). Yet, few prospective studies link these factors to risk of ischemic stroke.2,3,8,9,11-15 There appear to be no prospective data on the associations of factor VIII, antithrombin III (AT-III), protein C, or platelet count with incidence of ischemic stroke. Additional prospective studies are needed to clarify these potential new risk factors for stroke and to perhaps offer clues to stroke prevention. We therefore examined the association of plasma levels of several coagulation and anticoagulation proteins as well as the WBC count (for simplicity, referred to here collectively as “hemostatic factors”) with the incident ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

Study Population

The ARIC Study16 included a cohort totaling 15 792 persons between 45 and 64 years of age at recruitment in 1987 through 1989, probability sampled from Forsyth County, North Carolina; Jackson, Miss (blacks only); the northwest suburbs of Minneapolis, Minn; and Washington County, Maryland. Participants underwent reexamination in 1990 through 1992, in 1993 through 1995, and in 1996 through 1998.

Baseline Measurements

Blood was drawn after an 8-hour fasting period with minimal trauma from an antecubital vein. Samples were processed by a standardized protocol and stored at −70°C until assayed at the ARIC Hemostasis Laboratory at the University of Texas Medical School, Houston. Detailed methods for blood processing and measurement of hemostatic variables have been published.17,18 Fibrinogen was measured by the thrombin-time titration method; factor VII activity (VIIc) and factor VIII activity (VIIIc) by clotting assays; von Willebrand factor antigen and protein C antigen by ELISA; AT-III activity by a chromogenic substrate method; and activated partial thromboplastin time (aPTT) on an automated coagulometer. Reliability coefficients obtained from repeated testing of individuals over several weeks were 0.72 for fibrinogen, 0.78 for factor VIIc, 0.86 for factor VIIIc, 0.68 for von Willebrand factor, 0.56 for protein C, 0.42 for AT-III, and 0.92 for aPTT.19

Plasma total cholesterol and triglycerides were measured by an enzymatic method, and LDL cholesterol was calculated.20 HDL...
cholesterol was measured after dextran-magnesium precipitation of non-HDL lipoproteins. Prevalent diabetes mellitus was defined as a fasting glucose level $\geq$126 mg/dL, nonfasting glucose level $\geq$200 mg/dL, and/or a history of or treatment for diabetes. Platelet counts and WBCs were measured by Coulter counters.

The ratio of waist (umbilical level) and hip (maximum buttocks) circumferences was calculated as a measure of fat distribution. Three blood pressure measurements were taken with a random-zero sphygmomanometer; the last 2 measurements were averaged. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or use of antihypertensive medication. Physical activity was expressed as a sport index ranging from 1 (low) to 5 (high). Left ventricular hypertrophy was determined by Cornell voltage criteria for the resting ECG.

### Ascertainment of Incident Ischemic Stroke

Strokes were identified and classified according to published criteria based on the occurrence and duration of neurological signs and symptoms, the results of neuroimaging and other diagnostic procedures, and treatments provided. Strokes secondary to trauma, neoplasm, hematological abnormality, infection, or vasculitis were not counted, and a focal deficit lasting $<24$ hours was not considered a stroke. Over the 6 to 9 years of follow-up, there were 274 definite, probable, or possible incident strokes among participants with no history of stroke at baseline. CT or MRI was available for 83% of them. The strokes included 221 definite or probable ischemic strokes, which were the focus of this analysis.

### Data Analysis

After those with prevalent CHD, prevalent stroke, and unknown baseline stroke status were excluded, 14,713 of the 15,792 ARIC participants were included in the analysis. The exclusion of participants with prevalent CHD decreased the number of ischemic strokes for analysis from 221 to 191. Follow-up went from baseline to whichever of the following occurred first: ischemic stroke, death, last contact, or December 31, 1995.

Age-, race-, sex-, and ARIC community–adjusted means and SEMs of baseline continuous hemostatic variables for incident stroke cases and noncases were computed by ANCOVA. Relative risks (RR) (95% CI) of incident stroke in relation to the baseline variables were computed by proportional hazards regression. First, continuous hemostatic variables were used to compute standardized RRs (ie, per 1 SD increment). Hemostatic variable distributions were also divided into fourths, and proportional hazards regression was used to determine RRs (hazard rate ratios) and 95% CIs for the second, third, and highest fourth, with the lowest fourth used as the reference, and the linear trend across categories was tested by inclusion of a variable with values of 1, 2, 3, or 4 to designate the successive categories. The multivariable models adjusted initially for age (continuous), sex, race (black, white), and ARIC community; then sequentially for systolic blood pressure (continuous) and antihypertensive medications (yes/no), diabetes (yes/no), smoking (former, current, never, and pack-years), HDL cholesterol and LDL cholesterol (both continuous), waist-to-hip ratio (continuous), and education (<high school, high school, >high school).

