We conducted a prospective study of serial intravenous digital subtraction angiography to determine the relation of arterial disease risk factors and hemostatic variables with the presence of visible atheroma at the carotid bifurcation. Of the 492 patients with cerebrovascular disease or ischemic heart disease who entered the study, 354 had hematologic studies, including platelet aggregation in 230. Abnormal angiograms were associated with greater age, treated hypertension, current smoking, and lower hemoglobin levels but with higher uric acid, factor VIII, and fibrinogen concentrations. In patients presenting with isolated transient ischemic attacks, abnormal angiograms were also associated with higher levels of cholesterol and triglycerides. To study atheroma progression, the 230 patients with complete data at entry were recalled 2 years later. Repeat angiography in 209 patients showed progression of visible bifurcation disease in 13.4%. There was some evidence that progression was linked to higher age, hypertension, and more severe disease at entry, but further analysis was hampered by the small number of patients showing increased plaque size. The possible role of risk factors and hemostatic variables, especially fibrinogen, is discussed. Factors that did not correlate with progression of angiographically visible disease may also influence clinical end points by other mechanisms, such as thrombogenesis. (Stroke 1989;20:1466–1471)

Most clinical events in cerebrovascular disease and ischemic heart disease (IHD) appear to be due to thrombus formation related to atheromatous plaques in major arteries. Thus, there is evidence that myocardial infarction is usually due to thrombus formation or fissuring of a coronary plaque that was already causing a stenosis of at least 50–75%. When not due to cardiac embolism, strokes in the carotid territory can usually be attributed to thrombotic occlusion of a carotid stenosis of similar severity or to embolism into the middle cerebral artery of mural thrombus formed in the carotid artery or aorta.

In the search for precursors of atheroma and thrombotic events, various risk factors have been identified from epidemiologic studies. It is clear, however, that even the combined effect of well-recognized characteristics such as hypertension, hypercholesterolemia, smoking, diabetes, and obesity cannot fully account for the incidence of IHD or of stroke. It has also proved difficult to establish whether these familiar risk factors act as accelerants on the development of atheroma or as causes of thrombosis.

During recent years, growing recognition of the thrombotic component, particularly in IHD, has led to studies of the role of the hemostatic system. High plasma fibrinogen concentrations and high factor VII coagulant (VIIc) activity are associated with an increased risk of IHD, and in the case of fibrinogen this association has also been demonstrated for stroke. In fact, plasma fibrinogen concentration appears to be the strongest biochemical index of the risk of ischemic cardiovascular disease defined as the sum of IHD and stroke, and the same is probably true of IHD and stroke separately. The interpretation of the relation between fibrinogen concentration and cardiovascular disease risk is therefore of considerable importance since, if the relation were of causal significance, the possible prevention of cardiovascular disease by modifying fibrinogen levels would be of substantial interest. Fibrinogen
levels may contribute to cardiovascular disease in one or a combination of at least four ways. First, high levels probably contribute to the development of atheroma. Second, fibrinogen levels within the physiological range increase platelet aggregability. Finally, and contrary to some theoretical predictions, fibrinogen concentration appears to be a determinant of the amount of fibrin formed when coagulation is initiated in an animal model. It is, however, possible that high fibrinogen levels are an indirect manifestation of the extent of atheroma, bearing in mind that fibrinogen is an acute and chronic-phase protein the concentration of which tends to rise in response to a number of stimuli and that atheroma has many of the characteristics of an inflammatory response. Even if this is only a partial explanation for the relation between high fibrinogen levels and cardiovascular disease, in addition to environmental and genetic influences, high fibrinogen levels may still predispose to clinically manifest disease through the mechanism already outlined. Nonetheless, it is of both scientific and practical importance to determine the extent to which high concentrations of fibrinogen (and other hemostatic variables) are secondary to the extent of underlying atheroma and the extent to which they contribute to atheroma and thrombosis.

We investigated these issues by studying the extent and progression of atheromatous disease of the carotid bifurcation as visualized by intravenous digital subtraction angiography (IV DSA). We attempted to correlate the presence of visible disease with measures of both conventional risk factors and of hemostatic variables and then, by repeat angiography, we attempted to see whether either conventional risk factors or high levels of hemostatic variables are associated with the progression of arterial wall disease.

Subjects and Methods

We recruited 492 patients investigated for cerebrovascular disease or IHD; all patients gave consent for serial IV DSA of their cervical arteries. Their age, sex, blood pressure, smoking habit, diabetic status, and body mass index at entry were recorded along with their history of cardiac, cerebral, or retinal ischemic symptoms. The clinical examination included auscultation for neck bruits.

