Low Levels of High-Density Lipoprotein Cholesterol Are Associated With Echolucent Carotid Artery Plaques

The Tromsø Study

Ellisiv B. Mathiesen, MD; Kaare H. Bønaa, MD, PhD; Oddmund Joakimsen, MD, PhD

Background and Purpose—Ultrasound-assessed plaque morphology is an independent predictor of ischemic stroke. The purpose of this population-based cross-sectional nested case-control study was to examine the risk factors associated with carotid plaque morphology.

Methods—Ultrasonography of the right carotid artery was conducted on 6727 participants in a population health survey (response rate 79%). Plaque echogenicity, defined as reflectance of the emitted ultrasound signal, was scored as echolucent, predominantly echolucent, predominantly echogenic, or echogenic. Information on cardiovascular risk factors in all 216 participants who had carotid stenosis and in 223 control subjects matched by age and sex who did not have carotid stenosis was obtained from measurements of blood pressure, weight, height, and nonfasting blood samples and from a self-administered questionnaire.

Results—In both univariate and multivariate analyses, low levels of HDL cholesterol and increasing degree of stenosis were independently associated with an increased risk of having an echolucent plaque. For 1-SD increase in HDL cholesterol, the adjusted odds of being in a lower plaque echogenicity category decreased by 30% (OR 0.69, 95% CI 0.52 to 0.93).

Conclusions—These findings indicate that low levels of HDL cholesterol are associated with an increased risk of having echolucent, rupture-prone atherosclerotic plaques. (Stroke. 2001;32:1960-1965.)

Key Words: atherosclerosis ■ carotid stenosis ■ lipoproteins, HDL ■ ultrasonography

Recently, there has been an increasing awareness of the importance of the composition of the atherosclerotic carotid plaque as a major risk factor for stroke. From the study of coronary heart disease, it is known that plaques consisting of a lipid-rich core covered by a thin fibrous cap seem to be more rupture prone and more likely to cause clinical events.1-2 Plaque echogenicity as assessed by B-mode ultrasound has been found to reliably predict the content of soft tissue and the amount of calcification in carotid plaques.3-7 Plaques that appear echolucent on B-mode ultrasound are lipid rich, whereas echogenic plaques have a higher content of dense fibrous tissue and calcification. Several cross-sectional studies have reported an association between echolucent or hypoechoic plaques and a history of TIAs and stroke. Recently, we found in a prospective population-based study that plaque morphology was an independent predictor of ischemic cerebrovascular events,8 and others have reported similar results.9,10

Because plaque morphology can be used to predict future clinical events, it is important to study the risk factors associated with atherosclerotic plaque morphology. Little is known about this, and population-based data are not available. In a study of symptomatic patients with carotid stenosis, echolucent plaques were associated with elevated levels of fasting and postprandial triglyceride-rich lipoproteins.11 The purpose of the present study was to assess risk factors associated with carotid artery plaque morphology within the setting of a population-based study.

Subjects and Methods

Subjects

In 1994 to 1995, all inhabitants aged ≥25 years and living in the municipality of Tromsø were invited to participate in the fourth survey of the Tromsø Study; a prospective, population-based study on cardiovascular and other chronic diseases.12 The fourth survey consisted of 2 screening visits 4 to 12 weeks apart. All subjects between 55 to 74 years, random 5% samples of subjects in the other age groups, and a selected group of 308 high-risk men aged 40 to 54 years who had previously taken part in a dietary intervention trial were invited to the second screening visit, which included ultrasonography of the right carotid artery. A total of 6889 subjects attended, representing 79% of the eligible population. Ultrasonography of the right carotid artery in the neck was performed on 6727 persons; among these, both the right and left carotid arteries were examined in 784 persons. The selected group of high-risk men was excluded for the purpose of this paper. All 242 persons with
suspected stenosis and/or occlusion of 1 or both internal carotid arteries and a control group of 229 persons without right-sided stenosis/occlusion, matched by age and sex, were invited to participate in a follow-up study that included repeat ultrasonography of both the left and right carotid arteries. Among the 242 subjects with suspected stenosis, 2 persons did not want to participate in the follow-up study, 1 died shortly after the survey, and 14 persons did not fulfill the criteria for stenosis at the repeat ultrasound. They were excluded from the present analyses, as were 9 persons with exclusion of the carotid artery, because we could not reliably assess plaque morphology in occluded arteries. Four of the 229 control subjects had stenosis of the left carotid artery, and 1 had stenosis and 1 had occlusion of the right carotid artery, and they were excluded. Thus, a total of 216 subjects with stenosis and 223 subjects without stenosis were included in the study. Informed consent was obtained from the participants, and the regional ethical committee approved the study.

