Original Contributions

Risk Factors for Extracranial Carotid Artery Atherosclerosis

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We related risk factors, cardiovascular symptoms, and coronary status to the extent of extracranial carotid atherosclerosis as measured by B-mode ultrasonography in 376 volunteers hospitalized for elective coronary angiography. In a first analysis, we correlated risk factors and cardiovascular symptoms with carotid atherosclerosis. Univariate analysis showed that relations between many continuous risk factors and carotid atherosclerosis were graded and consistent for men and women. Multivariate analysis identified 6 significant variables (age, hypertension, pack-years smoked, and inversely, plasma concentrations of high density lipoprotein cholesterol and uric acid, and Framingham Type A score) that together accounted for 35% of the variability in extent of carotid atherosclerosis. In a second multivariate analysis, addition of coronary status (presence or absence of coronary stenosis as evaluated by coronary angiography) to the roster of candidate independent variables produced a new equation that accounted for an additional 5% of the variability in carotid atherosclerosis extent. Although much of the variability in extent of carotid atherosclerosis remains unexplained, these data define an association between coronary and carotid atherosclerosis that depends partly on shared exposure of both arteries to the same risk factors. They are also consistent with the concept that as yet undiscovered risk factors and/or genetic (e.g., arterial wall) factors common to both arterial beds also contribute to the relation between coronary and carotid atherosclerosis in human beings. (Stroke 1987; 18:990-996)

The relation between extracranial carotid atherosclerosis and transient ischemic attacks (TIAs) and cerebral infarction is similar to that between coronary atherosclerosis and angina pectoris, myocardial infarction, and sudden death. The extent to which investigators express interest in risk factors for coronary atherosclerosis is reflected by 200 citations referenced in a 1983 review.1 In contrast, relatively few publications have related risk factors to atherosclerosis of the intracranial and/or extracranial arterial system.2-23 Approximately one third of these are autopsy studies,18-22 and the remaining two thirds are studies of living people.

In all studies, age is the most important risk factor for carotid atherosclerosis; sex may also be important.

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The International Atherosclerosis Project22 showed more extensive cerebrovascular atherosclerosis in men than women at autopsy, and similar results were found in an angiography study.16 The male:female ratio of patients studied in virtually all reports exceeds 1.0. Hypertension,2-5, 10, 13, 14 diabetes mellitus,2-8, 12, 20 cigarette smoking,1, 3-9, and hyperlipidemia3-6, 9, 12, 13, 15, 17 have been associated with increased risk for cerebrovascular atherosclerosis. The inverse relation of high density lipoprotein (HDL) cholesterol or of the ratio of HDL:total cholesterol to carotid atherosclerosis has been demonstrated in several studies, but only 1 report of patients with familial hypercholesterolemia has shown a relation between low density lipoprotein (LDL) cholesterol and disease.3 All but 2 of these investigations3-6 have been carried out at autopsy or in individuals with symptomatic cerebrovascular disease, and the correlations between risk factors and carotid disease are inconsistent and weaker than correlations between risk factors and coronary atherosclerosis. Multivariate analysis has been used to relate risk factors to carotid atherosclerosis in 2 studies.5, 9 In 3 others,2-12 a greater number of risk factors has been found in cases with cerebrovascular disease than in matched controls.

Validation of a repeatable noninvasive method for quantifying the extent of extracranial carotid atherosclerosis using B-mode ultrasonography24 permits study of presymptomatic carotid atherosclerosis and
Subjects and Methods

Volunteers

Volunteers were selected from patients hospitalized for diagnostic coronary angiography undertaken to evaluate potential causes of symptoms of chest pain, arrhythmia, heart attack, etc. Twenty-five percent of all catheterized patients were excluded from the research study because of conditions that interfere with the ability to interpret plasma lipid concentrations (lipid-lowering drug use, kidney disease, liver disease, acute myocardial infarct, etc.) or conditions that interfere with the ability to interpret the coronary angiogram (previous coronary bypass graft or angioplasty). Other exclusion criteria included treatment with thyroid medications or prednisone. Of the remaining patients, almost 50% were men >50 years old with coronary disease. To not overrepresent this group, we randomly chose a fraction of men >50 with coronary atherosclerosis for study. Through similar processes, we accessed men and women older than and younger than 50, with and without coronary stenosis, at equal rates. We evaluated risk factors and noninvasively examined the carotid arteries in 376 patients (182 men, 194 women), which represented 65% of those remaining after exclusions and random selection. For the current study all patients with a history suggestive of TIA or stroke (n = 12) and all with aortic valvular disease (n = 29) were also excluded. All subjects ultimately chosen for study were administered a standardized questionnaire that evaluated angina pectoris and other symptoms of and risk factors for cardiovascular disease. Subjects also underwent a vascular examination including auscultation of the heart for murmurs and of the carotid arteries for bruits.