Of the 492 patients, 354 had blood samples drawn for tests of hemostatic function (hemoglobin, packed cell volume [PCV], whole-blood platelet count, and concentrations of cholesterol, triglycerides, uric acid, creatine kinase, fibrinogen, factors II, VII, VIII, IX, X, anti-thrombin III, and anti-thrombin III). In 230 of these 354 patients, the ED_{50} for platelet aggregation with adenosine diphosphate (ADP) was measured using the Born technique.

IV DSA was carried out using a standardized protocol, with biplanar views of the carotid bifurcation in all patients. Forty milliliters of a watersoluble nonionic contrast medium (Isohexol, 300 mg/ml; Nycomed Ltd., Norway) were injected into the superior vena cava through a cubital catheter at a rate of 25 ml/sec.

The initial films were reviewed and categorized by two blinded observers. Because of the limited definition of IV DSA, only broad categories of abnormality were distinguished. The carotid vessels were examined and measured and were scored as appearing normal, as showing wall irregularity (with either no visible encroachment into the lumen or a narrowing of >25%), as having stenosis of ≥25% (comparing the residual lumen with that of the nearest normal-appearing part of the vessel), or as showing occlusion. Each patient was characterized by the appearance of the more severely affected carotid artery.

In those patients with repeat angiography, the initial and repeat films were assessed as a set by both blinded observers who had no means of knowing which was the earlier of the two studies. A decision as to whether there was a difference between the two studies was made before the scoring was removed. Progression was then inferred if an initially normal carotid bifurcation showed irregularity or measurable narrowing on repeat angiography, if stenosis had increased by ≥20%, or if an initially patent vessel had become occluded on repeat angiography. Regression was inferred if an initially irregular vessel appeared normal on repeat angiography.

Complete clinical information at entry, with blood tests including platelet aggregation, and repeat angiography was available in 209 patients. This permitted us to study the effect of conventional risk factors and hematologic parameters on the incidence and progression of visible atheroma. As those patients on anticoagulants (n=29) showed levels of coagulation factors significantly different from the remaining patients, they were excluded from these assessments. As those patients on aspirin or dipyridamole (n=156) showed ED_{50} for platelet aggregation not different from the other patients, they were not excluded from the data on platelet behavior.

Many hemostatic variables had skewed distributions, and we normalized the distributions by logarithmic transformations before statistical tests were performed. In addition, blood pressure and some hemostatic variables showed a relation with age; therefore, correlation factors determined from these data were used to correct for this age dependence. We used Student's t tests, χ^2 tests, and logarithmic regression in the analysis. Because of the relatively large number of tests performed, probability values should be interpreted conservatively.

Results

Entry data were obtained on the entire study population of 492 patients (mean age 59.5 years, 339
men and 153 women). By history, 87% had been referred for the investigation of cerebrovascular disease. Of these 428 patients, 72% gave a history of a transient ischemic attack (TIA) at some stage, 9% had had a reversible ischemic neurologic deficit (RIND) in which symptoms had remitted within 1 month, and 33% had had a completed stroke. Some patients gave a history of more than one category of cerebrovascular event; for analysis such patients were categorized according to their most serious event (TIA < RIND < completed stroke). Nearly half (45%) of the entire study population of 492 patients were current smokers, a third were known to be hypertensive, and 7% were diabetic.

Examination revealed a mean ± SD systolic blood pressure of 142.9 ± 22.4 mm Hg and a mean ± SD diastolic blood pressure of 85.6 ± 11.4 mm Hg in the entire study population. Despite treatment, known hypertensive patients had a significantly higher blood pressure (mean ± SD systolic blood pressure 152 ± 22.5 mm Hg compared with 138 ± 21 mm Hg for the rest of the study population; *p < 0.005). A neck bruit was heard in 29% of the study population.

On initial IV DSA, 231 patients had no visible atheromatous changes at the carotid bifurcation. In 132 patients wall irregularity but only minimal encroachment into the lumen was noted. Narrowing of the lumen with ≥25% stenosis was recorded in 92 patients. One angiogram was impossible to code, a third were known to be hypertensive, and 7% were diabetic.

Abnormal angiograms were more common in patients with cerebrovascular disease than in those with IHD. Carotid occlusion was most common in patients with any completed stroke or RIND, and carotid stenosis was most common in those with TIAs or asymptomatic bruits (Table 1). Patients with normal angiograms were significantly younger than those with evidence of arterial plaque formation (Table 2). There was no significant difference in sex ratio, blood pressure, body mass index, or diabetic status between those with normal and those with abnormal angiograms. Patients on antihypertensive medication were significantly more likely to have abnormal angiograms (52% vs. 37%, *p < 0.01). Smoking was significantly more common in the patients with detectable atheroma (Table 2). Patients with cervical bruits were more likely to have abnormal angiograms. There was no evidence that smoking habit, diabetes, blood pressure, or body mass index was associated with increased severity of visible changes among those with abnormal angiograms, but the numbers are small for some of the subcategories.