Ultrasoundography

Details about the ultrasound methods and their reproducibility have been published previously. The ultrasound assessments both at screening and at the second visit were made by sonographers who were blinded to the laboratory data and to data from the questionnaires. Plaque morphology in terms of echogenicity was graded from 1 to 4 as echolucent, predominantly echolucent, predominantly echogenic, or echogenic, respectively (Figure 1). The vessel lumen was used as the reference structure for defining echoluency, and the bright echo-zone produced by the media-adventitia interface in the far wall was used as the reference structure for defining echogenicity. The reproducibility of the assessment of plaque echogenicity was tested by the use of the $\kappa$ statistic, which gave a simple $\kappa$ value of 0.56 (95% CI 0.38 to 0.74). The weighted $\kappa$ value was 0.65 (95% CI 0.51 to 0.79), which can be characterized as substantial. Stenosis of the carotid artery was considered to be present if 1 or both of the following criteria were met: (1) peak systolic velocity in tightest stenotic part ($PSV_r$) of $\geq 0.2$ m/s higher than peak systolic velocity at the point of reference ($PSV_v$), or $\geq 0.1$ m/s if the stenosis was located at the bifurcation or the bulb of the internal carotid artery. The distal part of the internal carotid artery (with parallel walls) was used as the point of reference. (2) Thirty-five percent or greater reduction in lumen diameter on a longitudinal B-mode scan. According to these criteria, 119 persons had 35% to 49% degree of stenosis, and 97 had 50% to 99% degree of stenosis. Occlusion was diagnosed when an open lumen of the artery was not visible on B-mode or if there was a visible occluding plaque in the artery, and there was no detectable flow in the artery by pulsed Doppler or by color Doppler. For the purpose of this report, the degree of stenosis was calculated with the equation $(1-PSV_r/PSV_v)\times100\%$, where PSV$_r$ denotes peak systolic velocity at the point of reference, and PSV$_v$ denotes the peak systolic velocity in the stenosis. One subject each had missing data on PSV$_r$ and on PSV$_v$. In these persons, the degree of stenosis was estimated by calculation of the lumen diameter reduction: (plaque thickness/lumen diameter)$\times100\%$. In the case of bilateral stenosis, which was present in 29%, the carotid artery with the highest degree of stenosis was selected. All measurements were made on-line, and printed images were made for later documentation.

Cardiovascular Risk Factors

Two self-administered questionnaires, checked by trained nurses, consisted of information about smoking habits, previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (all yes/no), treated hypertension (never/previous/current), and use of drugs. Height and weight were measured with the patients in light clothing without shoes; body mass index (BMI) was calculated as weight per height squared (kg/m$^2$). Blood pressure was recorded by the use of an automatic device (Dinamap Vital Signs Monitor) in a separate, quiet room by a specially trained nurse. After the participants had been seated for 2 minutes, 3 recordings were made at 2-minute intervals. The mean of the 2 last values is used in this report. Fibrinogen was measured using the PT-Fibrinogen reagent (Instrumentation Laboratory). White blood cell count was measured by the Coulter method with a Coulter Counter S-Plus STKR analyzer (Coulter Electronics Ltd.). Serum HDL cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride. Serum total cholesterol and triglyceride levels were analyzed by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides; Boehringer-Mannheim). Blood pressure and nonfasting blood lipid levels were measured at both the first and the second screening visit. Participants who at the first visit of the survey had blood pressure or lipid levels above certain limits were informed about this. It is possible that some of them received medical advice during the time between the first and the second visits that may have altered their risk factor levels. Because of this, measurements from the first visit were used in all analyses. All blood analyses were performed at the Department of Clinical Chemistry, University Hospital of Tromsø.

