Fibrinogen and the Albumin-Globulin Ratio in Recurrent Stroke

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Background and Purpose: In following patients initially recruited for a cross-sectional study of blood viscosity in ischemic cerebrovascular disease, it was noted that those having a low albumin-globulin ratio appeared to experience the majority of subsequent vascular events. Accordingly, a prospective study in which subjects were assigned to a high or low albumin-globulin cohort was undertaken to examine the relation between a low albumin-globulin ratio, the presence of clinical risk factors for stroke, and the occurrence of subsequent stroke, myocardial infarction, or vascular death.

Methods: Three groups of subjects were followed for an average of 1.5±0.8 years to ascertain vascular end points. Group 1 consisted of 126 patients with acute ischemic stroke; group 2 included 109 subjects matched with group 1 for age, medications, and recognized clinical risk factors for stroke; and group 3 was composed of 84 healthy volunteers, matched for age with groups 1 and 2. The median albumin-globulin ratio for group 1 at enrollment, 1.45, was used to dichotomize patients into two cohorts: all subjects with an albumin-globulin ratio of 1.45 or less were assigned to the “low” albumin-globulin cohort; those whose ratio was greater than 1.45 were assigned to the “high” albumin-globulin cohort. The occurrence of vascular end points was verified during subsequent hospitalizations and outpatient clinic visits and by telephone interviews of patients and providers.

Results: A total of 51 vascular events occurred, including 39 in group 1, 8 in group 2, and 4 in group 3. Subjects in either group 1 or 2 who were in the low albumin-globulin cohort had at least double the risk for a subsequent vascular event compared with their counterparts in the high albumin-globulin cohort (P<.01 and P<.03, respectively). In comparison with the high albumin-globulin cohort, significantly more patients in the low albumin-globulin cohort in group 1 had a history of prior stroke (P<.03). When groups 1 and 2 were combined, both a low albumin-globulin ratio and diabetes had a significant independent association with increased risk for subsequent vascular events in a Cox proportional-hazards model (P<.01 and P<.03, respectively).

Conclusions: The results of this study indicate that significantly increased risk for subsequent vascular events in stroke patients and in subjects with clinical risk factors for stroke is associated with a shift in the concentrations of blood proteins to a prothrombotic environment characterized by lower levels of albumin and an increased concentration of globulins and fibrinogen. (Stroke 1993;24:1133-1139)

Key Words • albumins • fibrinogen • globulins • stroke outcome

Up to 30% of subjects suffering cerebral infarction experience recurrent stroke, myocardial infarction (MI), or vascular death within 2 years of the initial event.1 Both prospective and retrospective studies indicate that a panoply of factors, including age, sex, stroke subtype, elevated blood glucose levels, and a prior history of diabetes mellitus or hypertension, are related to poor outcome or stroke recurrence.2-5 Prior stroke, transient ischemic attack of the brain (TIA), carotid stenosis, and atrial fibrillation are among the most important risk factors for stroke and stroke recurrence in some populations. In addition, certain viscous abnormalities of blood, particularly elevated hematocrit and fibrinogen levels, are recognized risk factors for stroke and may also be important in recurrent vascular events.6 Specifically, an increase in erythrocyte aggregability, which is correlated with both a lower albumin-globulin (A-G) ratio and higher levels of plasma fibrinogen, has been found in acute as well as chronic occlusive cerebrovascular disease.7 In following stroke patients recruited for a study of blood viscosity factors we noted that acute stroke patients with a low A-G ratio appeared to experience a preponderance of recurrent vascular events. Accordingly, we prospectively examined the relation between a low A-G ratio and the occurrence of subsequent stroke, MI, or vascular death to gain insight into the mechanisms underlying the linkage of various clinical risk factors for stroke with recurrent ischemic cerebrovascular disease.