### Results

In a previous report, we noted correlations among the hemostasis variables: factor VIIIc with von Willebrand factor (Pearson $r=0.71$); factor VIIIc and von Willebrand factor with aPTT (Pearson $r=-0.31$ and $-0.46$); factor VIIc and von Willebrand factor with fibrinogen ($r=0.26$ and 0.29); WBC count with fibrinogen ($r=0.29$); WBC with platelet count ($r=0.24$); and factor VIIc with protein C ($r=0.40$).

Over the median of 7.2 years of follow-up, there were 94 incident ischemic strokes in men and 97 in women; there were 88 in blacks and 103 in whites. These latter numbers correspond to rates per 1000 person-years of 3.6 in blacks and 1.5 in whites. The age-, sex-, race-, and community-adjusted baseline mean values of fibrinogen, factor VIIc, factor VIIIc, von Willebrand factor, and WBC count were higher ($P<0.05$) for those who experienced an ischemic stroke than for those who did not (Table 1). The RRs of ischemic stroke per SD increment for these variables ranged from 1.19 to 1.36. There was little evidence of an association for protein C, AT-III, aPTT, and platelet count, so they are not presented further.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Stroke</th>
<th>No Stroke</th>
<th>$P$</th>
<th>RR per SD*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>324</td>
<td>302</td>
<td>&lt;0.0001</td>
<td>1.34</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>Factor VIIIc, %</td>
<td>124</td>
<td>119</td>
<td>0.02</td>
<td>1.19</td>
<td>1.0–1.4</td>
</tr>
<tr>
<td>Factor VIIc, %</td>
<td>144</td>
<td>131</td>
<td>&lt;0.0001</td>
<td>1.34</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>von Willebrand factor, %</td>
<td>136</td>
<td>117</td>
<td>&lt;0.0001</td>
<td>1.36</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>Protein C, $\mu$g/mL</td>
<td>3.17</td>
<td>3.18</td>
<td>0.82</td>
<td>0.99</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>AT III, %</td>
<td>112</td>
<td>111</td>
<td>0.57</td>
<td>1.07</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>aPTT, s</td>
<td>28.7</td>
<td>29.1</td>
<td>0.07</td>
<td>0.86</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>Platelet count, $10^3$ cells/mm$^3$</td>
<td>265</td>
<td>259</td>
<td>0.22</td>
<td>1.07</td>
<td>1.0–1.2</td>
</tr>
<tr>
<td>WBC, $10^3$ cells/mm$^3$</td>
<td>6.78</td>
<td>6.08</td>
<td>&lt;0.0001</td>
<td>1.26</td>
<td>1.2–1.4</td>
</tr>
</tbody>
</table>

*Approximate SDs: fibrinogen, 65 mg/dL; factor VIIc, 29%; factor VIIIc, 39%; von Willebrand factor, 48%; protein C, 0.62 $\mu$g/mL; AT III, 22%; aPTT, 3 seconds; platelet count, 74,000 cells/mm$^3$; WBC, 1900 cells/mm$^3$. 

Folsom et al Hemostatic Factors and Ischemic Stroke 737

Downloaded from http://circ.ahajournals.org/ by guest on August 31, 2017

Objectives: To evaluate the relationship between multiple hemostatic factors and incident ischemic stroke.

Methods: The relationship between baseline laboratory measures of coagulation and fibrinolysis and incident stroke was evaluated in the Atherosclerosis Risk in Communities (ARIC) Study of black and white adults (n=15,792) aged 45–64 years. Incident ischemic stroke was defined as a nontraumatic ischemic stroke on neuroimaging and/or death related to a neurologic deficit of $<24$ hours duration. Participants were followed for 6–9 years. Relative risks (RR) and 95% confidence intervals (CI) were computed by proportional hazards regression. First, continuous hemostatic variables were used to compute standardized RRs (ie, per 1 SD increment). Hemostatic variable distributions were also divided into fourths, and proportional hazards regression was used to determine RRs (hazard rate ratios) and 95% CIs for the second, third, and highest fourth, with the lowest fourth used as the reference, and the linear trend across categories was tested by inclusion of a variable with values of 1, 2, 3, or 4 to designate the successive categories. The multivariable models adjusted initially for age (continuous), sex, race (black, white), and ARIC community; then sequentially for systolic blood pressure (continuous) and antihypertensive medications (yes/no), diabetes (yes/no), smoking (former, current, never, and pack-years), HDL cholesterol and LDL cholesterol (both continuous), waist-to-hip ratio (continuous), and education (<high school, high school, >high school).

