Lipoprotein and Apolipoprotein Profile in Men With Ischemic Stroke

Role of Lipoprotein (a), Triglyceride-Rich Lipoproteins, and Apolipoprotein E Polymorphism

Juan Pedro-Botet, MD; Mariano Senti, MD; Xavier Nogués, MD; Juan Rubiés-Prat, MD; Jaume Roquer, MD; Luis D’Olhaberriague, MD; and Josep Olive, MD

Background and Purpose: The role of lipoprotein abnormalities in the development of ischemic cerebrovascular disease has not been sufficiently clarified. The aim of this study was to identify the lipoprotein profile in ischemic cerebrovascular disease and the possible role of apolipoprotein E polymorphism.

Methods: The relation between the concentrations of lipoprotein (a), intermediate density lipoproteins, apolipoprotein A-I, apolipoprotein B, apolipoprotein E, and other lipoproteins was studied in 100 men with ischemic cerebrovascular disease (48 atherothrombotic, 28 lacunar, and 24 of unknown type) and in 100 healthy age-matched men as a control group.

Results: Patients with ischemic cerebrovascular disease had significantly higher levels of lipoprotein (a), lipids carried by intermediate density lipoproteins, and low density lipoprotein cholesterol and lower levels of high density lipoproteins than control subjects. Patients with atherothrombotic infarction had higher total serum cholesterol and low density lipoprotein cholesterol concentrations than patients with lacunar infarction. To assess lipoprotein abnormalities in normolipidemic subjects, a subgroup of 38 patients with ischemic cerebrovascular disease and 53 control subjects, both with serum cholesterol levels <5.2 mmol/l (200 mg/dl) and triglycerides <2.3 mmol/l (200 mg/dl), was analyzed. Serum lipoprotein (a), lipids carried by very low density lipoproteins and intermediate density lipoproteins, and low density lipoprotein triglycerides were significantly higher in normolipidemic patients compared with normolipidemic control subjects, whereas high density lipoprotein cholesterol levels were lower. Apolipoprotein E polymorphism in our ischemic cerebrovascular patients differed from that of the control group, with the e4 allele being more prevalent.

Conclusions: Increased serum lipoprotein (a) levels and intermediate density lipoprotein abnormalities together with decreased high density lipoprotein levels are major risk factors for ischemic cerebrovascular disease, even in normocholesterolemic and normotriglyceridemic subjects. Finally, the e4 allele could probably be a predisposing genetic marker for ischemic cerebrovascular disease. (Stroke 1992;23:1556-1562)

Key Words • lacunar infarction • lipids • lipoproteins • risk factors

The relation between serum lipids and lipoproteins in ischemic cerebrovascular disease (ICVD) is not as clear-cut as in coronary heart disease (CHD). Several studies of lipid-related risk factors in ICVD have varied greatly in their definition of cerebrovascular end points, assessment of concomitant risk factors, lipids and lipoproteins analyzed, and findings. Classification of ischemic stroke into atherothrombotic and lacunar subtypes based on presumed pathogenetic mechanisms has only occasionally been attempted. There is overwhelming evidence relating high levels of low density lipoproteins (LDL) with CHD and low levels of high density lipoproteins (HDL) with CHD and peripheral vascular disease, but their relation to cerebrovascular atherosclerosis is controversial. Over recent years, triglyceride-rich lipoprotein abnormalities have been strongly associated with CHD and peripheral vascular disease. Apolipoprotein (apo) E, a constituent of very low density lipoprotein (VLDL) and HDL, plays a critical role in the catabolism of triglyceride-rich lipoproteins and cholesterol homeostasis. Some studies have indicated that among the three codominant alleles of apo E, e2, e3, and e4, the latter is associated with an increased risk for CHD. On the other hand, there are no data con-
cerning the possible role of triglyceride-rich lipoproteins, mainly intermediate density lipoproteins (IDL), and apo E polymorphism in the development of ICVD.