Subjects and Methods

During a 3-year period, patients with acute stroke (group 1) or with risk factors for stroke (group 2) together with healthy volunteers (group 3) were re-
recruited from the hospitals and clinics of the Portland Veterans Affairs Medical Center and Oregon Health Sciences University (OHSU) into a comparative study of rheological abnormalities in acute stroke. Subjects with hemorrhagic stroke, vasculitis, cancer, or severe debilitating systemic illness were excluded. Computed brain tomographic exams (CT) or magnetic resonance imaging of the brain were obtained on 98% of the patients in group 1. Of these, 88% had scans consistent with the diagnosis of cerebrovascular disease; the remainder demonstrated nonspecific abnormalities. Classification of the probable stroke mechanism was made using standardized criteria similar to those of the National Institute of Neurological and Communicative Disorders and Stroke National Stroke Data Bank.\textsuperscript{4} Atheroembolism was the probable mechanism for cerebrovascular symptoms in 54% of cases, lacunar infarction in 25%, cardioembolism in 12%, and 9% were attributable to multiple possibilities or unidentified factors. Subjects who reported prior TIA or stroke were eligible for inclusion as a subgroup within group 1.

Group 2 served as a “positive” control to estimate the contribution of medications and stroke risk factors to the viscous abnormalities found in subjects with acute stroke. For inclusion in this group patients had at least one well-defined stroke risk factor such as hypertension, diabetes mellitus, tobacco use, documented atherosclerosis, or cardiac disease linked to increased risk for stroke, such as atrial fibrillation. Subjects with a history of stroke or TIA were eligible provided they had not experienced cerebrovascular symptoms for a minimum of 6 months before enrollment. The majority of subjects had at least two, and more than 25% had at least three recognized risk factors for stroke, the most prevalent being hypertension and cardiac disease. Forty-three percent of patients in this group had received a CT scan of the brain. Of those scanned, 30% had CT abnormalities, a figure consistent with a clinical history of prior stroke or TIA (43%) and/or prior carotid endarterectomy (20%) recorded for subjects in this group.

Group 3, consisting of healthy individuals with no prior history of treatment for chronic disease or use of prescription medications, controlled for the contribution of medications and stroke risk factors to the viscosity values for group 2. Volunteers denied a prior history of cerebrovascular or cardiovascular disease or the presence of risk factors for stroke, were taking no prescription medications, and had never smoked or were exsmokers. Volunteers were enrolled only after their complete blood count (CBC) and serum chemistry values were found to be within the normal range for the laboratory at OHSU. Subjects in all groups were classified as exsmokers if they had abstained from smoking for at least 6 months before enrollment. The composition of these groups has been described previously and is summarized in Table 1.\textsuperscript{8}

All patients gave written informed consent to participate and undergo phlebotomy by neurology staff assigned to this study. For acute stroke subjects the mean ±SD time interval between the onset of stroke and laboratory measurements was 4.2 ± 3.5 days. Nonfusing blood samples were drawn usually between 8 AM and 11 AM from an antecubital vein and anticoagulated with either the disodium salt of ethylenediaminetetraacetic acid for CBC or diluted 9:1 (vol/vol) in a solution of 3.8% sodium citrate for fibrinogen measurement. Samples were also collected without anticoagulation for serum chemistry determinations. Measurements were performed as follows by laboratories of the Clinical Pathology Department at OHSU: CBC was determined using a Coulter Electronics SIV Plus Analyzer (Coulter Corp, Hialeah, Fla), serum chemistries by a Hitachi 737 Analyzer (Scientific Instruments, Mountain View, Calif), and fibrinogen by a modified thrombin clotting time using Dade reagents (AHS del Caribe, Inc, Aguada, Puerto Rico). For further analysis of blood protein changes both globulin and the A-G ratio were calculated from total protein and albumin values: Globulin = Total Protein – Albumin, and A-G Ratio = Albumin/Globulin. In the context of this report globulin refers to all serum proteins other than albumin. Subjects in all groups were assigned to a “low A-G” or “high A-G” (ratio) cohort after their laboratory values at enrollment into the study had been determined. Subjects in the low A-G cohort had A-G ratios that were 1.45 or less, the median value for the A-G ratio in group 1.