Statistical Analysis

Differences between mean values were tested for statistical significance by the Student’s $t$ test or by ANOVA, and differences between proportions were tested by $\chi^2$ tests. Linear trend was tested by multiple regression analysis and by a $\chi^2$ test for trend. We performed pooled analyses of women and men, because the results were similar in women and men. Logarithmically transformed values of triglycerides were used to approximate normal distribution, and adjust-
ments for time since last meal were made, but because this had virtually no impact on results, nontransformed and unadjusted values were used. The independent relationship between risk factors and plaque morphology was tested by logistic regression analysis (cumulative ordinal logit model), where plaque morphology (4 categories coded as 1 indicates echolucent plaque; 2, predominantly echolucent; 3, predominantly echogenic; and 4, echogenic plaque) was treated as the dependent variable, and risk factors were treated as independent variables. The model calculates the OR for being in a lower (ie, more echoluent) category of the dependent variable. A score test confirmed that the proportional odds assumption was met ($\chi^2$ score test 14.4, 12 df, $P=0.27$). Only variables that were statistically significant in univariate analysis were included in the multivariate model, along with age and sex. Interaction with age and sex was examined with plaque morphology as the dependent variable and the independent variables of risk factor, age (or sex), and risk factor*age (or sex). CIs for proportions and $\chi^2$ for trend in proportions were calculated with the Epi Info software package (Version 6.04, 1997). The SAS software package was used for the other statistical analyses (SAS®, release 6.12, 1996). A 2-sided $P<0.05$ value was considered significant.

### Results

Subjects with carotid stenosis had significantly higher mean levels of cholesterol, triglycerides, fibrinogen, white blood cell count, and systolic blood pressure and were more likely to smoke than were control subjects (Table 1). HDL cholesterol was lower in cases than control subjects, but the difference was not statistically significant. Age, sex distribution, BMI, and diastolic blood pressure were similar for cases and control subjects.

Low echogenicity (echolucency) was associated with significantly lower levels of HDL cholesterol and higher levels of triglycerides and systolic blood pressure (Table 2). The proportion of subjects with echolucent and predominantly echolucent plaques was 69% in the lowest tertile of HDL cholesterol (<1.23 mmol/L), 58% in the middle tertile (1.23 mmol/L), and 47% in the highest tertile (1.23 mmol/L). Diastolic blood pressure was similar for cases and control subjects.

### Table 1. Characteristics of Participants With and Without Carotid Stenosis: The Tromsø Study

<table>
<thead>
<tr>
<th>Carotid Stenosis</th>
<th>Yes (n=216)</th>
<th>No (n=223)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>56.9</td>
<td>59.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.2 (5.6)</td>
<td>67.7 (5.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.2 (4.1)</td>
<td>25.8 (3.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>7.27 (1.28)</td>
<td>6.86 (1.20)</td>
<td>0.0006</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.46 (0.42)</td>
<td>1.52 (0.42)</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.91 (1.00)</td>
<td>1.61 (0.82)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Fibrinogen, mmol/L</td>
<td>3.8 (1.0)</td>
<td>3.6 (0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>White blood cell count, E.09/L</td>
<td>7.3 (1.9)</td>
<td>6.6 (1.8)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>156.6 (24.3)</td>
<td>149.1 (22.2)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.3 (14.2)</td>
<td>84.5 (12.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Current smoking</td>
<td>38.4</td>
<td>25.1</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percentages. $^*$Student’s t test was used for comparison of mean values, and $\chi^2$ test was used for comparison of proportions.

### Table 2. Risk Factor Levels in Subjects With Stenotic Plaques Stratified According to Plaque Echogenicity: The Tromsø Study