Hematologic data were obtained in 354 patients, all of whom had IV DSA. The number of blood samples successfully assayed was >326 for all hematologic variables. The mean age of this subgroup, comprising 241 men and 113 women, was 59.5 years. The reason for IV DSA was investigation of cerebrovascular disease in 86% of this subpopulation.

Of the 304 patients with cerebrovascular disease in the subpopulation studied hematologically, 73.4% had had a TIA, 10.5% a RIND, and 37.8% a completed stroke. Some had a history of more than one category of event. One third were known to be hypertensive, 44% smoked, and 8% were diabetics. In these basic characteristics, therefore, these

### Table 1. Appearances of Carotid Bifurcation on Intravenous Digital Subtraction Angiography in 491 Patients Investigated for Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Clinical evidence of cerebrovascular disease</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. RIND/completed stroke</td>
<td>86</td>
<td>46</td>
<td>46</td>
<td>25</td>
<td>30</td>
<td>16</td>
<td>24</td>
<td>13</td>
<td>186</td>
<td>100</td>
</tr>
<tr>
<td>B. TIA/bruit</td>
<td>102</td>
<td>42</td>
<td>70</td>
<td>29</td>
<td>58</td>
<td>24</td>
<td>11</td>
<td>5</td>
<td>241</td>
<td>100</td>
</tr>
<tr>
<td>C. None</td>
<td>43</td>
<td>67</td>
<td>16</td>
<td>25</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>231</td>
<td>47</td>
<td>132</td>
<td>27</td>
<td>92</td>
<td>19</td>
<td>36</td>
<td>7</td>
<td>491</td>
<td>100</td>
</tr>
</tbody>
</table>

RIND, reversible ischemic neurologic deficit; TIA, transient ischemic attack. One patient with angiograms impossible to code was excluded from this analysis.

*Χ²=13.7 compared with (B+C); *p < 0.01.

†Χ²=8.82 compared with (A+C); *p < 0.025.

‡Χ²=12.1 compared with (A+B); *p < 0.01.

### Table 2. Appearances of Carotid Arteries on Intravenous Digital Subtraction Angiography in 491 Patients Investigated for Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Normal (n=231)</th>
<th>Abnormal (n=260)</th>
<th>Statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>56.1</td>
<td>61.8</td>
<td>t=5.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SD</td>
<td>11.0</td>
<td>9.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex ratio (male:female)</td>
<td>2.01</td>
<td>2.45</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, age-corrected (mm Hg)</td>
<td>142.7</td>
<td>144.1</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.19</td>
<td>24.87</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>5.2</td>
<td>8.1</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>39</td>
<td>50</td>
<td>Χ²=6.45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cervical bruit (no.)</td>
<td>14</td>
<td>43</td>
<td>Χ²=36.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

One patient with angiograms impossible to code was excluded from this analysis. NS, difference not significant.
patients were no different from the rest of the study population. As shown in Table 3, abnormal angiograms among the 354 patients with hematologic data were associated with a lower hemoglobin and with higher uric acid, fibrinogen, and factor VIII rag concentrations. Linear logistic regression of these variables on angiographic change showed that progression, although the number of patient-years of follow-up are small, particularly for diabetics. Patients with more severe arterial disease at entry proved more likely to show progression, which occurred in 18% of those with one vessel occluded and in 34% of those whose worst lesion was a stenosis. By contrast, only 13% of those with no more than wall irregularity showed progression, and only 6.8% of those with normal vessels developed visible changes during follow-up ($\chi^2=21.4$, $p<0.001$).

Progression did not relate to blood pressure at entry, but those whose angiograms were thought to have shown progression had higher systolic and diastolic blood pressures at the time of the second study (Table 5), although the effect is modest.

Smokers and diabetics showed no greater evidence of progression, although the number of patient-years of follow-up are small, particularly for diabetics.

No hematologic parameter showed any correlation with angiographic change. Thus, mean PCV, platelet count, levels of hemoglobin, cholesterol,
triglycerides, uric acid, creatine kinase, the ED$_{50}$ of ADP platelet aggregation, and concentrations of fibrinogen, factors II, VII, VIII, and X, and antithrombin III were not significantly different in those who showed progression compared with those whose vessels appeared unchanged or less severely affected at repeat angiography.

**Discussion**

The patients in this study population were symptomatic, with histories suggesting the presence of cerebrovascular disease or IHD. The sex ratio and mean age of the patients and the prevalence of hypertension, smoking, diabetes, and obesity all suggest that this is a fairly typical group of patients under investigation for vascular disease.