If the association of serum lipids, lipoproteins, apolipoproteins, and apo E phenotypes with stroke risk parallels that of CHD, lipid abnormalities would most probably be encountered in patients with stroke caused by large-vessel atherosclerosis rather than lacunar infarction. Thus, the aim of this study was to examine the serum concentrations of lipids, lipoproteins, and apolipoproteins in patients with ischemic stroke to evaluate the apo E phenotype distribution and to determine whether differences in lipoprotein and apolipoprotein profiles could be demonstrated between male survivors of atherothrombotic brain infarction and lacunar stroke.

Subjects and Methods

Subjects

One hundred consecutive outpatient men aged 41–85 years (mean, 64.4 years), survivors of ischemic noncardioembolic stroke and evaluated by the neurology departments of three municipal hospitals over a 6-month period, were included in the study. Based on the results of clinical examination, computed tomography (CT), electrocardiogram, and Doppler ultrasonography with spectral analysis (common, external, and internal carotid arteries; vertebral arteries at the retromastoid level; and subclavian arteries), ischemic stroke was classified as atherothrombotic infarction, lacunar infarction, or ICVD of unknown type according to the Classification of Cerebrovascular Diseases III. In 48 patients the diagnosis of atherothrombotic infarction was based on the following criteria: 1) clinical evidence of ischemic stroke; 2) cranial CT consistent with ischemic stroke with no evidence of intraparenchymal, intraventricular, or subarachnoid hemorrhage or coincident lacunar infarct; 3) absence of major predisposing factors to cardiogenic stroke including atrial fibrillation, valvular heart disease, prosthetic heart valves, endocarditis, acute myocardial infarction, dilated cardiomyopathy, or ventricular aneurysm; and 4) Doppler ultrasonography showing either blood flow alterations suggesting stenosis of the corresponding extracranial artery or ulcerated atheroma plate(s) without stenosis. Twenty-eight patients had isolated lacunar infarction with the following inclusion criteria: 1) symptoms of lacunar stroke consisting of one of the five main classic lacunar syndromes described by Fisher (pure motor stroke, clumsy hand–dysarthria, ataxic hemiparesis, pure sensory or sensorimotor stroke); 2) cranial CT showing either lacunar infarct or normal CT scan; 3) Doppler ultrasonography showing no evidence of extracranial arterial disease, and 4) absence of a cardiogenic source of embolus (see above). ICVD of unknown type, which cannot easily be classified clinically as belonging to either of the other two subtypes, was diagnosed in the remaining 24 patients. Handicap was measured using the Rankin Disability Scale, and all patients ranged from grades 1 to 3 at the time of the study.

Patients with CHD (including asymptomatic patients with electrocardiographic evidence of previous myocardial infarction), vasculitis, diabetes mellitus, and other endocrine, liver, and renal diseases were excluded. Body mass index of patients was 25.2±3.0 (mean±SD). Forty-nine patients had never been smokers, and smoking history was recorded in 31 of whom 30 were smokers at the time of the study. Thirty-five patients had hypertension, and 28 of them received treatment with angiotensin-converting enzyme inhibitors or calcium channel blockers.

One hundred men age-matched (by 10-year age groups) with the patients were used as controls and recruited from hospital and university staff, nonretributed blood donors, and subjects who attended the ophthalmology outpatient clinic for visual acuity examination. This control group was judged free of any illness by history, clinical examination, and routine laboratory data. Forty-five had never been smokers, 15 were ex-smokers, and 40 were current smokers. Body mass index of controls was 25.2±2.8. Exclusion criteria for both patients and controls were alcohol consumption >40 g/day, body mass index >30, or both. None of the subjects were receiving therapy known to cause changes in lipid and lipoprotein profiles.