Evaluation of Carotid and Coronary Atherosclerosis

Real-time B-mode imaging of the extracranial carotid arteries was performed using a Biosound compact real-time imager (Indianapolis, Ind.) with an 8-MHz mechanical sector scanner probe and a digital scan converter. Subjects were examined in a sitting position, and common and internal carotid arteries were examined in the anterior oblique, lateral, posterior oblique, and transverse views. The sonographer performing the scan obtained axial thickness measurements of plaques visualized at standard sites. Scan images, sonographer comments, and measurements were recorded on videotape for interpretation and storage.

The B-mode data for each subject were combined into a single carotid artery score by summing the maximum axial thicknesses at each standard site. The few scores that exceeded 24 mm were truncated to 24 mm. Previously we documented that the correlation coefficient for repeat determinations of this score (2 studies separated by 6 months) was 0.88.

Selective coronary angiography was performed by the percutaneous technique using either Judkins or multipurpose catheters. Coronary stenosis was coded as present if any vessel had ≥50% stenosis and as absent if all vessels were free of any stenosis. Subjects with coronary stenosis and those with normal coronary arteries were chosen for study, whereas patients with coronary stenosis that obstructed the lumen by <50% (nonobstructive disease) were excluded from the study.

Evaluation of Risk Factor Variables and Cardiovascular Symptoms

Seventeen risk factor variables and cardiovascular symptoms were evaluated in all subjects; the information was obtained from the clinical history, physical examination, electrocardiogram, and analysis of blood drawn from fasting subjects before catheterization as previously described.

In addition to age and sex, the following 8 items were evaluated from history and physical examination: 1) history of smoking was recorded as pack-years; 2) family history was recorded as positive if a parent or sibling suffered a myocardial infarct and/or sudden nontraumatic death before the age of 60; 3) history of myocardial infarction was recorded as present if the subject had ever been told by a physician that he/she had had an infarct; 4) history of angina pectoris was elicited by Rose questionnaire; 5) Type A score was assessed by the Framingham Type A questionnaire; 6) hypertension was coded as present if the subject had a history of hypertension and/or if the blood pressure measured in the hospital exceeded 150/95 mm Hg (otherwise it was coded absent); 7) diabetes mellitus was coded as present if the subject had ever been told by a physician that he/she had diabetes, if the subject was treated at the time of hospitalization with oral hypoglycemic agents or insulin, and/or if the subject's fasting glucose in the hospital exceeded 140 mg/dl (otherwise it was coded absent); and 8) percent ideal body weight was obtained by reference to standard Metropolitan Life Insurance tables. Results of the following laboratory tests were recorded: 1) left ventricular hypertrophy (LVH) was coded as present if voltage on electrocardiography met either the criteria of Sokolow and Lyon or Romhilt and Estes. Hemoglobin (g/dl) was measured by the Coulter −S + hematology analyzer (Hialeah, Fla.), 3) uric acid was measured using a standard automated technique (Technicon SMAC, Tarrytown, N.Y.), and 4) lipids and lipoproteins were measured using Lipid Research Clinic methodology. For this, plasma was ultracentrifuged at d = 1.006 to float very low density lipoproteins and chylomicrons, and LDL cholesterol was quantified by the difference between d = 1.006 infranate cholesterol before and after precipitation of LDL by heparin manganese.

Plasma concentrations of triglyceride and total, LDL, and HDL cholesterol were tested for association with the extent of carotid atherosclerosis.
**Statistical Evaluation**

The extent of atherosclerosis was related to candidate risk factor variables in univariate analyses by linear regression. Candidate independent variables were related to the extent of carotid atherosclerosis by multivariate stepwise linear regression analysis with backward elimination. The analysis was run twice, first excluding and then including coronary status as a candidate independent variable. Only variables significant at \( p \leq 0.01 \) were retained in the equation. Univariate analysis and linear regression were carried out using the BMDP statistical package according to standard statistical techniques. Because of the skewed distribution of plasma triglyceride concentrations, their logarithms rather than the raw data were entered into the regression equations.