Results: In a previous report, we noted correlations among the hemostasis variables: factor VIIIc with von Willebrand factor (Pearson $r=0.71$); factor VIIIc and von Willebrand factor with aPTT (Pearson $r=-0.31$ and $-0.46$); factor VIIc and von Willebrand factor with fibrinogen ($r=0.26$ and 0.29); WBC count with fibrinogen ($r=0.29$); WBC with platelet count ($r=0.24$); and factor VIIc with protein C ($r=0.40$).

Over the median of 7.2 years of follow-up, there were 94 incident ischemic strokes in men and 97 in women; there were 88 in blacks and 103 in whites. These latter numbers correspond to rates per 1000 person-years of 3.6 in blacks and 1.5 in whites. The age-, sex-, race-, and community-adjusted baseline mean values of fibrinogen, factor VIIc, factor VIIIc, von Willebrand factor, and WBC count were higher ($P<0.05$) for those who experienced an ischemic stroke than for those who did not (Table 1). The RRs of ischemic stroke per SD increment for these variables ranged from 1.19 to 1.36. There was little evidence of an association for protein C, AT-III, aPTT, and platelet count, so they are not presented further.

When the standardized RRs (Table 1) were multivariately adjusted (Table 2), the RRs for fibrinogen, factor VIIc, von Willebrand factor, and WBC count decreased to 1.13 to 1.26 but were still statistically significant ($P<0.05$). However, factor VIIc (RR=1.03) was no longer significant. There was no obvious difference in the association of incident ischemic stroke with these hemostasis variables between men and
women, blacks and whites, hypertensives and nonhypertensives (Table 2), or current smokers and nonsmokers (not shown) or between participants with carotid intima-media thickness above versus below the median (not shown). In the multivariable model, protein C proved to be weakly inversely associated with incident ischemic stroke, with a standardized RR of 0.89 (Table 2).

Because several of these factors are known to be interrelated, another multivariable model was run including von Willebrand factor, factor VIIIc, fibrinogen, WBC count, and protein C adjusted for the same covariates as in Table 2. In this simultaneous model, only von Willebrand factor (RR per SD = 1.22, 95% CI = 1.03 to 1.44) remained statistically significantly associated with ischemic stroke incidence.

As Table 3 shows, from the lowest to the highest fourths, the adjusted RR of stroke rose 1.93-fold and 1.71-fold for factor VIIIc and von Willebrand factor, respectively. It rose 1.26-fold for fibrinogen and 1.50-fold for WBC. The RR for the highest versus lowest fourth of protein C was 0.65. Although several of the associations depicted in Table 3 appeared to be nonlinear, quadratic terms in the continuous variable models proved to be not statistically significant.

For comparison, in the Figure we present RRs for incident ischemic stroke versus incident CHD in the ARIC cohort. In general, fibrinogen and WBC were more strongly associated with CHD, whereas von Willebrand factor, factor VIIIc, and protein C were more strongly associated with stroke, although the confidence limits for both end points consistently overlapped.

**Discussion**

The ARIC Study assessed whether levels of several markers of hemostatic function or inflammation in middle-aged adults free of cardiovascular disease predict the incidence of ischemic stroke during an average of 7.2 years of follow-up. Ischemic stroke incidence was positively and moderately strongly associated with factor VIIIc and von Willebrand factor and was positively and more weakly associated with WBC count and fibrinogen. There was a negative but statistically nonsignificant association with protein C after adjustment for other risk factors. Ischemic stroke was not independently associated with aPTT, factor VIIc, AT-III, or platelet count, as was also true for CHD incidence in the ARIC cohort.