Lipoprotein Analysis

Blood samples were obtained in the morning after an overnight fast, subjects were seated during phlebotomy, and serum was collected a minimum of 3 months after a qualifying stroke. VLDL fraction (d<1.006 g/ml) was isolated by preparative ultracentrifugation in a Cen-trikon ultracentrifuge (Kontron Instruments, Milan, Italy) using a TFT 50.38 rotor (Kontron Instruments). The other lipoproteins (IDL, 1.006<d<1.019 g/ml; LDL, 1.019<d<1.063 g/ml; and HDL, d>1.063 g/ml) were isolated by density gradient ultracentrifugation in a TST 41.14 rotor. Serum cholesterol and serum triglycerides were assayed enzymatically, as well as cholesterol and triglycerides of lipoprotein fractions. Proteins of each isolated fraction were determined by a colorimetric method. Serum apo A-I and serum apo B were quantified by immunonephelometry with reagents supplied by Beckman Instruments (Fullerton, Calif.), and serum apo E concentration was determined by radial immunodiffusion (Daichi Pure Chemical Co., Tokyo, Japan). Apo E polymorphism was studied by isoelectric focusing from delipidated VLDL as described previously by Eto et al. Serum concentration of Lp(a) was quantified by enzymoimmunoanalysis in TintElize Lp(a) microplates (Biopool, Umea, Sweden) with a lower limit of 1 mg/dl sensitivity, and a control Lp(a) was supplied by Biopool.

Statistical Analysis

Assumption of normal distribution for continuous variables was tested by the Kolmogorov-Smirnoff statistics. Comparison between two groups was made using Student's t test for independent samples. Lipoprotein values in the different apo E phenotypes were compared by one-way analysis of variance, and differences between groups were tested by Tukey's test. The relations between continuous variables were examined by Spearman's correlation coefficients. Contingency tables of apo E phenotypes in patients and controls were compared by χ² square test.

Discriminant analysis was performed based on a stepwise forward–backward procedure. The significance of a variable's contribution was determined from the final F-to-remove statistic. We used log-transformed
Lp(a) values because the distribution of Lp(a) clearly deviated from normality. Significance levels were set at 0.05 in all cases.

**Results**

**Serum Lipid, Lipoprotein, and Apolipoprotein Concentrations**

Lipids carried by IDL, LDL, and serum Lp(a) were significantly higher in patients with ICVD, whereas HDL cholesterol levels were lower (Table 1). There were no significant differences in apo E concentrations between patients (34.2 ± 14.2 mg/l) and control subjects (31.0 ± 11.2 mg/l). Other lipids, lipoprotein, and apolipoprotein concentrations together with a VLDL triglyceride/HDL cholesterol ratio in patients and control subjects are shown in Table 1. Lipid, lipoprotein, and apolipoprotein concentrations showed no significant differences between patients with atherothrombotic stroke and those with lacunar infarction, except for total serum cholesterol and LDL cholesterol (Table 1).

**Lipids and Other Vascular Risk Factors and Ischemic Cerebrovascular Disease**

**Hypertension.** There were no significant differences in the prevalence of hypertension among the three different subtypes of ICVD (35.4% of those with atherothrombotic ICVD, 42.8% of those with lacunar stroke, and 25% of those with unknown type ICVD). Neither were any significant differences found when the lipid profile in the ICVD group as a whole was compared according to the hypertension variable. Similarly, no differences were ob-
E Phenotypes

Ischemic Cerebrovascular Disease and Apolipoprotein

Pedro-Bo et al Lipoprotein Profile in Ischemic Stroke

TABLE 2. Lipid, Lipoprotein, and Apolipoprotein Profiles in Normolipidemic Control Subjects and Patients with Ischemic Cerebrovascular Disease