**Table 1. Relation of B-Mode Score to Age and Sex**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Men</th>
<th>Age ( \leq 50 )</th>
<th>Age ( &gt;50 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without attribute</td>
<td>Without attribute</td>
</tr>
<tr>
<td>Coronary stenosis</td>
<td></td>
<td>3.1 ±2.8 (29)</td>
<td>3.9 ±3.7 (58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>3.8 ±3.6 (52)</td>
<td>3.3 ±3.2 (35)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>3.5 ±3.4 (77)</td>
<td>4.3 ±3.9 (10)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td>3.6 ±3.4 (78)</td>
<td>3.9 ±3.5 (9)</td>
</tr>
<tr>
<td>Heart attack history</td>
<td></td>
<td>3.5 ±3.4 (50)</td>
<td>3.7 ±3.5 (37)</td>
</tr>
<tr>
<td>Angina history</td>
<td></td>
<td>3.1 ±2.8 (34)</td>
<td>3.9 ±3.8 (53)</td>
</tr>
</tbody>
</table>

Values are mean B-mode score ±SD for \( n \) individuals.

**Results**

Descriptive data defining clinical characteristics of the subject population and relating B-mode scores to selected clinical parameters are presented in Table 1 and Figure 1 (dichotomous and continuous variables, respectively). For descriptive purposes the subject population has been divided according to sex and (in Table 1) age. The descriptive data of Table 1 and Figure 1 agree with the statistical analyses (Tables 2–4). The data in Figure 1 suggest a graded (dose-response) relation between risk factors and B-mode score and demonstrate the constancy of the relation for men and women in the subject population. Data in Table 1 also suggest the constancy of the relation between risk factors and B-mode score for men and women older than and younger than 50.

For statistical analyses men and women were grouped together and sex was tested for its role as a candidate independent variable. Univariate analysis of the relation between risk factors and B-mode scores is presented in Table 2. In the univariate analysis, age, coronary stenosis, hypertension, pack-years smoked, history of diabetes, LVH, log plasma triglyceride concentration, history of heart attack, and plasma total cholesterol concentration were positively associated with the extent of carotid atherosclerosis, whereas Framingham Type A score and plasma HDL cholesterol concentration were negatively associated \( (p<0.05, \) Table 2). Sex, uric acid concentration, percent ideal body weight, family history of coronary disease, hemoglobin, LDL cholesterol concentration, and history of angina pectoris were not significantly associated with the extent of extracranial carotid atherosclerosis by univariate analysis.

Stepwise multiple linear regression, backward elimination, was used next to identify risk factor variables and cardiovascular symptoms that were independently associated with the extent of extracranial carotid atherosclerosis. The 6 variables that remained in the equation were age, hypertension, smoking, HDL cholesterol concentration, uric acid concentration, and Framingham Type A score (Table 3); the last 3 were inversely related to the extent of extracranial carotid atherosclerosis. These 6 risk factors accounted for \( >35\% \) of the variability in the extent of carotid atherosclerosis \( (R^2 = 0.355) \).

**Table 2. Relation of Risk Factors, Symptoms, and Coronary Stenosis to B-mode Score: Univariate Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Standardized regression estimate</th>
<th>( p )</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.43</td>
<td>0.0001</td>
<td>0.1946</td>
</tr>
<tr>
<td>Coronary stenosis</td>
<td>1.88</td>
<td>0.0001</td>
<td>0.1169</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.48</td>
<td>0.0001</td>
<td>0.0722</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.10</td>
<td>0.0001</td>
<td>0.0407</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.05</td>
<td>0.0002</td>
<td>0.0360</td>
</tr>
<tr>
<td>Framingham Type A score</td>
<td>-1.03</td>
<td>0.0003</td>
<td>0.0349</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>0.88</td>
<td>0.0019</td>
<td>0.0258</td>
</tr>
<tr>
<td>HDL cholesterol concentration</td>
<td>-0.88</td>
<td>0.0019</td>
<td>0.0256</td>
</tr>
<tr>
<td>Log triglyceride concentration</td>
<td>0.80</td>
<td>0.0051</td>
<td>0.0209</td>
</tr>
<tr>
<td>Heart attack history</td>
<td>0.70</td>
<td>0.0142</td>
<td>0.0161</td>
</tr>
<tr>
<td>Total cholesterol concentration</td>
<td>0.64</td>
<td>0.0232</td>
<td>0.0111</td>
</tr>
<tr>
<td>Angina history</td>
<td>0.55</td>
<td>0.0520</td>
<td>0.0101</td>
</tr>
<tr>
<td>LDL cholesterol concentration</td>
<td>0.41</td>
<td>0.1460</td>
<td>0.0057</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.38</td>
<td>0.1842</td>
<td>0.0047</td>
</tr>
<tr>
<td>Family history</td>
<td>0.38</td>
<td>0.1857</td>
<td>0.0047</td>
</tr>
<tr>
<td>Percent ideal body weight</td>
<td>0.18</td>
<td>0.5316</td>
<td>0.0011</td>
</tr>
<tr>
<td>Uric acid concentration</td>
<td>0.08</td>
<td>0.7923</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.03</td>
<td>0.9228</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; LDL, low density lipoprotein.
Table 1. Continued