Follow-up information about new cerebrovascular and related events was obtained for the majority of individuals recruited, and subjects lost to follow-up (20/339) did not differ significantly with respect to age or other important risk factors. Complete blood protein profiles at enrollment and follow-up information were obtained on 126 of 133 subjects (95%) who were initially recruited for group 1, 109 of 115 (95%) for group 2, and 84 of 91 (92%) for group 3. Approximately 30% of subjects in groups 1 and 2 were assessed on a regular basis at neurological clinics at the two named institutions. Another 20% of subjects in these groups were hospitalized within 2 years of initial recruitment for either recurrent vascular events or other medical problems. The remaining patients or a member of their immediate family and all volunteers were interviewed by phone by a neurological nurse practitioner at approximately 6- to 9-month intervals after enrollment. The primary end points for analysis were recurrent stroke, MI, or vascular death. Subjects who suffered TIA were counted in the “nonevent” group for primary analysis. Death was considered to be “vascular” if a subject died within hours of onset of cardiac symptoms. Deaths due to nonvascular causes such as cancer were recorded but excluded from the primary analysis. Whenever a recurrent stroke, TIA, MI, or vascular death was reported,

<table>
<thead>
<tr>
<th>Table 1. Population Followed for Recurrent Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age at entry (y; mean±SD)</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Prior stroke</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Smoking history</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Former</td>
</tr>
<tr>
<td>Never</td>
</tr>
</tbody>
</table>

Values (except age) are percentages.
confirmation was obtained by review of the medical record or phone interview with the primary medical provider. Subjects were censored after the occurrence of the first new event or death due to nonvascular cause.

Summary statistics were calculated for each continuous variable; frequency data were summarized by expressing the variable as a percentage. Statistical significance of differences between two groups was assessed with Student's t test for continuous variables and by Fisher's Exact Test for frequencies. Median values for subjects with acute ischemic stroke (group 1) were used to dichotomize values for both the A-G ratio and fibrinogen for the calculation of risk ratios. Univariate risk ratios and their significance as well as Cox proportional-hazards models were estimated using stata, version 3.0.10 Kaplan-Meier estimates of survival curves and the Mantel-Cox estimate of the significance of differences between curves were determined with bmdp-1l.10

Results

The distribution of risk factors for stroke in at-risk and stroke patients was comparable, as shown in Table 1. Medication usage was also similar for these two groups, with 73% of group 1 and 70% of group 2 receiving three or more medications. Aspirin and related antiaggregatory medications were being taken by 69% of group 1 and 59% of group 2, as well as by 25% of the age-matched control subjects, group 3. The average (±SD) length of follow-up for all subjects was 1.5±0.8 years, ranging from 1.3±0.8 in the stroke group to 1.9±0.8 in the control group. During this interval 51 primary end point events were identified among subjects from the three groups, with nearly 80% occurring in group 1, as shown in Table 2. New strokes or vascular deaths were the predominant end points in both groups 1 and 2, with only 1 MI occurring in each group. In contrast, all 4 end points in the nominally healthy age-matched control group were MIs, 1 of which resulted in vascular death. Seventy-six percent of all end points (39 cases) were confirmed by review of the relevant medical records, and 24% (12 cases) were ascertained by telephone contact. The 12 primary end points identified by phone contact included 6 strokes, 3 vascular deaths, and 3 acute Mls. Two of the 3 subjects with acute MI were hospitalized elsewhere and underwent either emergency coronary angioplasty or coronary artery bypass grafting. The 6 subjects with stroke were admitted to other hospitals or nursing homes with a diagnosis of stroke. In the 3 cases of vascular death, family members were informed by their doctor that the probable cause of death was of a vascular nature, ie, heart attack, heart rhythm disturbance, or stroke.

The majority of primary vascular end points occurred in the stroke group, whose annualized rate for vascular events approached 24%, compared with 4.4% in the at-risk group and 2.5% in the control group. The average time interval between an indexing cerebral infarction and a subsequent event was 6.2 months for vascular death, 9.5 months for recurrent stroke, and 12.0 months for myocardial infarction. In addition to the 51 primary end point events there were among all groups an additional 9 nonvascular deaths, 6 of which were related to cancer, 2 to automobile accidents, and 1 to congestive heart failure. A further 20 individuals, 11 in group 1 and 9 in group 2, suffered TIA during the follow-up.