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Patients</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=53)</td>
<td>(n=38)</td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.46±0.56</td>
<td>4.42±0.59</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.99±0.33</td>
<td>1.23±0.41</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>1.45±0.36</td>
<td>1.45±0.41</td>
<td>NS</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.84±0.14</td>
<td>0.88±0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>0.10±0.09</td>
<td>0.20±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.24±0.14</td>
<td>0.33±0.14</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.44±0.26</td>
<td>0.58±0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.09±0.05</td>
<td>0.21±0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDL</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.15±0.15</td>
<td>0.29±0.44</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.11±0.08</td>
<td>0.17±0.15</td>
<td>&lt;0.05</td>
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<tr>
<td>Proteins</td>
<td>0.06±0.06</td>
<td>0.08±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
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<tr>
<td>Cholesterol</td>
<td>2.66±0.62</td>
<td>2.74±0.58</td>
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</tr>
<tr>
<td>Triglycerides</td>
<td>0.18±0.08</td>
<td>0.27±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.45±0.13</td>
<td>0.52±0.20</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
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<td></td>
</tr>
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<td>Cholesterol</td>
<td>1.07±0.27</td>
<td>0.86±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.06±0.03</td>
<td>0.08±0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proteins</td>
<td>1.25±0.17</td>
<td>1.09±0.17</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>VLDL-T/HDL-C</td>
<td>0.45±0.31</td>
<td>0.78±0.47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD. Lipids are expressed in mmol/l, Lp(a) and proteins in g/l.

Apo, apolipoprotein; Lp(a), lipoprotein(a); VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; T, triglycerides; C, cholesterol.

FIGURE 1. Bar graph of prevalence of apolipoprotein E phenotypes in control subjects and patients with ischemic cerebrovascular disease.

E polymorphism in the atherothrombotic ICVD group was distributed as follows: 14.6% E3/E2, 50% E3/E3, 0% E4/E2, 29.1% E4/E3, 4.2% E4/E4, and 2.1% E2/E2. This distribution did not differ from that of the lacunar ICVD group (10.7% E3/E2, 35.7% E3/E3, 0% E4/E2, 21.4% E4/E3, 10.7% E4/E4, and 3.5% E2/E2). According to the apo E phenotypes, lipid and lipoprotein concentrations showed no significant differences either in the control group or in the ICVD group.

Univariate and Multivariate Analyses

Table 3 lists the correlation coefficients between lipid, lipoprotein, and apolipoprotein variables. Serum cholesterol correlated with LDL cholesterol and serum apo B. There was a significant positive correlation between the three measured components of IDL. IDL triglycerides also correlated positively with VLDL triglycerides. HDL cholesterol showed a negative correlation with serum triglyceride-rich lipoproteins. On the other hand, there was no significant correlation between Lp(a) concentration and any other variable.

Discriminant analysis was performed to study possible risk factors for ICV D. The dependent variable was the presence or absence of cerebrovascular disease. The standardized discriminant function coefficients (Table 4) indicated that Lp(a) and HDL constituted the best predictors for presence or absence of ICVD, rather than other lipids or lipoproteins such as LDL cholesterol and LDL cholesterol. Again, discriminant analysis was performed with the two groups of ICVD patients defined as atherothrombotic or lacunar. The standardized discriminant function coefficients (Table 4) indicated that serum cholesterol and LDL cholesterol are the two significant predictors for lacunar or atherothrombotic ICVD.

