**Progress Review**

**Relation Between Blood Lipids, Lipoproteins, and Cerebrovascular Atherosclerosis**

A Review

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Although blood lipids and lipoproteins are strongly related to coronary atherosclerosis, their association with cerebrovascular atherosclerosis is less clear. A review of more than 20 publications in which a relation was sought between plasma lipid and lipoprotein concentrations and cerebrovascular atherosclerosis leads to the general conclusion that such a relation exists and that it is stronger in older than in younger individuals. A relation was found between blood lipids and/or lipoproteins and the extent and/or severity of cerebrovascular atherosclerosis in all but three of 26 reviewed studies. However, the specific nature of the relation is obscure because the various studies cannot easily be compared with one another. Interstudy variations in lipoprotein fraction analyzed, methodology for the analysis of lipids and lipoproteins, arterial segment examined, population sampled, control selection in case-control studies, statistical analytic approach taken, and methodology for the assessment of arterial disease preclude pooled analyses. There is a clear need for further evaluation of this relation using standardized and up-to-date methodologies both for analyses of lipids and lipoproteins and for assessment of cerebrovascular disease in symptom-free volunteers as well as in symptomatic patients. *(Stroke 1988;19:423–430)*

While there is an overwhelming amount of evidence relating high levels of blood total and low density lipoprotein (LDL)-cholesterol and low levels of high density lipoprotein (HDL)-cholesterol with coronary atherosclerosis, the relation between blood lipids and lipoproteins and cerebrovascular atherosclerosis is less clear. Epidemiologic studies have failed to demonstrate a consistent association between blood lipid concentrations and lipoprotein abnormalities and clinical manifestations, for example, cerebral infarction. If lipids do relate to atherosclerosis, then a possible explanation for this apparent contradiction is that risk factors for symptomatic cerebrovascular disease may not necessarily be the same as those for atherosclerosis in general, that is, the factors associated with the precipitation of the clinical event may differ from those related to the underlying process of atherosclerosis. Because lipids are often sampled following stroke, relations, or the lack of such, between blood lipids and stroke manifestations cannot automatically be extrapolated to the relation between blood lipids and atherosclerosis without intra-arterial examinations. It has been shown that blood total cholesterol decreases after acute myocardial infarction and stays reduced for up to several weeks. Stroke is also accompanied by transient reductions in blood lipid and lipoprotein levels, and thus, results from some stroke studies may not apply in studies of asymptomatic atherosclerotic disease.

This review assesses evidence regarding the possible relation between blood lipids and lipoproteins and cerebrovascular atherosclerotic lesions.

**Ascertaining Presence of Atherosclerosis**

Whereas most studies of the relation between blood lipid concentrations and stroke have combined cerebrovascular disease secondary to extracranial and intracranial atherosclerosis into one group with a defined outcome, most studies investigating the effects of lipid concentrations on severity and degree of atherosclerosis have differentiated between intracranial and extracranial arteries and have investigated lesions at various arterial sites.

The methods used to identify atherosclerosis range from autopsy of diseased individuals to noninvasive procedures that can be employed in healthy, asymptomatic subjects. Studies of autopsied persons usually represent a biased population sample and are not randomly selected; thus, their generalizability can be questioned. In addition, most autopsy studies report only on intracranial arteries because neck arteries are often not available for autopsy.

Angiography can be used to image stenosis within both the intracranial and extracranial circulation, thus...
facilitating analysis of different sites. However, this is an imprecise method with high intraobserver and interobserver variation. Nevertheless, such analysis is an important tool in the study of the relation between various risk factors and atherosclerosis because symptoms sometimes poorly reflect pathology. Analysis of different sites is important because the effect of hypertension probably primarily affects the small intracranial vessels, whereas lipoprotein abnormalities appear to affect mainly the larger cerebral arteries.10-12

The role of plasma lipids on progression of atherosclerosis has also been investigated in patients who have undergone endarterectomy and have developed recurrent stenosis. As far as we are aware, published studies on this relation have exclusively employed angiography.