<table>
<thead>
<tr>
<th>Plaque Echogenicity</th>
<th>Echolucent (n=25)</th>
<th>Predominantly Echolucent (n=101)</th>
<th>Predominantly Echogenic (n=69)</th>
<th>Echogenic (n=21)</th>
<th>$P$ for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>72.0 (18)</td>
<td>56.4 (57)</td>
<td>55.1 (38)</td>
<td>47.6 (10)</td>
<td>0.4</td>
</tr>
<tr>
<td>Age, y</td>
<td>67.4 (6.0)</td>
<td>68.0 (5.8)</td>
<td>68.8 (5.4)</td>
<td>68.7 (4.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.0 (4.3)</td>
<td>26.8 (3.8)</td>
<td>26.1 (4.7)</td>
<td>24.7 (3.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>7.47 (1.49)</td>
<td>7.29 (1.22)</td>
<td>7.23 (1.24)</td>
<td>7.13 (1.48)</td>
<td>0.9</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.38 (0.38)</td>
<td>1.38 (0.39)</td>
<td>1.49 (0.41)</td>
<td>1.78 (0.53)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.94 (1.11)</td>
<td>2.09 (1.04)</td>
<td>1.83 (0.91)</td>
<td>1.26 (0.65)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Fibrinogen, mmol/L</td>
<td>4.1 (1.1)</td>
<td>3.8 (0.9)</td>
<td>3.9 (1.0)</td>
<td>3.7 (0.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>White blood cell count, E.09/L</td>
<td>7.7 (2.0)</td>
<td>7.3 (1.9)</td>
<td>7.2 (1.9)</td>
<td>7.2 (1.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>167.7 (28.5)</td>
<td>156.4 (24.2)</td>
<td>154.8 (23.9)</td>
<td>150.2 (17.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>90.6 (17.2)</td>
<td>84.3 (14.4)</td>
<td>85.9 (13.7)</td>
<td>81.9 (9.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Current smoking</td>
<td>44.0 (11)</td>
<td>38.6 (39)</td>
<td>33.3 (23)</td>
<td>47.6 (10)</td>
<td>0.2</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>56.7 (24.6)</td>
<td>49.3 (22.9)</td>
<td>42.1 (22.6)</td>
<td>43.5 (21.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>36.0 (9)</td>
<td>36.6 (37)</td>
<td>29.0 (20)</td>
<td>33.3 (7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>20.0 (5)</td>
<td>31.9 (32)</td>
<td>26.1 (18)</td>
<td>23.8 (5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4.0 (1)</td>
<td>17.8 (18)</td>
<td>15.9 (11)</td>
<td>19.1 (4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.0 (2)</td>
<td>4.0 (4)</td>
<td>4.4 (3)</td>
<td>5.0 (1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>8.0 (2)</td>
<td>6.9 (7)</td>
<td>7.3 (5)</td>
<td>19.5 (4)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percentages (n). $^*$ANOVA. $^†$Multiple linear regression. $^‡$$\chi^2$ for linear trend.
to 1.58 mmol/L), and 48% in the highest tertile ($\geq$1.59 mmol/L) ($P$ for trend = 0.009, Figure 2). Echolucent plaques tended to be more stenotic than echogenic plaques. There was no significant association between plaque echogenicity and age or the levels of total cholesterol, diastolic blood pressure, fibrinogen, white blood cell count, BMI, or smoking habits (Table 2), and there was no significant association between plaque echogenicity and current treatment of hypertension or a history of myocardial infarction, angina pectoris, diabetes mellitus, or stroke (Table 2). The age-adjusted proportion of echolucent plaques was twice as high in men as in women (7.0% and 3.2%, respectively), but the difference was not statistically significant ($P$ = 0.2).

Low levels of HDL cholesterol were also associated with an increased risk of plaque echolucency when we controlled for systolic blood pressure and the degree of stenosis (Table 3). For 1-SD increase in HDL cholesterol, the odds of being in a lower plaque echogenicity category decreased by $\approx$30%.

There was no interaction between HDL and sex or age. Systolic blood pressure, degree of stenosis, and age (inverse) were also associated with plaque echolucency in the multivariate model. Triglyceride levels were not associated with plaque morphology when we controlled for the other risk factors (Table 3). We also tested whether the mean values of triglycerides and of HDL measured at the first and second visits performed differently than single measurements. In multivariate analysis with HDL, triglycerides, age, sex, degree of stenosis, and systolic blood pressure as covariates, the OR for lower plaque echogenicity by 1-SD increase in triglycerides was 1.18 (95% CI 0.88 to 1.59), and that for 1-SD increase in HDL was 0.72 (95% CI 0.53 to 0.97). Thus, the results were essentially the same. Thirteen subjects were using cholesterol-lowering medication. The exclusion of these subjects did not change the results.

In 162 participants, assessment of plaque morphology in the plaque with the highest degree of stenosis was also done at the screening examination, and we therefore were able to examine the reproducibility of the findings. By using screening data, we found in multivariate analysis that an increase in HDL cholesterol by 1 SD gave an OR of 0.64 (95% CI 0.44 to 0.92; $P$ = 0.017) for having an echolucent plaque, that is, essentially the same result as when we used data obtained at the second ultrasound examination (Table 3). When using data from the screening, we found no significant association between plaque echogenicity and systolic blood pressure (OR 0.93, 95% CI 0.67 to 1.30).

**Discussion**

Previously, in a follow-up study with the same participants as in the present study, we found a higher risk for future ischemic cerebrovascular events in subjects with echolucent plaques. Information on the determinants of plaque morphology may help target interventions to stabilize the plaque so it becomes less likely to rupture. This population-based study showed that subjects with echolucent plaques had significantly lower HDL cholesterol levels, more severe stenosis, and higher systolic blood pressure levels and were younger than subjects with high plaque echogenicity. Studies that compared the relationship between ultrasound plaque echogenicity and histological content of plaques have found that echolucent plaques are typically lipid rich, whereas echogenic plaques contain more fibrous tissue and are often calcified.