Discussion

Stroke is one of the leading causes of death in developed countries and constitutes a major source of disability in persons older than age 60 years. The influence on ICVD of several potent CHD and peripheral vascular disease risk factors, such as lipid and lipoprotein abnormalities, is unclear. Classification of ICVD into atherothrombotic and lacunar subtypes and the exclusion of cardioembolic stroke may have allowed...
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TABLE 3. Spearman’s Correlation Coefficients in Patients With Ischemic Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Serum</th>
<th>Serum C</th>
<th>Serum T</th>
<th>VLDL-C</th>
<th>VLDL-T</th>
<th>IDL-C</th>
<th>IDL-T</th>
<th>IDL-P</th>
<th>LDL-C</th>
<th>LDL-P</th>
<th>HDL-C</th>
<th>Apo A-I</th>
<th>Apo B</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum C</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Serum T</td>
<td>0.12</td>
<td>1.00</td>
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<tr>
<td>VLDL-C</td>
<td>0.16</td>
<td>0.51*</td>
<td>1.00</td>
<td></td>
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</tr>
<tr>
<td>VLDL-T</td>
<td>0.08</td>
<td>0.86*</td>
<td>0.59*</td>
<td>1.00</td>
<td></td>
<td></td>
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<tr>
<td>IDL-C</td>
<td>-0.03</td>
<td>0.20†</td>
<td>0.08</td>
<td>0.01</td>
<td>1.00</td>
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<tr>
<td>IDL-T</td>
<td>-0.03</td>
<td>0.53*</td>
<td>0.21†</td>
<td>0.34*</td>
<td>0.70*</td>
<td>1.00</td>
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<tr>
<td>IDL-P</td>
<td>-0.16</td>
<td>0.09</td>
<td>0.13</td>
<td>0.01</td>
<td>0.42*</td>
<td>0.46*</td>
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<tr>
<td>LDL-C</td>
<td>0.78*</td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
<td>-0.25†</td>
<td>-0.26†</td>
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<td>LDL-P</td>
<td>0.19</td>
<td>0.10</td>
<td>0.06</td>
<td>0.03</td>
<td>0.29†</td>
<td>0.22†</td>
<td>0.28†</td>
<td>0.19</td>
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<td>HDL-C</td>
<td>0.19</td>
<td>-0.36*</td>
<td>-0.29†</td>
<td>-0.32†</td>
<td>-0.24†</td>
<td>-0.28†</td>
<td>-0.17</td>
<td>0.21†</td>
<td>0.05</td>
<td>1.00</td>
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<tr>
<td>Apo A-I</td>
<td>0.05</td>
<td>-0.24†</td>
<td>0.15</td>
<td>-0.13</td>
<td>0.07</td>
<td>-0.02</td>
<td>0.29†</td>
<td>-0.07</td>
<td>0.03</td>
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<tr>
<td>Apo B</td>
<td>0.44*</td>
<td>0.17</td>
<td>0.03</td>
<td>0.13</td>
<td>-0.17</td>
<td>-0.09</td>
<td>-0.37*</td>
<td>0.41*</td>
<td>0.15</td>
<td>0.08</td>
<td>-0.37*</td>
<td>1.00</td>
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<tr>
<td>Lp(a)</td>
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<td>0.13</td>
<td>-0.07</td>
<td>0.07</td>
<td>-0.09</td>
<td>0.07</td>
<td>-0.01</td>
<td>0.01</td>
<td>-0.09</td>
<td>-0.07</td>
<td>-0.01</td>
<td>0.11</td>
<td>1.00</td>
</tr>
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</table>

C, cholesterol; T, triglycerides; P, proteins; VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; Apo, apolipoproteins; Lp(a), lipoprotein(a).

*p<0.01, †p<0.05.

differences to emerge. The 24% of ICVD of unknown type in the current study concurs with the percentage found in other studies.24

Elevated total cholesterol and triglyceride concentrations were found to be associated with stroke in some studies,34-36 whereas others found no association between serum triglycerides and stroke.37 In the current study, no differences were observed between cholesterol and triglycerides in patients and control subjects. As occurs in CHD, we found higher LDL cholesterol concentrations and lower HDL in patients compared with control subjects. The discriminant analysis indicated that HDL constituted the best marker for the presence or absence of ICVD.

Stroke data registries38-40 have recognized the importance of lacunar infarction disease and have separated this type from others, including large-artery thrombosis. It is not clear, however, how the risk factor profiles for these two distinct manifestations of cerebrovascular disease differ. While only two studies found differences in HDL cholesterol concentrations,10,13 our most striking differential finding between atherothrombotic infarction and lacunar stroke was that total cholesterol and LDL cholesterol were higher in the former. These distinctive differences are not influenced by age, smoking, hypertension, or apo E polymorphism. Similarly, discriminant analysis showed total cholesterol and LDL cholesterol to be predictive lipid variables for classification in either of the patient subgroups. Thus, in view of these data, the lipoprotein profile in the atherothrombotic group appears to more closely resemble that of the CHD group.