The most novel findings of this study were the associations for von Willebrand factor, factor VIII, which were somewhat stronger for ischemic stroke than for CHD incidence in ARIC (Figure). ARIC participants in the upper fourth of von Willebrand factor values had a 1.7-fold higher

### Table 2. Adjusted* RRs per SD† and 95% CI for Incident Ischemic Stroke in Relation to Hemostasis Variables, ARIC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Race</th>
<th>Sex</th>
<th>Hypertension Status‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Blacks</td>
<td>Whites</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.13</td>
<td>1.16</td>
<td>1.07</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.99–1.30</td>
<td>0.97–1.38</td>
<td>0.87–1.31</td>
</tr>
<tr>
<td>Factor VIIc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.03</td>
<td>1.10</td>
<td>0.96</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.88–1.21</td>
<td>0.88–1.36</td>
<td>0.76–1.22</td>
</tr>
<tr>
<td>Factor VIIIc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.20</td>
<td>1.21</td>
<td>1.12</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.05–1.37</td>
<td>1.04–1.41</td>
<td>0.88–1.41</td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.26</td>
<td>1.30</td>
<td>1.18</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.12–1.43</td>
<td>1.12–1.51</td>
<td>0.97–1.45</td>
</tr>
<tr>
<td>Protein C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>0.89</td>
<td>0.91</td>
<td>0.89</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.75–1.00</td>
<td>0.71–1.17</td>
<td>0.70–1.12</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1.18</td>
<td>1.19</td>
<td>1.18</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.04–1.34</td>
<td>1.01–1.41</td>
<td>0.97–1.44</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, community, race (except where stratified), systolic blood pressure and antihypertensive medication status (except where stratified), left ventricular hypertrophy, diabetes, HDL cholesterol, LDL cholesterol, waist-to-hip ratio, education, and smoking status and amount. Number of cases = 166 total; 73 blacks, 93 whites; 81 men, 85 women; 110 hypertensive, 56 not hypertensive.

†See Table 1 for approximate SD increments.

‡Hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or taking antihypertensive medication.
risk of developing ischemic stroke than did those in the lowest fourth. Other prospective studies have linked von Willebrand factor or factor VIIIc with CHD incidence or recurrence and with mortality after stroke. However, only the Edinburgh Artery Study has prospectively examined von Willebrand factor and stroke incidence.11 The Edinburgh study, however, had only 45 stroke cases, and although the median von Willebrand factor concentration was 20% higher in stroke cases than in those remaining free of cardiovascular disease (similar to our difference in means), the difference was not statistically significant.

Plasma von Willebrand factor, which is synthesized primarily by vascular endothelial cells, has 3 major activities: (1) mediating platelet adhesion to damaged arterial walls, (2) mediating platelet aggregation at high shear stress, and (3) binding and stabilizing factor VIIIc. Vascular injury or stress increases von Willebrand factor synthesis, so an elevated plasma von Willebrand factor level may reflect excessive endothelial stress. Increased von Willebrand factor levels therefore may augment platelet adhesion, enhance shear stress–induced platelet aggregation, and increase plasma factor VIIIc levels, thereby increasing risk of cerebral thrombosis when atherosclerotic plaques rupture.

To the best of our knowledge, ARIC is the first study to report a positive association of plasma VIIIc levels with ischemic stroke incidence. Plasma factor VIIIc levels are closely related to von Willebrand factor levels (r=0.71 in ARIC), because free factor VIII is unstable, and its stability is greatly increased by binding to von Willebrand factor. It is unknown whether increased plasma VIIIc levels are simply...
due to high levels of von Willebrand factor or to other causes and whether an increased level of factor VIIIc enhances thrombus formation. Factor VIII serves as a cofactor for IXa. On activated platelet surfaces and in the presence of calcium, factor IXa and VIIIa catalyze the conversion of factor X to Xa, which in turn catalyzes the formation of thrombin. It is conceivable that an increased plasma VIIIc level may accelerate thrombin generation and consequently increase fibrin and platelet aggregate formation.

The positive associations of fibrinogen and WBC count with ischemic stroke were weaker than for CHD in this cohort. The fibrinogen association with ischemic stroke was also weaker than in other prospective studies of stroke.\(^2^,\(^3^,\(^1^1\)\) Fibrinogen is an acute-phase reactant, whose plasma level is increased by inflammation. Recent prospective studies have shown that the level of C-reactive protein, another major acute-phase reactant and a marker of inflammation, is a risk factor for CHD\(^8^–\(^1^0\)\) and stroke.\(^8^,\(^9\)\) Insofar as fibrinogen and WBC count reflect inflammation, our finding of a weaker association of plasma fibrinogen levels and WBC count with ischemic stroke than CHD suggests that inflammation may be less important in the pathogenesis of ischemic stroke than CHD. Nevertheless, there are direct mechanisms by which elevated fibrinogen could increase stroke risk. Fibrinogen mediates platelet aggregation, is a major contributor to blood viscosity and fibrin thrombi, and may be involved in smooth muscle migration and proliferation.\(^1\)