During the past few years, noninvasive procedures employing continuous-wave Doppler sonography and high-resolution B-mode scanning have become available to study even mild vascular lesions and wall irregularities of extracranial neck arteries.13-14 This development has enabled investigators to study asymptomatic healthy subjects as well as symptomatic patients and thus cover a wider range of atherosclerotic lesions than that previously possible.

Whereas angiography and pulse-wave Doppler sonography assess the arterial lumen, B-mode ultrasonography is capable of measuring wall thickness rather than disturbed flow patterns (lumen stenosis). Since atherosclerosis initially may involve a thickening of the wall but because of arterial dilatation no narrowing of the lumen, lesions apparent on B-mode ultrasonography may not show up at angiography or Doppler interrogation.15,16

An overview of the reviewed studies is given in Table 1. The discussion focuses on the study design pertinent to the investigation reviewed, and within each section the studies are listed in chronological order according to year of publication. The designs of the reviewed studies fall into three main categories: cross-sectional correlation studies, case-control studies (including studies of restenosis following endarterectomy), and prospective cohort studies.

**Cross-sectional/Correlation Studies**

In a review (not included in Table 1) of international autopsy studies, Solberg and Strong17 ranked 12 location-race groups according to the mean extent of raised lesions in the aorta and in the coronary and cerebral arteries and the mean serum cholesterol concentration (based on data gathered from the literature). The ranking for raised lesions was positively and significantly correlated with the ranking by serum cholesterol concentration within deciles. The authors concluded that these data conform to the hypothesis that geographic differences in extent of atherosclerosis can be explained in part by differences in serum cholesterol concentration among populations.

We are aware of 10 cross-sectional studies that have reported on the relation between blood lipids and cerebrovascular atherosclerosis. Results from these studies are generally presented as either univariate11,18-22 or multivariate correlations23-25 using the entire study population or as subgroup comparisons, that is, patients with less or more than a certain amount of narrowing of the arterial lumen.22,25

Two studies were conducted among neurologically asymptomatic patients,21,22 and one included neurologically asymptomatic patients hospitalized for coronary symptoms.26 The other seven studies included patients with varying degrees of neurologic disease, and blood specimens for lipid analysis were obtained at different intervals of time after stroke. These dissimilarities complicate the integration of the studies’ results.

In a study of patients admitted for diagnostic angiography, Ballantyne et al27 found no differences in plasma total cholesterol or fasting triglycerides when comparing patients with and without atheroma causing a > 25% stenosis of the lumen of the internal carotid artery. However, in the group without atheroma, the investigators included patients with ≤ 25% stenosis, thus narrowing the range of lesions investigated.

Because angiography consistently underestimates extent of atherosclerotic arterial disease,27,28 the choice of 25% stenosis as the discriminator between the two analysis groups probably misclassified some patients.

Mathew et al11 investigated the relation between location of lesions and lipid levels > 25 days after the onset of neurologic symptoms. The percentage of patients with hyperlipoproteinemia (predominantly Type IV hyperlipoproteinemia, with elevated triglycerides and prebeta-lipoprotein) was significantly higher in a group with atherosclerotic lesions limited to extracranial (51%) or intracranial (44%) major vessels compared with the total population (32%), with the group with only intracranial small-vessel disease (14%), or with patients with normal angiograms (8%). Plasma total cholesterol values were not significantly different between the groups.

In a study by Bansal et al,19 carotid angiography and serum lipid analyses were performed 3 weeks after the onset of stroke. When comparing 14 patients with abnormal angiograms to the remaining 16 patients with normal angiograms, the former group had significantly higher mean levels of total cholesterol (188 vs. 168 mg/dl) and triglycerides (142 vs. 103 mg/dl).