<table>
<thead>
<tr>
<th>Age ≤50</th>
<th>Age &gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without attribute</td>
<td>With attribute</td>
</tr>
<tr>
<td>2.3±2.3 (38)</td>
<td>4.8±4.2 (46)</td>
</tr>
<tr>
<td>2.8±3.2 (48)</td>
<td>5.0±4.0 (36)</td>
</tr>
<tr>
<td>3.5±3.8 (72)</td>
<td>5.0±3.0 (12)</td>
</tr>
<tr>
<td>3.8±3.7 (82)</td>
<td>— (2)</td>
</tr>
<tr>
<td>3.3±3.3 (60)</td>
<td>4.9±4.4 (24)</td>
</tr>
<tr>
<td>2.5±2.5 (29)</td>
<td>4.3±4.0 (55)</td>
</tr>
</tbody>
</table>

We next evaluated the influence of coronary status on the possible relation between the extent of extracranial carotid atherosclerosis, risk factors, and symptom status. Coronary status as a candidate independent variable was entered into a second regression equation with all variables that had been tested in the first multivariate analysis. The 6 significant risk factor variables of the first regression equation were retained in the second analysis, and in addition, presence of coronary disease and LVH were entered (Table 4). Inclusion of these variables in the equation increased the coefficient of determination by 5% (R² = 0.402).

Discussion

Although the literature relating risk factors to symptomatic cerebrovascular disease is extensive and although numerous studies have related risk factors to extent of coronary atherosclerosis (reviewed in Reference 1), similar attention has not been given to atherosclerosis of the extracranial carotid arteries. Only 2 studies have used multivariate analysis to relate risk factors to carotid atherosclerosis, and relations between atherosclerosis of the carotid and coronary arteries have previously been studied only at autopsy. To test for associations of various risk factors and cardiovascular symptoms with the extent of extracranial carotid atherosclerosis, we evaluated standardized risk factors and noninvasively studied the carotid arteries in patients undergoing coronary angiography. In our study a very strong relation (p<0.001) was found between the extent of carotid atherosclerosis and age, coronary stenosis, hypertension, and smoking on univariate testing. Significant associations were also found for diabetes, Framingham Type A score, LVH, plasma HDL cholesterol concentration, log plasma triglyceride concentration, heart attack history, and plasma total cholesterol concentration. Sex and percent ideal body weight were not significantly related to the extent of extracranial carotid atherosclerosis on univariate testing. When we tested the independence of these associations through multivariate analysis (excluding coronary stenosis as a candidate independent variable), age, hypertension, and cigarette smoking were positively related to the extent of carotid atherosclerosis, whereas HDL cholesterol concentration, uric acid concentration, and Type A score were negatively related.

Age is an extremely important risk factor for symptomatic cerebrovascular disease, and age emerged as an important risk factor variable for the extent of carotid atherosclerosis as well. Our previous univariate analysis showed age to be an important risk factor for carotid atherosclerosis, and when its contribution has been assessed it has been found related to carotid atherosclerosis.

Whereas hypertension is undoubtedly the most important risk factor for atherothrombotic events, it is inconsistently found to be associated or not associated with carotid atherosclerosis defined angiographically. Only 2 studies used multivariate analysis, and they drew opposite conclusions. Similarly, a recent study failed to find hypertension to be a risk