As shown in Table 3, approximately 50% of group 1, 25% of group 2, and 11% of group 3 subjects constituted the low A-G cohort. Within each group the age, sex, distribution of subjects with hypertension, and current

### Table 2. Distribution of Recurrent Vascular Events

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low*</td>
<td>High†</td>
<td>Low*</td>
</tr>
<tr>
<td>New stroke</td>
<td>15</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Vascular death</td>
<td>11</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

*Albumin-globulin (A-G) ratio ≤1.45; †A-G ratio >1.45.

### Table 3. Distribution of Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low*</td>
<td>High†</td>
<td>Low*</td>
</tr>
<tr>
<td>Age at enrollment (y; mean±SD)</td>
<td>65.4±12.0</td>
<td>65.0±10.9</td>
<td>64.2±11.4</td>
</tr>
<tr>
<td>Women</td>
<td>12</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>History of prior stroke</td>
<td>53†</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>52</td>
<td>51</td>
<td>64‡</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>46</td>
<td>53</td>
<td>31</td>
</tr>
</tbody>
</table>

Values (except age) are percentages.

*Albumin-globulin (A-G) ratio ≤1.45; †A-G ratio >1.45.

‡P<.03, §P<.04 by Fisher's Exact Test to compare low vs high A-G ratio cohort within groups.
tobacco users did not differ significantly between cohorts. On the other hand, a history of prior stroke was more likely in the low A-G cohort in group 1 (P<.03), whereas a history of ischemic heart disease was more prevalent in the low A-G cohort in group 2 (P<.04). Diabetes was more common in the low A-G cohort in both groups 1 and 2, but the difference was not significant. Table 4 shows laboratory values at enrollment for the high and low A-G cohorts in each group of subjects. Not only is albumin significantly lower, but globulins are also significantly higher in the low A-G cohort of all three groups. Fibrinogen is also higher in the low A-G cohort of each group, but the significant difference between fibrinogen levels in low vs high A-G cohorts declines progressively from group 1 to group 3. Finally, even though diabetes was more prevalent in the low A-G cohort of both groups 1 and 2 (compare Table 3), the nonfasting glucose values did not differ significantly between high and low A-G cohorts in either group.

Table 5 summarizes the univariate estimates of relative risk (RR) for a new stroke, MI, or vascular death for group 1, group 2, and for groups 1 and 2 combined. Both stroke and at-risk patients in the low A-G ratio cohort had a significantly higher risk for a new event (P<.01 and P<.03, respectively) than their counterparts in the high A-G ratio cohort. When data were analyzed by assigning subjects to a high or low fibrinogen cohort based on the median value at enrollment for fibrinogen (397 mg/dL) in group 1, those in the high fibrinogen cohort in group 1, but not in group 2, were also at increased risk. Conversely, there was a trend toward increased risk for a vascular event associated with ischemic heart disease in group 2 (P<.06) but not in group 1. For stroke and at-risk patients combined, those in the low A-G cohort were at higher risk for a vascular event (RR=3.2, P<.0001) than those in the high fibrinogen cohort (RR=2.0, P<.02). Likewise, for the combined groups the risk of a vascular end point was also increased for those with either a history of prior stroke (RR=1.9, P<.02) or diabetes (RR=2.1, P<.01). A Cox proportional-hazards model was used to determine which variables in Table 5 were independently associ-

### Table 4. Laboratory Values Measured at Enrollment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low* (n=65)</td>
<td>High† (n=61)</td>
<td>Low* (n=29)</td>
</tr>
<tr>
<td>A/G ratio</td>
<td>1.23±0.17‡</td>
<td>1.72±0.26‡</td>
<td>1.29±0.12‡</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.79±0.51†</td>
<td>4.26±0.33‡</td>
<td>4.13±0.42‡</td>
</tr>
<tr>
<td>Globulins (g/dL)</td>
<td>3.11±0.39‡</td>
<td>2.52±0.34‡</td>
<td>3.22±0.33‡</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>433±110†</td>
<td>376±71†</td>
<td>368±85§</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>153±74</td>
<td>148±77</td>
<td>139±75</td>
</tr>
</tbody>
</table>

Values are mean±SD.  
*Albumin-globulin (A-G) ratio ≤1.45; †A-G ratio >1.45.  
‡P<.0001, §P<.0003, ¶P<.0001, ¶¶P<.05, #P<.03 by Student’s two-tailed t test to compare laboratory values in low vs high A-G cohorts within groups.