Rössner et al20 found no significant correlation between total cholesterol and triglycerides and the degree of carotid atherosclerosis in a study of stroke patients. Extent of atherosclerosis was dichotomized as "none or slight" and "moderate or severe," providing the opportunity for some misclassification. It is important to note that patients in this study were < 55 years old since it has been shown that in younger individuals atherosclerosis is not as strongly linked to symptomatic disease as in older people.29

In a study of 462 patients between 20 and 70 years of age with reversible ischemic attacks, Candelise et al20 quantified atherosclerosis score by combining extracranial and intracranial scores. The extracranial score was based on the angiographic findings in 11 arterial segments and the intracranial score on 21
segments. They reported an interaction between atherosclerosis score and age; 36% of the patients < 45 years of age had a normal angiogram compared with 17% of the patients > 45 years. In the subgroup of patients with abnormal angiograms the mean extracranial and intracranial vascular scores were not significantly different in the two age groups. However, since alteration of lipid metabolism was defined as combined dyslipidemias Types I, IIa, IIB, III, IV, and V, the individual effects of total cholesterol and triglycerides could not be separated.

Van Merode et al21 found a significant association between stenosis of at least one carotid artery and low serum HDL: total cholesterol ratios in a randomly selected sample of men > 50 years of age. Mean total cholesterol was 264 mg/dl in 23 men with lesions compared with an average of 240 mg/dl among 54 subjects with no carotid abnormalities.

A highly significant correlation between severity and number of stenotic lesions in the common and internal carotid arteries and degree of hypercholesterolemia was observed by Postiglione et al.22 Those with carotid lesions had significantly higher LDL-cholesterol and the apoprotein associated with LDL-cholesterol (Apo B) and lower concentrations of HDL-cholesterol and the apoprotein associated with HDL-cholesterol (Apo A) compared with those with no lesions.

Ford et al23 found that after controlling for age in multiple regression analyses, the next-best predictor of mean (left plus right) severity of stenosis in the carotid bifurcation was the total: HDL-cholesterol ratio. Also after controlling for age, there was an inverse relation between HDL-cholesterol and percent stenosis, while fasting triglyceride concentration correlated positively but weakly with the amount of stenosis. Total cholesterol and LDL-cholesterol did not correlate significantly with bifurcation stenosis after controlling for the effect of age.

Passero et al24 investigated the extent and severity of atherosclerosis, quantified using extracranial and intracranial cerebrovascular scores based on the number and severity of the lesions in 11 extracranial and 21 intracranial arterial segments. Sex- and site-specific analyses revealed that the strongest association between increased cholesterol and prevalence of atherosclerosis was seen in extracranial arteries in men. This relation was also present in multivariate analysis. Both univariate and multivariate analysis showed that none of the factors analyzed correlated with the extent and severity of intracranial lesions.

Crouse et al25 studied the relation of age, sex, diabetes, hypertension, total and lipoprotein cholesterol, triglycerides, left ventricular hypertrophy, pack-years of cigarette smoking, and percent ideal body weight with the extent of axial wall thickening of internal and common carotid arteries. Univariate analysis showed a significant relation between levels of total plasma cholesterol, total plasma triglycerides, and plasma HDL-cholesterol concentrations and extent of carotid atherosclerosis. Only the inverse relation with HDL-cholesterol persisted in multivariate analysis. Of interest, in this study presence of coronary disease also surfaced as a risk factor for carotid atherosclerosis in univariate analysis and as an independent risk factor in multivariate analysis.

Case-Control Studies

The eight case-control studies that we could locate in our literature search focused on extracranial carotid atherosclerosis as the feature distinguishing the patient group.

Randrup and Pakkenberg26 found significantly elevated plasma total cholesterol (220 mg/dl) and fasting triglycerides (116 mg/dl) in apoplectic patients with total occlusion of a cerebral artery but not in patients with cerebral circulatory insufficiency without occlusion (total cholesterol and triglycerides 214 and 115 mg/dl, respectively) when compared with age- and sex-matched controls (203 and 100 mg/dl, total cholesterol and triglycerides, respectively).