**TABLE 3.** Cumulative Ordinal Logistic Regression Model for Risk Factors Associated With Plaque Echolucency: The Tromsø Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SD</th>
<th>OR*</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>5.6</td>
<td>0.74</td>
<td>0.57–0.97</td>
<td>0.026</td>
</tr>
<tr>
<td>Male sex</td>
<td>...</td>
<td>1.27</td>
<td>0.75–2.15</td>
<td>0.4</td>
</tr>
<tr>
<td>Degree of stenosis, %</td>
<td>23.2</td>
<td>1.38</td>
<td>1.07–1.80</td>
<td>0.015</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.42</td>
<td>0.69</td>
<td>0.52–0.93</td>
<td>0.013</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.00</td>
<td>1.17</td>
<td>0.88–1.57</td>
<td>0.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>24.3</td>
<td>1.35</td>
<td>1.03–1.76</td>
<td>0.031</td>
</tr>
</tbody>
</table>

*The adjusted OR predicts the probability of being in a lower category for 1-SD increase in the independent variable, except for male sex, where the OR predicts the odds of men being in a lower category compared with the odds of women. Only subjects with stenosis are included in the model.*
confirming the validity of the ultrasound method.\textsuperscript{3–7} The reproducibility of the method is acceptable.\textsuperscript{11,13–15}

This is the first study to show an association between HDL cholesterol and plaque morphology. A smaller study of selected symptomatic patients with carotid stenosis found that echolucent plaques were associated with elevated levels of fasting and postprandial triglyceride-rich lipoproteins but not with levels of HDL cholesterol.\textsuperscript{11}

There is a strong inverse association between HDL cholesterol and risk of coronary heart disease.\textsuperscript{16,17} An inverse relationship between HDL cholesterol and cerebrovascular disease has also been demonstrated, as well as between HDL cholesterol and carotid atherosclerosis,\textsuperscript{18} although the results are not as consistent as those for coronary heart disease. The exact mechanism of the protective effect of HDL has been a subject of debate. HDL plays a central role in the removal of cholesterol from cells, and one theory postulates that HDL has a direct antiatherogenic effect by reversing cholesterol transport from the peripheral tissues to the liver.\textsuperscript{19} Direct visualization of lipid transport by HDL in perfused arteries has recently been demonstrated.\textsuperscript{20} Another theory emphasizes the strong inverse relationship between HDL cholesterol and triglycerides and suggests that HDL has no direct effect of its own but acts as a metabolic marker of triglyceride-rich lipoproteins.\textsuperscript{21} The present study could be interpreted in favor of the first theory, because the relationship between HDL cholesterol and plaque morphology remained significant when adjusted for triglyceride levels. However, the results of multivariate statistical analyses, including both triglycerides and HDL cholesterol, may be difficult to interpret due to the metabolic interrelationship between HDL and triglyceride-rich lipoproteins.\textsuperscript{22} Furthermore, the larger variability of triglyceride levels may result in an underestimation of the relationships between triglycerides and disease.\textsuperscript{23} Measurements of fasting triglyceride levels can lower some of this variability, but people are in a nonfasting state most of their time.\textsuperscript{24} Variability in triglyceride levels may result in an underestimation of the true relationship between them.\textsuperscript{36}

In a previous study,\textsuperscript{30} we observed that men had a significantly higher percentage of echolucent plaques than women. This was also found in the present study, but the difference between women and men was not significant, due to the lower number of participants. Our studies suggest that part of the gender difference in cardiovascular disease may be associated with gender differences in plaque morphology. Women have higher HDL cholesterol levels than do men starting in puberty and continuing throughout old age\textsuperscript{31} and therefore may be less likely than men to develop echolucent, rupture-prone atherosclerotic plaques.

There are some limitations to this study. The number of subjects in each plaque echogenicity group was low, and this may have limited the statistical power of the analyses. Although reproducibility on plaque echogenicity was good, some misclassification probably occurred. Computerized quantification of plaque morphology could probably improve the ultrasound assessment of plaque morphology.\textsuperscript{32,33} We may also assume that there were some misclassification of the degree of stenosis, but the interobserver agreement for the grading of stenosis in the present study has been found to be acceptable,\textsuperscript{14} and the method has been validated in previous studies.\textsuperscript{34,35} Any misclassification with respect to both the risk factors and plaque echogenicity would most likely lead to underestimation of the true relationship between them.\textsuperscript{36}

On the basis of the present population-based observational data, we hypothesize that HDL cholesterol contributes in the development of echolucent atherosclerotic plaques. However, because we used a cross-sectional study design, this hypothesis requires further investigation in experimental studies.

**Acknowledgments**

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**References**


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