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Figure 1. Relation of B-mode score to age, pack-years smoked, high density lipoprotein (HDL) cholesterol (mg/dl), and Framingham Type A score for men and women. Equations defining individual regression lines are for females: B-Mode = 0.24(Age) - 6.7; B-Mode = 0.06(Pack-years) + 5.1; B-Mode = -0.12(HDL cholesterol) + 10.9; and B-Mode = -4.74(Type A) + 8.04. For males: B-Mode = 0.26(Age) - 7.7; B-Mode = 0.04(Pack-years) + 4.7; B-Mode = -0.03(HDL cholesterol) + 7.1; and B-Mode = -4.36(Type A) + 8.2.
factor for the progression of carotid atherosclerosis. 35
In our study B-mode ultrasonography was used to
identify mural lesions, and hypertension appeared as an
independent risk factor in multivariate analysis.
Cigarette smoking has been found to be a significant
risk factor for carotid atherosclerosis in 4 studies 25-912
but not in 1 other. 14 Both studies that used multivariate
analysis found a positive relation. 5-9 Cigarette smoking
has also been related to development of clinical cere-
brovascular events in cohort studies, 36-39 although studies
not showing a positive relation are also common
(reviewed in Reference 37). In this study, pack-years of
cigarette smoking was related to the extent of carot-
id atherosclerosis in multivariate analysis.
Plasma concentrations of lipids and lipoproteins
have been related to carotid artery atherosclerosis in most
6-6,12,13,17 but not all reports. 9,14 The 2 that used multivariate
analysis disagreed as to the role of lipids and lipoproteins 5,9 HDL cholesterol concentration,
where tested, has most consistently shown an inverse
relation to carotid atherosclerosis. Of interest, popula-
tion-based studies do not agree as to the relation be-
tween lipids, lipoproteins, and clinical central nervous
system events. In some studies, LDL cholesterol con-
centration has paradoxically shown an inverse relation
to events. 38 We found HDL cholesterol concentration
to be independently and inversely related to the extent
of carotid atherosclerosis in multivariate analysis,
whereas plasma concentrations of triglyceride, total
cholesterol, and LDL cholesterol, in agreement with a
prior report, 3 were not significant and did not remain in
the equation. Use of the HDL:total cholesterol or
HDL:LDL ratios did not improve our ability to explain
variability in the extent of extracranial atherosclerosis.

Blood levels of uric acid were unexpectedly inverse-
ly related to the extent of extracranial carotid athero-
sclerosis as was the Framingham Type A score. A
recent review of risk factors for stroke 34 did not men-
tion a relation between uric acid concentrations and
cerebrovascular disease. The inverse relation between
uric acid concentrations and the extent of extracranial
carotid atherosclerosis found in this study is not ex-
plained. Similarly, the inverse relation with Type A
score is unexpected. A previous study found a positive
association between Type A score and extracranial
carotid disease in patients referred to a cerebrovascular
laboratory for suspected cerebral ischemia. 7 Patients
with cerebrovascular symptoms were excluded from
our study, so our subjects are not strictly comparable
with those in the previous study. Previous studies of
angiography populations have also failed to consistently
demonstrate a relation between Type A score and
coronary disease (reviewed in Reference 40).

Absent from the multivariate risk factor profiles
were sex, history of diabetes, family history of coro-
nary disease, percent ideal body weight, history of
myocardial infarction, history of angina pectoris, he-
moglobin, and plasma concentrations of triglyceride,
total cholesterol, and LDL cholesterol. Sex was not a
significant risk factor even in univariate analysis. Per-
haps in agreement with this observation, sex is not as
strong a risk factor for cerebrovascular as for cardio-
vascular events. 37 In addition, our selection process no
doubt reduced gender-related differences. For this
study we attempted to select men and women with and
without coronary disease at equivalent rates, resulting
in an oversampling of women with coronary disease
(50% of the women in this study had coronary dis-
 ease). Since coronary disease appears to be an im-
portant correlate of carotid atherosclerosis, enrichment
of the subject population with women who had coronary
disease may have masked a male-female differential in
carotid atherosclerosis seen in other studies in which
women with coronary disease are less prevalent. Al-
though diabetes was associated with the extent of
extracranial atherosclerosis in univariate analysis, diabe-
tes was removed from the regression equation in the
multivariate analysis. Previous studies have also found
diabetes to be associated with extracranial carotid
atherosclerosis in univariate analysis, 2,12 but it has not
previously been examined by multivariate analysis.
Except as regards plasma lipids and lipoprotein fractions
(reviewed above), previous studies provide no
information concerning the relation of the remaining
excluded variables and the extent of extracranial carot-
oid atherosclerosis.