Duncan et al27 examined plasma cholesterol in endarterectomy candidates with angiographic evidence for stenosis of at least one internal carotid artery. Cases with recent (not defined) cerebral infarction were excluded because the authors suggested that such an event might influence the levels of plasma lipids. Compared with age- and sex-matched controls who were admitted to the hospital for valvular heart surgery, cases had significantly higher total cholesterol (221 vs. 193 mg/dl). Fasting triglycerides were also significantly higher in cases than in controls (157 vs. 129 mg/dl).

Terrence and Rao,32 in a study of 95 men and 43 women undergoing endarterectomy for carotid vascular disease, observed significantly higher mean fasting triglycerides compared with an older-than-50-years normal laboratory control group (218 vs. 95 mg/dl). They excluded all cases with a recent (not defined) history of myocardial infarction or atrial fibrillation from the study. Total cholesterol was not significantly different between the two groups.

As part of a larger case-control study, patients with clinical evidence (not defined) of cerebral arteriosclerosis and with angiographically confirmed atherosclerosis had significantly lower levels of HDL-, HDL<sub>2</sub>- and HDL<sub>3</sub>-cholesterol compared with age-matched controls.33 HDL-cholesterol was 31 mg/dl in male and 39 mg/dl in female cases versus 46 mg/dl in male and 55 mg/dl in female controls. Total cholesterol and fasting triglycerides were higher in cases than in controls, but not significantly so.

Bogousslavsky et al34 found significantly higher mean blood total cholesterol levels (224 mg/dl) among men with internal carotid artery occlusion compared with age-matched controls with normal angiography or Doppler ultrasonography of the precerebral vessels (201 mg/dl). Mean total cholesterol in patients having 40–80% stenosis (216 mg/dl) was not significantly different from that of the two previous groups. Control women had lower but not significantly lower total cholesterol levels than the groups with stenosis or occlusion of the internal carotid artery (228 vs. 259 and
TABLE 1. Studies on the Relation Between Blood Lipids, Lipoproteins, and Cerebrovascular Atherosclerosis