### Table 5. Relative Risk for a Vascular Event (Univariate)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Groups 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low A-G ratio</td>
<td>2.1*</td>
<td>4.6</td>
<td>3.2</td>
</tr>
<tr>
<td>(≤1.45)</td>
<td>1.2-3.8†</td>
<td>1.2-18.0</td>
<td>1.8-5.6</td>
</tr>
<tr>
<td>&lt;.01†</td>
<td>&lt;.03</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>High fibrinogen</td>
<td>1.9</td>
<td>0.4</td>
<td>2.0</td>
</tr>
<tr>
<td>(≥397 mg/dL)</td>
<td>1.1-3.3</td>
<td>0.05-2.8</td>
<td>1.2-3.3</td>
</tr>
<tr>
<td>&lt;.03</td>
<td>NS</td>
<td>&lt;.02</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.6</td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td>1.0-2.8</td>
<td>0.08-14.1</td>
<td>1.2-3.5</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>History of prior stroke</td>
<td>1.6</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>1.0-2.7</td>
<td>0.4-5.5</td>
<td>1.1-3.1</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt;.02</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.3</td>
<td>6.3</td>
<td>1.6</td>
</tr>
<tr>
<td>0.8-2.2</td>
<td>0.8-51.0</td>
<td>1.0-2.8</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>&lt;.06</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.1</td>
<td>2.1</td>
<td>1.2</td>
</tr>
<tr>
<td>0.6-1.8</td>
<td>0.5-10.0</td>
<td>0.7-2.0</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

A-G, albumin-globulin; NS, not significant.  
*Relative risk; 95% confidence interval; †P determined by Fisher’s Exact Test.
beamer et al. fibrinogen, a-g ratio, and recurrent stroke

line graph in which cumulative proportion of stroke patients free of recurrent stroke, myocardial infarction, and vascular death are grouped into low (≤1.45) or high (>1.45) albumin-globulin (a-g) ratio cohorts. six subjects who had an event ≤30 days after enrollment were excluded from analysis. vertical axis is drawn to a logarithmic scale. the difference between cohorts for event-free survival is significant (p < .01, mantel-cox).

ated with increased risk for vascular end points. none of these factors remained independently significant in group 1 alone, but when groups 1 and 2 were combined, both low a-g ratio (hazard ratio [hr] = 2.4, 95% confidence interval [ci] = 1.2 to 4.7, p < .01) and the presence of diabetes (hr = 2.1, 95% ci = 1.1 to 4.1, p < .03) were independently significant.

the figure shows the cumulative proportion of patients with acute ischemic stroke who survived without a new vascular end point. the curves compare event-free survival between the low and high a-g ratio cohorts in group 1. we excluded from survival analysis six patients who suffered a primary end point 30 days or less after enrollment to reflect the conservative viewpoint that these events might not be clearly separable from the original indexing infarction. laboratory values in these six subjects, however, did not differ significantly from those of other stroke patients with recurrent events, ie, fibrinogen averaged 458 ± 102 mg/dl, albumin, 3.97 ± 0.58 g/dl, and the a-g ratio, 1.31 ± 0.18. even with these six subjects excluded, event-free survival for the low a-g ratio cohort was significantly less than that for the high a-g ratio cohort in group 1 (p < .01, mantel-cox). event-free survival calculated for groups 1 and 2 combined, as well as for groups 1, 2, and 3 combined, was also significantly less for subjects in the low a-g ratio cohort (both p < .00001, mantel-cox, curves not shown).