Age is the foremost risk factor for clinical events such as stroke, and the extent of raised arterial plaques in the aorta has been shown to be age-related in an autopsy study. Our study also demonstrates that visible plaque formation at the carotid bifurcation and its progression are age-related.

There is strong male preponderance in the incidence of stroke and heart attack as reflected in the sex ratio we found in this symptomatic study population. However, our angiographic comparison revealed no difference between men and women. The International Atheroma Project showed more atheroma in the coronary arteries of autopsied men but no sex difference in the amount of aortic disease, so there may be regional differences within the vascular tree.

Autopsy data suggest that plaque growth, particularly in the coronary arteries, is more marked in diabetics. We failed to show any increase in the rate of progression of visible carotid disease in diabetics, but the numbers are small. The role of diabetes as a risk factor may also relate to abnormalities of platelet function or fibrinolysis.

Hypertension is the single most important treatable risk factor for stroke. Part of the effect probably relates to the role of hypertension in lacunar stroke, related to small-vessel disease; there is also evidence that raised plaques are more common in hypertensives at autopsy. We showed that progression of angiographic atherosclerotic changes in the carotid artery is associated with significantly higher systolic and diastolic blood pressures. It is uncertain whether hypertension provokes plaque growth through hemodynamic effects or by increasing transudation of plasma lipids through the endothelium.

We found smoking to be more common among patients with abnormal angiograms in our cross-sectional study, although progression was not significantly greater among smokers. Autopsy data show evidence of greater plaque development in smokers, at least in the aorta and coronary arteries, and it has been suggested that this relates to endothelial damage.

There was a significant association between fibrinogen level and the extent of atheroma at entry to the study. This is in accord with some though not all other studies, suggesting a similar relation with atheroma in the coronary circulation. From cross-sectional data, however, it is not possible to say whether high fibrinogen levels cause atheroma or are in some way a consequence of it. In our follow-up, there was no demonstrable association between fibrinogen levels and progression of atheroma. This might mean that high fibrinogen levels are more likely to be a consequence than a cause of atheroma. Equally, high fibrinogen levels may lead to clinical disease more through their effect on thrombogenesis than through atherogenesis. Our data do not enable us to distinguish between these possibilities. Our prospective observations depend on progression of atheroma in only 28 patients followed over a relatively short time, so we cannot rule out the possibility of an association between fibrinogen concentration and a change in the extent of atheroma over a longer time. There is no evidence from our study that factor VII is associated with either the initial extent or the progression of atheroma. Unlike fibrinogen, factor VII activity tends to decline rather than to rise in response to nonspecific stimuli.

The only previous angiographic study of the natural history of carotid artery lesions was reported by Javid et al; 93 patients selected for the presence of carotid stenosis (up to 60% narrowing of the lumen) had repeat angiography after 1–9 (mean 3) years. In 32 patients, stenosis had increased by at least 25%/yr; 19 patients showed less severe progression. The high rate of progression may partly reflect the greater sensitivity of arterial angiography, but it is probably also related to the selection of patients with established stenosis since within the study progression was found to be related to the severity of disease when first investigated. Hypertension but not diabetes was also predictive of progression.

Roederer et al studied 167 patients with asymptomatic carotid bruits by serial duplex scanning; 38% showed evidence of progression, a rate greater than that in our study, probably reflecting the greater sensitivity of ultrasound in the monitoring of small plaques. Only three of the 167 patients showed progression from one category to another in...
a scale of six categories from 0 to 100% stenosis, and in each patient this was due to thrombotic occlusion of a stenosis of <50%. Age, diabetes, and smoking contributed to the risk of plaque growth.

In the Toronto Asymptomatic Cervical Bruit Study, Norris and Bornstein found 28% with progression and 4% with regression among 496 arteries over 2 years using continuous-wave Doppler ultrasonography. Severity of stenosis and coincident IHD were the only factors affecting prognosis. The Doppler system used fails to detect <40% stenosis, so that study was of grosser changes than those detected by Hennerici et al. and Roederer et al.

Probably because of the lower sensitivity of IV DSA, we detected a lower rate of progression, which made detection of risk factors for progression difficult; however, age, hypertension, and smoking emerged with obvious therapeutic implications. Our study is the first to attempt to distinguish among hemostatic variables whether risk factor status relates to plaque growth or by exclusion is deemed to relate to thrombogenesis, which triggers clinical events. Although we were frustrated in our primary aim, the data highlight the association of plasma fibrinogen concentration as a potentially modifiable factor in the presence of visible carotid atheroma.

What is needed now is a prospective study using state-of-the-art duplex scanning to detect the most important clinical and laboratory risk factors for the progression of atheroma so that preventive strategies can be devised.

References


Key Words: angiography • carotid artery diseases • risk factors
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