<table>
<thead>
<tr>
<th>Investigated arteries</th>
<th>Method</th>
<th>Study group</th>
<th>Age (yr)</th>
<th>Associations with lesions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Cross-sectional</strong></td>
<td></td>
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</tr>
<tr>
<td>Intra- and extracranial</td>
<td>Angiography</td>
<td>57 M, 43 W</td>
<td>35-64</td>
<td>51</td>
</tr>
<tr>
<td>Carotid, vertebral, intracranial</td>
<td>Angiography</td>
<td>99 M, 64 W</td>
<td>37-87</td>
<td>62</td>
</tr>
<tr>
<td>Carotid</td>
<td>Angiography</td>
<td>30</td>
<td>Univariate</td>
<td>+</td>
</tr>
<tr>
<td>Carotid</td>
<td>Pulsed-wave Doppler</td>
<td>100 M</td>
<td>50-69</td>
<td>Univariate</td>
</tr>
<tr>
<td>Intra- and extracranial</td>
<td>Angiography</td>
<td>462</td>
<td>20-70</td>
<td>Multivariate</td>
</tr>
<tr>
<td>Common, internal carotid</td>
<td>Pulsed-wave Doppler</td>
<td>15 M, 15 W</td>
<td>Univariate</td>
<td>+</td>
</tr>
<tr>
<td>Carotid bifurcation</td>
<td>Angiography</td>
<td>74 M, 47 W</td>
<td>62</td>
<td>Multivariate</td>
</tr>
<tr>
<td>Intra- and extracranial</td>
<td>Angiography</td>
<td>340 M, 122 W</td>
<td>≤70</td>
<td>Multivariate</td>
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<td>Carotid</td>
<td>B-mode ultrasonography</td>
<td>182 M, 194 W</td>
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<tr>
<td><strong>Case-control</strong></td>
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<tr>
<td>Internal carotid</td>
<td>Angiography</td>
<td>26 M, 15 W</td>
<td>Univariate</td>
<td>+</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>Angiography/endarterectomy</td>
<td>56 M, 19 W</td>
<td>42-77</td>
<td>60</td>
</tr>
<tr>
<td>Carotid</td>
<td>Angiography/endarterectomy</td>
<td>95 M, 43 W</td>
<td>37-79</td>
<td>62</td>
</tr>
<tr>
<td>Supra-aortic trunks</td>
<td>Angiography</td>
<td>24 M, 6 W</td>
<td>Univariate</td>
<td>(+)</td>
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<tr>
<td>Internal carotid</td>
<td>Angiography</td>
<td>121 M, 38 W</td>
<td>&gt;50</td>
<td>Univariate</td>
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<tr>
<td>Internal, common carotid</td>
<td>B-mode and Doppler ultrasonography</td>
<td>52</td>
<td>&gt;40</td>
<td>Univariate</td>
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<tr>
<td>Carotid</td>
<td>B-mode ultrasonography</td>
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<td>Univariate</td>
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<tr>
<td>Carotid</td>
<td>B-mode and Doppler ultrasonography</td>
<td>32 M, 23 W</td>
<td>&gt;60</td>
<td>Univariate</td>
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<td><strong>Restenosis (case-control)</strong></td>
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<tr>
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<td>Angiography</td>
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<td>47-69</td>
<td>58</td>
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<tr>
<td>Carotid</td>
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<td>13 M, 7 W</td>
<td>55</td>
<td>Univariate</td>
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<td><strong>Prospective</strong></td>
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<tr>
<td>Basilar, circle of Willis</td>
<td>Autopsy</td>
<td>42 M</td>
<td>60-69</td>
<td>Univariate</td>
</tr>
<tr>
<td>Intracranial carotid</td>
<td>Autopsy</td>
<td>244</td>
<td>40-90</td>
<td>Univariate</td>
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<tr>
<td>Major intracranial</td>
<td>Autopsy</td>
<td>129 M</td>
<td>40-69</td>
<td>Univariate</td>
</tr>
<tr>
<td>Circle of Willis</td>
<td>Autopsy</td>
<td>198 M</td>
<td>45-68</td>
<td>Multivariate</td>
</tr>
</tbody>
</table>

TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; M, men; W, women; dyslipidemia, combined Types I, IIa, IIb, III, IV, and V; TIAs, transient ischemic attacks; CHD, coronary heart disease. +, significant positive association; (+), positive association, not significant; 0, no significant association; (-), negative association, not significant; —, significant negative association.

*Extracranial and intracranial major vessels only.
†Age at death.
‡Age at entry into study.
§Large arteries of circle of Willis only.
|| Large arteries of circle of Willis only.
**Small arteries of circle of Willis only.

251 mg/dl, respectively. No significant differences were found among the three groups for triglyceride levels in either sex.