To determine whether there might be an association
between coronary and carotid atherosclerosis, we car-
ried out the regression analysis a second time entering

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**Table 3. Relation of Risk Factors to B-mode Score: Multivariate Analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Standardized regression estimate</th>
<th>Standard error of estimate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.45</td>
<td>0.25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.30</td>
<td>0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.08</td>
<td>0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-1.15</td>
<td>0.25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.91</td>
<td>0.25</td>
<td>0.0003</td>
</tr>
<tr>
<td>Framingham Type A score</td>
<td>-0.69</td>
<td>0.24</td>
<td>0.0044</td>
</tr>
</tbody>
</table>

Multiple $R^2 = 0.355$

**Table 4. Relation of Risk Factors and Coronary Stenosis to B-mode Score: Multivariate Analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Standardized regression estimate</th>
<th>Standard error of estimate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.23</td>
<td>0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.23</td>
<td>0.23</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coronary stenosis</td>
<td>1.20</td>
<td>0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.86</td>
<td>0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.84</td>
<td>0.24</td>
<td>0.0005</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.80</td>
<td>0.25</td>
<td>0.0018</td>
</tr>
<tr>
<td>Framingham Type A score</td>
<td>-0.69</td>
<td>0.23</td>
<td>0.0029</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>0.58</td>
<td>0.22</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

Multiple $R^2 = 0.406$

HDL, high density lipoprotein.
coronary status as a candidate independent variable and testing for its retention in the equation. In this repeat analysis, all 6 risk factors that were previously related to the extent of extracranial carotid atherosclerosis remained in the equation. A risk factor variable not previously retained in the equation relating risk factors to extent of extracranial carotid atherosclerosis, LVH, now remained in the equation. A similar independent effect of LVH has been found for symptomatic coronary and cerebrovascular disease. Finally, coronary stenosis also remained in the equation relating risk factors to the extent of carotid atherosclerosis. A correlation between coronary and carotid atherosclerosis has been noted in previous autopsy studies, however, since risk factors for disease of the coronary and carotid arteries are similar, it could be argued that this association merely reflects shared risk factors. Since coronary status remained in the second regression equation as an independent variable, the data of this study suggest that whereas some of the association between coronary and carotid atherosclerosis may be explained by shared risk factors, in addition either both coronary and carotid atherosclerosis are related to a risk factor or factors not measured in this study, or there are genetic factors that predispose individuals with atherosclerosis of the coronary arteries to develop atherosclerosis at other arterial sites. Although the addition of coronary status and LVH to the regression equation increased $R^2$ to 0.402, it is evident that a great deal of variability in the extent of extracranial carotid atherosclerosis remains unexplained even by this model.

Lack of consistency among previous studies and between previous studies and ours is partly explained by differences in the definition of the outcome variable. The severity of stenosis has been used to define outcome in the majority of previous studies, but the extent of mural thickening was used in this report and a few others. As discussed previously, evaluation of the extent of mural thickening should, in theory, relate more strongly to risk factors than does percent stenosis since 1) intimal thickening can develop in the absence of stenosis, 2) the method takes into consideration the extent of disease in a dose-response fashion. Howev-

er, this approach precludes analysis of the severity and thus the hemodynamic significance of atherosclerosis at any individual site. Measurement technique has also varied from study to study and has included carotid angiography, pulsed Doppler analysis, and, in this study, B-mode ultrasonography (as mentioned previously, B-mode ultrasonography measures wall thickness rather than disturbed flow patterns that reflect lumen stenosis). Inconsistency also arises partly from differences between this subject population with symptomatic cardiovascular disease and others with symptomatic cerebrovascular disease and partly from differences in analytic approach (univariate as opposed to multivariate analysis). Potential for bias results from the hospital base of the subject population since patients were referred for coronary angiography for a variety of cardiovascular complaints. Also, a number of potential sources for bias arise from the case–comparison nature of the study. Sources for bias have been reviewed in detail by Pearson. In studies such as these, the disadvantages of study design must be weighed against the advantages that proceed from knowledge of coronary status. Coronary symptoms are at best imperfect indications of underlying coronary disease, and, therefore, when the outcome variable may be influenced by or relate to coronary atherosclerosis, direct assessment of coronary stenosis may be potentially valuable. Our choice of a subject population undergoing angiography affords a unique opportunity to examine the relations between carotid artery atherosclerosis, coronary atherosclerosis, and risk factors but simultaneously dictates a case–comparison design with its inherent pitfalls. The association between coronary and carotid atherosclerosis noted in this study is independent and strong; nonetheless it is evident that much work remains to be done to clarify our understanding of risk factors for carotid atherosclerosis since most of the variability in the extent of carotid atherosclerosis remains unexplained by risk factors or by the described association between coronary and carotid atherosclerosis.

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