WBC count was associated with ischemic stroke in a previous prospective study of atomic bomb survivors, but potential confounding by smoking was not explored.\(^1^3\) In a prospective study of US adults, Gillum found WBC count to be weakly associated with stroke, but not after adjustment for smoking.\(^1^4\) Oxidant-generating stimuli (eg, smoking) raise the WBC count, and WBC counts contribute to blood viscosity, inflammation, and vascular injury through endothelial adhesion and by release of oxygen radicals and proteolytic enzymes.\(^7\)

We found the associations of hemostatic factors with ischemic stroke incidence to be similar in blacks and whites (Table 2). Yet, compared with whites, blacks in ARIC have 15% to 20% higher von Willebrand factor and factor VIIIc levels, 3% higher fibrinogen levels, but 10% to 15% lower WBC counts. Whether differences in these factors could explain racial differences in stroke is unclear. Statistical adjustment for von Willebrand factor or factor VIIIc tended to reduce the association between race and ischemic stroke, whereas adjustment for WBC count strengthened it (data not shown).

The negative association of plasma protein C level with ischemic stroke, although not statistically significant with this sample size, contrasts with the lack of any association between protein C and CHD in this cohort.\(^5\) Plasma protein C exists as a zymogen, and after activation by thrombomodulin-bound thrombin, activated protein C in the presence of protein S degrades factor Va and VIIIa, thereby inhibiting the coagulation reaction. Although a reduced protein C level in hereditary protein C deficiency is an established risk factor for venous thromboembolism, low protein C level has not been reported previously to be a prospective risk factor for arterial thrombosis. The
inverse association between protein C and ischemic stroke was apparent only after multivariable adjustment and therefore should be interpreted cautiously, especially in light of the protein C measurement variability.19

Although the Northwick Park Heart Study reported a strong positive association between factor VIIc and CHD mortality,1 several other studies have failed to replicate this.5,28,29 We know of no previous studies of factor VIIc and stroke incidence. Our findings do not suggest that factor VII plays a role in the pathogenesis of ischemic stroke.

Potential limitations of this study warrant consideration. ARIC made a single assessment of hemostatic factors, which may lead to misclassification of the habitual hemostatic factor levels of some individuals. Correction for measurement unreliability19 strengthens the standardized RR estimates shown in Table 1 (eg, fibrinogen to RR = 1.50, von Willebrand factor to RR = 1.57, and factor VIIc to RR = 1.41). We had no baseline measure of fibrinolytic capacity, although studies are planned on stored samples. Others have shown that impaired fibrinolytic capacity is a strong risk factor for stroke.11,30 The interpretation of the weaker associations of hemostatic factors with stroke after multivariable adjustment is complicated. The adjusting factors may be confounding variables, at least in part, but several stroke risk factors (eg, smoking) may also operate through hemostatic mechanisms. Thus, the true RRs probably lie between the minimally adjusted and fully adjusted values.

Taken together with previous evidence, our study suggests that to a modest degree, these markers of hemostatic function or inflammation can identify groups of people at increased risk of ischemic stroke. These factors also may play a pathophysiological role in stroke by enhancing atherosclerosis or thrombosis of the carotid or cerebral arteries, by reducing blood flow in the cerebral microvasculature, or by enhancing tissue injury from ischemic infarction. In the ARIC Study, fibrinogen was cross-sectionally associated with carotid intima-media thickness, but von Willebrand factor, factor VIIc, and protein C were not;11 this suggests that increased carotid atherosclerosis is not an important mechanism by which these factors increase risk of stroke.

Interestingly, aspirin is more efficacious in preventing myocardial infarction in men with high C-reactive protein values.8 Aspirin might also prevent ischemic stroke better in the setting of increased hemostatic factors. Nevertheless, none of the RRs observed here was as large as the >2-fold elevated RRs for potentially modifiable major stroke risk factors, such as hypertension, diabetes, and cigarette smoking. Thus, the value of screening for and modifying these new risk markers as an additional means to prevent stroke clearly remains to be established.

Acknowledgments

The ARIC Study was funded by contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute.

References


Prospective Study of Markers of Hemostatic Function With Risk of Ischemic Stroke
Aaron R. Folsom, Wayne D. Rosamond, Eyal Shahar, Lawton S. Cooper, Nena Aleksic, F.
Javier Nieto, Mandy L. Rasmussen and Kenneth K. Wu
for the Atherosclerosis Risk in Communities (ARIC) Study Investigators

Circulation. 1999;100:736-742
doi: 10.1161/01.CIR.100.7.736

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/100/7/736