In a study comparing survivors of cerebral infarction with subjects with no symptoms (sex distribution not stated), Kölltringer and Jürgens found that mean serum total and LDL-cholesterol and lipoprotein A [Lp(a)] were significantly higher in groups with smooth-surface...
TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases Comments</th>
<th>Controls Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballantyne et al. 1974</td>
<td>10 subjects had neurologic symptoms</td>
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<tr>
<td>Mathew et al. 1975</td>
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<tr>
<td>Bansal et al. 1975</td>
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<td>Rüssner et al. 1978</td>
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<tr>
<td>Candelise et al. 1984</td>
<td>Reversible ischemic attacks</td>
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</tr>
<tr>
<td>van Merode et al. 1985</td>
<td>Randomly selected, neurologically</td>
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<td>Postiglione et al. 1985</td>
<td>Familial hypercholesterolemia</td>
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<tr>
<td>Ford et al. 1985</td>
<td>47 had TIA. 33 had cerebral infarctions</td>
<td></td>
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<tr>
<td>Passero et al. 1987</td>
<td>Reversible ischemic attacks</td>
<td></td>
</tr>
<tr>
<td>Crouse et al. 1987</td>
<td>Neurologically asymptomatic with and without CHD</td>
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</tr>
<tr>
<td>Randrup and Pakkenberg. 1967</td>
<td>Apoplectic with occlusion</td>
<td>CHD without coronary occlusion</td>
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<td>Duncan et al. 1977</td>
<td>Apoplectic without occlusion</td>
<td>CHD without coronary occlusion</td>
</tr>
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<td>Terrence and Rao. 1983</td>
<td>Excluding recent cerebral infarction</td>
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<td>Fellin et al. 1985</td>
<td>“Clinical” cerebrovascular disease</td>
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<td>Mixed clinical symptoms</td>
<td>Excluding CHD</td>
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<td>Költringer and Jürgens. 1985</td>
<td>Cerebral infarction</td>
<td>Coronary status unknown</td>
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<td>Cerebral infarction. TIA</td>
<td>Excluding CHD</td>
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<td>Lo et al. 1986</td>
<td>TIAs. asymptomatic bruits</td>
<td>Excluding CHD</td>
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<td>Hertzberg et al. 1979</td>
<td>Reoperation 7-156 mos</td>
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<td>Claggett et al. 1983</td>
<td>Reoperation 6-180 mos</td>
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<td>Paterson et al. 1963</td>
<td>Hospitalized sample</td>
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<td>Sadoshima et al. 1980</td>
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<td>Holme et al. 1981</td>
<td>Population-based</td>
<td></td>
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<tr>
<td>Reed et al. 1987</td>
<td>Population-based, excluding cases with cardiovascular disease at entry</td>
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</table>

plaques and with ulcerations compared with a control group with no detectable plaques (14, 33, and 4 mg/dl, respectively). The control group consisted of 9 men and 12 women, the group with smooth-surface plaques of 27 men and 15 women, and the group with ulcerations of 19 men and 18 women. Mean ages were 59, 68, and 69 years, respectively, in the three groups. Mean total cholesterol was 189 mg/dl in the control group versus 207 and 222 mg/dl in the groups with smooth-surface plaques and ulcerations, respectively. LDL-cholesterol was also significantly different in the three groups; 100, 123, and 140 mg/dl, respectively. Fasting triglycerides were higher in the two plaque groups, but these differences did not reach statistical significance.

Similar findings were reported by Zenker et al. Compared with a control group of 26 men and 11 women of the same mean age, Lp(a) was significantly higher in the patient group, and also correlated significantly with the atherosclerosis score of the extracranial carotid arteries. However, total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, and the LDL: HDL cholesterol ratio did not differ significantly between the control and cerebrovascular disease groups.
Finally, compared with age- and sex-matched controls, Lo et al\textsuperscript{37} found plasma concentrations of total cholesterol to be significantly higher in cerebrovascular disease patients with confirmed carotid atheroma.

**Restenosis Following Endarterectomy**

Although we identified four reports that evaluated the role of plasma lipid and lipoprotein concentrations as determinants of restenosis following endarterectomy,\textsuperscript{38-41} it is important to note that the factors related to restenosis may be unique to that condition and may not be typical of atherosclerotic progression in persons who have not undergone endarterectomy. These studies obviously focus on extracranial carotid atherosclerosis, and in each study some lipid parameter was associated with restenosis of the operated extracranial carotid artery. Hertzler et al\textsuperscript{38} found that patients with angiographically documented recurrent stenosis had significantly higher mean values of total cholesterol than a random control group of 50 carotid-endarterectomized patients without symptomatic recurrent stenosis (297 vs. 228 mg/dl). On the other hand, Clagett et al\textsuperscript{40} found no significant differences in levels of cholesterol and triglycerides and in the total: HDL cholesterol ratio between patients with recurrent stenosis and eight matched controls without symptoms of recurrent stenosis. HDL-cholesterol, however, was significantly higher among controls than among restenosis cases (45 vs. 37 mg/dl). A potential problem in these two studies relates to the absence of repeat angiography of the controls, some of whom may have experienced asymptomatic restenosis.