discussion

the results of this study indicate that stroke patients and subjects with clinical risk factors for stroke who have a low a-g ratio (1.45 or less) have a significantly increased risk for subsequent stroke, mi, or vascular death. the low a-g ratio in these individuals reflects not only a decrease in albumin concentration but also an increase in serum globulins and is inversely related to plasma fibrinogen concentration (r = −.44). thus, the risk for vascular events in these patients appears to be associated with an overall shift in the pattern of blood proteins characterized by both higher fibrinogen and globulin levels and a lower concentration of albumin. in a recent retrospective study of 625 stroke survivors, recurrent stroke was strongly associated with elevated levels of plasma fibrinogen.11 although resch and colleagues emphasized the pivotal role of hyperfibrinogenemia as a cause of increased risk of recurrent stroke, the data in our report indicate that a low a-g ratio (1.45 or less) is equally prognostic for future vascular events. in the present study stroke patients in the low a-g cohort had a twofold higher risk for a recurrent vascular event than those in the high a-g cohort (p < .02) and were at a slightly higher risk (rr = 2.1, p < .01) for a recurrent vascular event than stroke patients in the high fibrinogen cohort (rr = 1.9, p < .03). likewise, at-risk patients in the low a-g cohort, but not those in the high fibrinogen cohort, were also at greater risk for a vascular end point (rr = 4.6, p < .03).

perhaps because of the small sample size for group 1 (n = 126), no blood protein abnormality or clinical risk factor was independently associated with an increased risk for a recurrent vascular event in stroke patients when analyzed by a cox proportional-hazards model. on the other hand, when stroke patients were combined with the at-risk group or with both groups 2 and 3, a low a-g ratio (1.45 or less), but not high fibrinogen (397 mg/dl or more), was independently associated with a higher risk for a vascular end point (cox proportional-hazards models, both p < .01). the median a-g ratio for patients in group 1, 1.45, was used to dichotomize subjects in all three groups into high and low a-g ratio cohorts for analysis. therefore, the value for the a-g ratio associated with greater risk for recurrent vascular disease might vary according to the population studied, although the acute stroke patients followed in this study appear comparable to those followed for recurrent events by others. for example, the annualized event rates of 12% for recurrent stroke and 25% for recurrent stroke, mi, and vascular death combined agree well with other reports.1412

diabetes was more common in the low a-g ratio cohort compared with the high a-g ratio cohort in both groups 1 and 2 (table 3), although nonfasting blood glucose levels did not differ between cohorts in either group. diabetes was also the only established clinical risk factor for stroke to be independently associated with a significantly higher risk for a vascular end point in a cox proportional hazards model combining groups 1 and 2. these findings are consistent with the study of diabetic stroke patients by olsson and colleagues,13 which demonstrated an increased risk of stroke recurrence because of the amplification of stroke risk factors by diabetes. on the other hand, a history of prior stroke, although present in 53% of the low a-g cohort of group 1 and 43% of the low a-g cohort in group 2, was not independently associated with increased risk for vascular end points in the cox multivariate model. the relatively small sample size and brief duration of follow-up limit our ability to examine further the potential
relations between a low A-G ratio and clinical risk factors for recurrent vascular disease, particularly diabetes and a history of prior stroke. A larger prospective investigation including more patients with first-ever stroke could help to provide answers to some of the questions raised by these data.

Although the mechanisms responsible for the low A-G ratio and elevated plasma fibrinogen remain unclear, one possibility is that a low A/G ratio is a marker for the severity of the pathophysiological changes related to chronic diseases, such as diabetes, ischemic heart disease, hypertension, or the sequelae of tobacco use. For example, a low A-G ratio could be the consequence of transcapillary albumin loss. Proteinuria, which can occur with microvascular renal disease, is associated with significant risk for cardiovascular events; in addition, microalbuminuria is increasingly recognized as a predictor of stroke and other cardiovascular events even in nondiabetic subjects. In this setting albuminuria reflects widespread vascular damage and therefore might be useful as an index of vascular risk. 