Lp(a) has been shown to be associated with cardiovascular disease44 and has been found to be increased in patients with ICVD.43,44-45 This also occurred in the present study, even in normolipidemic patients. This

TABLE 4. Independence of Risk Factors for Patients With Ischemic Cerebrovascular Disease and for Those With Lacunar or Atherothrombotic Infarction

<table>
<thead>
<tr>
<th>All ICVD patients</th>
<th>Patients with lacunar or atherothrombotic infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>p</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.15</td>
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<tr>
<td>Triglycerides</td>
<td>0.18</td>
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<td>Apo A-I</td>
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<td>0.23</td>
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<td>Lp(a)</td>
<td>0.58</td>
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<tr>
<td>VLDL cholesterol</td>
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<tr>
<td>VLDL triglycerides</td>
<td>0.11</td>
</tr>
<tr>
<td>IDL cholesterol</td>
<td>0.37</td>
</tr>
<tr>
<td>IDL triglycerides</td>
<td>0.27</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.30</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.57</td>
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</table>

ICVD, ischemic cerebrovascular disease; B, standardized discriminant function coefficient; Apo, apolipoprotein; Lp(a), lipoprotein(a); VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins.
finding supports the hypothesis that Lp(a) is a marker for atherosclerosis. In the present study no association was found between Lp(a) concentration and hypertension. Such an association has been recently described by Asplund et al., who partially attributed this association to the use of β-blockers.

Since apolipoproteins may be better discriminators for atherosclerosis than lipids, at least in CHD, recent studies have examined the protein component of lipoproteins in ICVD. Apo A-I and apo B concentrations in ICVD patients were normal in one study, as in the present study, whereas another reported a decrease in apo A-I in both patients with cortical infarction and patients with lacunar infarction. In addition to familial dysbetalipoproteinemia, other abnormalities in IDL composition in patients with chronic renal failure and diabetes mellitus have been described and may contribute to the development of atherosclerosis in these patients. Similarly, abnormalities in IDL composition in patients with CHD and peripheral vascular disease have been reported, and recent evidence points to a close relation between abnormalities in IDL composition and CHD and peripheral vascular disease in hypercholesterolemia and also normocholesterolemic patients. In the present study, we found an increase in IDL cholesterol and IDL triglycerides in patients with ICVD. The atherogenic potential of triglyceride-rich lipoproteins might be due to alterations in the catabolism of these lipoproteins or their remnants. Moreover, the VLDL triglyceride/HDL cholesterol ratio, which reflects triglyceride catabolism, was significantly higher in the entire group of ICVD patients and even in normotriglyceridemic patients, suggesting an impaired metabolism of triglyceride-rich lipoproteins.

For many years it has been accepted that lacunes are caused by hypertensive small-vessel disease. However, the role of hypertension in the pathogenesis of lacunar infarction has been questioned. In the present study, no significant differences were found in the prevalence of hypertension between the different ICVD subtypes. This supports the idea that lacunar infarction may be due to a diversity of etiopathogenic mechanisms.

The prevalence of the different apo E phenotypes in our control group was similar to that previously reported in other European populations. The higher prevalence of E4 polymorphism in patients with ICVD found in the present study has also been described in patients with CHD and recently in a short series of patients with ICVD. However, a clear relation between apo E polymorphism and plasma lipid levels was not evident in the present study and in other studies. Thus, the relation between apo E allele frequencies and ICVD may be suggestive but not convincing.

In addition to hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption, the present study emphasizes the role of lipidprotein disturbances as a major risk factor for ICVD. Moreover, the fact that increased Lp(a) levels and IDL abnormalities were also found in a subgroup of patients with normocholesterolemia and normotriglyceridemia led to their being considered as risk factors for atherosclerosis. Finally, it is noteworthy that total serum cholesterol and LDL cholesterol are higher in patients with atherothrombotic infarction than in those with lacunar stroke.

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