Two other studies of restenosis following endarterectomy were reviewed but are not included in Table 1 due to their different study design and objectives. Cantelmo et al\textsuperscript{41} reported that "a high proportion" of patients with recurrent stenosis had hyperlipidemia, although this was not defined. Cosman et al\textsuperscript{42} found that of seven patients with restenosis within 24 months of carotid endarterectomy, six had Type II or Type IV hyperlipoproteinemia. This represented 3.6% of the total number of endarterectomies. However, the investigators attributed this early restenosis to rapid, exuberant myointimal proliferation, histologically distinct from the atherosclerotic plaque that is the usual cause of late restenosis.

**Prospective Cohort Studies**

In our review of the literature we found only four studies that were designed to examine the relation between plasma lipid concentrations and cerebrovascular atherosclerosis prospectively. Paterson et al\textsuperscript{43} found a significant correlation between serum total cholesterol concentration and arterial plaque thickness in the basilar artery, circle of Willis, and approximately half an inch of each of the major vessels arising therefrom.

A Japanese study\textsuperscript{44} found no significant relation between serum total cholesterol and combined severity of atherosclerosis in carotid, vertebral, and basilar arteries as well as in the circle of Willis together with its main branches, although in general those subjects with higher cholesterol values had more atherosclerosis. In this study, subjects in each decile over 40 years were divided into tertiles according to their cholesterol values and the number of autopsied cases was relatively small, ranging from 12 to 34 in each tertile, so the power to detect significant differences within each age group was relatively low. Also, it is important to note that the highest tertile of serum cholesterol started at 180 mg/dl; this would usually represent the lowest tertile of cholesterol values in western Caucasian populations.

In the Oslo Study,\textsuperscript{44} the percentage of the intimal surface covered with raised lesions in intracranial major arteries was positively correlated with serum total cholesterol concentration (measured from a few weeks to 6 years prior to death). HDL-cholesterol concentration was negatively, but not significantly, related to lesions, but the ratio of HDL-cholesterol to non-HDL–cholesterol showed a significant although weak correlation with the magnitude of lesions. In stepwise multiple regression analyses, serum total cholesterol concentration was the only significant risk factor identified other than systolic or diastolic blood pressure.

In the Honolulu Heart Program in Hawaii,\textsuperscript{45} age-adjusted mean atherosclerosis in the large arteries of the circle of Willis was consistently related to serum total cholesterol. Atherosclerosis in the small arteries of the circle of Willis was consistently positively associated with serum triglycerides. These relations were also significant in multiple regression analyses after including age, blood pressure, serum glucose, height, body mass index, alcohol use, and cigarette use in the model.

**Discussion**

Of the studies reviewed, only two\textsuperscript{18,20} of the nine cross-sectional and one of the four prospective\textsuperscript{46} studies failed to find a relation between some plasma lipid and/or lipoprotein concentrations and cerebrovascular atherosclerosis. All of the case–control studies found such a relation. Problematic in the comparison of results from case–control studies is the selection of control groups. In the majority of the studies, the status of the carotid arteries of the control group is not known. Before the introduction of noninvasive imaging methods it was impossible to use a control group that was both asymptomatic and demonstrably free of atherosclerosis because only patients with symptoms underwent angiography. This situation produced, in general, two kinds of studies: those with symptom-free controls who did not undergo angiography and were therefore not necessarily free of disease\textsuperscript{26,30,31,37} and those with angiogram-negative controls who were not necessarily symptom-free.\textsuperscript{42,43} In an effort to assure the symptom-free status of controls in the former studies, many investigators eliminated patients with coronary as well as cerebrovascular symptoms from the control group.\textsuperscript{35,36,37}

Whether to include patients with coronary artery atherosclerotic disease among the control group is of
obvious importance in view of the overrepresentation of such patients among those with cerebrovascular atherosclerosis and the strong association of plasma lipid and lipoprotein levels with coronary disease. Removing symptomatic coronary patients from the control population without simultaneously removing them from the case population will exaggerate mean differences between the cases and controls, whereas inclusion (or oversampling) of symptomatic patients among controls limits generalizability. At the very least it would seem to be essential to control for coronary disease in studies of the relation between lipid and lipoprotein concentrations and cerebrovascular atherosclerosis.