Elevated fibrinogen levels, a recognized risk factor for both stroke and MI, and a low A-G ratio were found in many at-risk patients as well as in acute stroke subjects in the present study.9,20 The concentration of fibrinogen and albumin, which are, respectively, positive and negative acute-phase reactants synthesized by the liver, is regulated by an interplay of cytokines including interleukins 1, 6, and 11 and transforming growth factor-β.21-25 Nevertheless, two serial studies of patients with acute cerebral infarction failed to find significant increases in C-reactive protein, the classic indicator of an acute-phase response, except in cases with preexisting bacterial infections.26,27 Therefore, the linkage of elevated fibrinogen and depressed A-G ratio in the at-risk as well as in the stroke population in the present study suggests that a chronic rather than acute shift in protein synthesis, which progresses with disease severity, is associated with an increased risk for recurrent vascular disease. The low event rate observed in group 3 is consistent with this interpretation. Only four control subjects experienced a vascular event, all of which were first-ever MIs (one fatal). The A-G ratios for these four individuals averaged 1.71±0.22, well above the 1.45 cutoff for the low A-G cohort.

Studies of rural Japanese have reported that an A-G ratio of less than 1.5, a value remarkably similar to that found in the present study, is prognostic for stroke.28,29 Data from a recent prospective British study also showed a marked increase in mortality rates with decreasing serum albumin concentrations, an association that persisted even after adjustment for other risk factors and exclusion of subjects who died during the first 5 years of follow-up.30 As an index of nutritional status, serum albumin is neither highly specific nor sensitive, owing to the large number of factors that may alter its metabolism and distribution.31 Protein malnutrition is therefore unlikely to be the principal cause of the lower A-G ratio in subjects with recurrent vascular events in the present study. Malnutrition in patients admitted to hospital with acute stroke appears to be most strongly associated with advanced age (74 years or older) and concurrent infections.32 In our study the 22 stroke subjects aged 74 years or older had an average (±SD) A-G ratio of 1.46±0.28, and only 7% of stroke subjects were being treated for infection at the time of laboratory testing. Likewise, since the age of subjects in the low and high A-G cohorts did not differ, any decline in albumin synthesis with aging would not have impacted the results reported here.33 Finally, it should be kept in mind, as shown in Table 4, that not only was albumin significantly lower, but globulins were also significantly higher in the low A-G ratio cohort among all three groups. The A-G ratio was actually more highly correlated with the globulin fraction (r = −.84) than with albumin (r = .61).

Regardless of the underlying cause, low serum albumin and elevated globulins combined with high levels of fibrinogen may carry an increased risk for recurrent thrombotic episodes because of alterations in hemostasis and blood viscosity. Several studies indicate that elevated blood viscosity, due in part to hyperfibrinogenemia, may be prolonged after stroke and thereby contribute to an increased risk for recurrent stroke.8,11,34 Serum globulins, elevated in patients in the low A-G cohort in the present study, can also exhibit a fibrinogen-like influence on blood viscosity, particularly under conditions of low flow favoring thrombosis.35 As a necessary cofactor for platelet aggregation, fibrinogen promotes both platelet and erythrocyte aggregation, as well as adhesion of these elements to the vascular endothelium, whereas albumin opposes the prothrombotic effects of fibrinogen.36 The increase in erythrocyte and platelet aggregability in a low-albumin, high-globulin, and high-fibrinogen environment may also amplify the prothrombotic changes in coagulation factors previously observed in stroke patients.34,36,39 Finally, since coagulation proteins are also synthesized in the liver, a low A-G ratio in some stroke patients may signal that overall hepatic synthesis is altered toward a pattern of protein production that favors a prothrombotic state.

Although recent attention has focused on the role of fibrinogen as a risk factor for stroke, the data presented here indicate that additional protein alterations, principally a decline in serum albumin and increase in serum globulin, are also associated with increased risk for subsequent vascular disease. The knowledge that a broader spectrum of blood protein changes than previously recognized is associated with increased risk for thrombotic episodes may both facilitate early identification of stroke patients at increased risk for recurrent events and also provide potential new avenues for prevention.

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