Studies that have investigated different arteries or arterial segments within the cerebrovascular system may not necessarily yield similar results, and when investigators report on combined atherosclerosis in intracranial and extracranial arteries, or in differently sized arteries within the cranium, interpretation is difficult. Because blood lipids may affect the development of atherosclerosis differently in intracranial large and small arteries, one should not expect to find consistent results.

The intracranial arteries, which until recently could only be investigated in vivo using angiography, may soon be examined by the newly developed transcranial Doppler sonography. This procedure, which noninvasively interrogates intracranial arteries, combined with present methods for noninvasively imaging extracranial neck arteries will expand our ability to examine atherosclerotic lesions and their risk factors in asymptomatic as well as in symptomatic patients.

As reviewed by Bierman and Ross, the importance of hyperlipidemia as a significant risk factor for symptomatic cardiovascular disease has been found to decrease as a function of age. In contrast, our review suggests that hyperlipidemia seems to be a stronger risk factor for cerebrovascular atherosclerosis with advancing age. In fact, some of the discrepant results between the above studies may in part be due to the age distribution of the patients. The mean age of patients in the cross-sectional studies, which found significant relations between blood lipid and lipoprotein concentrations and atherosclerosis, was higher compared with the two studies that found no such significant relations. This suggests a possible interaction between age and blood lipids on cerebral arterial plaque formation. Another issue is whether it is in fact appropriate to statistically "adjust" for age when studying the effect of blood lipids on atherosclerosis. Because there is such a close link between atherosclerosis and aging, adjusting for age may in fact reduce the strength of the association between lipids and atherosclerosis in populations in which lipid levels are also strongly related to age.

Most of the studies reviewed in this paper were performed on men. None were done exclusively in women, and in three studies the patients' sex or the sex distribution was not stated. In the International Atherosclerosis Project men had more extensive raised atherosclerotic lesions than women in all cerebral arteries and in almost all age groups. Also, men had significantly more lesions in the carotid arteries for groups > 55 and in the intracranial arteries for those 65–69 years of age.

The majority of the reviewed studies were performed on Caucasians. Only two included blacks, and in these, results were not presented separately for each race. Because blacks as well as Japanese tend to have more intracranial atherosclerosis than American Caucasians, it is important to study and report separately the relation between plasma lipid concentrations and cerebrovascular atherosclerosis for different racial groups. This is especially important if, as Heyden et al suggested, there are etiologic and pathogenetic ethnic differences between vascular diseases of the extracranial and intracranial cerebral arteries.

The role of lipids and lipoproteins in the etiology of atherosclerosis is not completely clear. Lipoproteins may enter arterial walls through intact or damaged vascular endothelium and cause or complicate atherosclerotic plaques. Serum lipids or specific lipid subfractions may act differently on intracranial and extracranial arteries and on small and large intracranial vessels. Studies are needed to evaluate the role of lipids and lipoproteins in atherosclerosis, with strict attention to the site of the vascular pathology. It is necessary to study the etiology of cerebrovascular diseases by prospective studies to establish if such a relation exists and to study a possible sequential relation between blood lipids, atherosclerosis, and occlusive disease. Studies are needed that include adequate sample sizes of asymptomatic as well as symptomatic populations, using multivariate analysis to evaluate findings and to define the independence of these associations. In conclusion, this review supports the view that, although the relation may not be as strong, the effect of blood lipids on cerebral atherosclerosis is similar to their effect on coronary atherosclerosis, at least in older subjects.

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