Echolucent Plaques Are Associated With High Risk of Ischemic Cerebrovascular Events in Carotid Stenosis
The Tromsø Study

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

Background—The purpose of the study was to assess in a prospective design whether plaque morphology is associated with risk of ischemic stroke and other cerebrovascular events in subjects with carotid stenosis.

Methods and Results—A total of 223 subjects with carotid stenosis (123 with 35% to 49% degree of stenosis, 100 with 50% to 99% stenosis) and 215 control subjects matched by age and sex who participated in a population health survey at baseline were followed up for 3 years. Plaque echogenicity was assessed by ultrasound at baseline and scored as echolucent, predominantly echolucent, predominantly echogenic, or echogenic. Forty-four subjects experienced 1 ischemic cerebrovascular events in the follow-up period. Plaque echogenicity, degree of stenosis, and white blood cell count were independent predictors of cerebrovascular events. The unadjusted relative risk for cerebrovascular events was 13.0 (95% CI 4.5 to 37.4) in subjects with echolucent plaques and 3.7 (95% CI 0.7 to 18.2) in subjects with echogenic plaques when subjects without stenosis were used as the reference. The adjusted relative risk for cerebrovascular events in subjects with echolucent plaques was 4.6 (95% CI 1.1 to 18.9), and there was a significant linear trend (P=0.015) for higher risk with increasing plaque echolucency. The adjusted relative risk for a 10% increase in the degree of stenosis was 1.2 (95% CI 1.04 to 1.4).

Conclusions—Subjects with echolucent atherosclerotic plaques have increased risk of ischemic cerebrovascular events independent of degree of stenosis and cardiovascular risk factors. Subjects at high risk for ischemic vascular events may be identified by ultrasound assessment of plaque morphology. (Circulation. 2001;103:2171-2175.)

Key Words: plaque ❖ ultrasonics ❖ carotid arteries ❖ stenosis ❖ stroke ❖ follow-up studies

Stroke is the second leading cause of death in the world, with stenotic atheromatous plaques of the carotid bifurcation as one of the important risk factors. The degree of stenosis is recognized as an important risk factor for stroke. It is well known, however, that many high-grade stenoses remain stable and never cause cerebrovascular events, whereas others rapidly produce serious, potentially life-threatening disease. Thus, there has been a search for additional risk factors that might help identify the individuals with a high risk for stroke.

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. Plaques that appear echolucent on B-mode ultrasound are lipid-rich, whereas echogenic plaques have a higher content of fibrous tissue and calcification. Plaque echogenicity has been reported to be associated with stroke and other cerebrovascular events in univariate analysis in previous studies. Most of these were cross-sectional, but an association has also been found in prospective studies. Only 2 prospective studies have made adjustments for other cerebrovascular risk factors. In a majority of previous studies, the participants were symptomatic patients referred to ultrasoundography and/or carotid endarterectomy, whereas little is known about plaque echogenicity and the risk of stroke in the general population of stenotic subjects.

The purpose of the present study was to assess, in a population-based, prospective design, whether plaque morphology is an independent predictor of stroke and other cerebrovascular events.

Methods
In the fourth survey of the Tromsø Study in 1994 to 1995, a total of 6727 persons, 77% of the eligible population, were examined with ultrasound of the carotid arteries, and among these, 237 subjects were found to have stenosis or occlusion of the carotid artery. After 3 years, all subjects with carotid stenosis and 227 control subjects without stenosis, matched by age and sex and recruited from the study population, were invited to a follow-up examination. Ten subjects (2 with stenosis and 8 without) did not want to participate, and 5 subjects (1 with stenosis and 4 without) had moved out of the region and were excluded from the study. Informed consent was obtained from the participants, and the regional ethical committee approved the study.

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Circulation is available at http://www.circulationaha.org
Details about the ultrasound methods have been published previously.\textsuperscript{17,18} Briefly, high-resolution B-mode and color Doppler/pulsed-wave Doppler ultrasonography of both carotid arteries were performed with an ultrasound scanner (Acuson Xp10 128 ART) equipped with a linear-array 5- to 7-MHz transducer. Plaque morphology in terms of echogenicity, defined as reflectance of the emitted ultrasound signal, was assessed in a modified version of the classification proposed by Gray-Weale et al\textsuperscript{19,20} and graded from 1 to 4 as echoluent, predominantly echoluent, predominantly echogenic, or echogenic. The vessel lumen was used as the reference structure for defining echolucency, and the bright echo zone produced by the media-adventitia interface in the far wall was used as the reference structure for defining echogenicity. We have previously assessed interobserver reproducibility of plaque morphology in stenotic arteries, with acceptable results ($k=0.56$, 95\% CI 0.38 to 0.74).\textsuperscript{18} Subjects with plaques that could not be classified because of either occlusion of the carotid artery ($n=10$) or too much echo shadowing or unsatisfactory image quality ($n=1$) were excluded. Plaque morphology was not recorded in 1 subject. Thus, assessment of plaque morphology was available in 226 cases at baseline, but because of nonparticipation in the follow-up study, a total of 223 cases and 215 controls were included in the analyses.

The degree of stenosis was calculated by the following equation: $(1-PSVr/PSVs):\times 100\%$, where $PSVr$ denotes peak systolic velocity at the point of reference (here, the distal carotid artery) and $PSVs$ the peak systolic velocity in the stenosis. One subject had missing data on $PSVr$ and another on $PSVs$. In these persons, the degree of stenosis was estimated by calculating lumen diameter reduction: (plaque thickness/lumen diameter) $\times 100\%$. An increase in $PSVr$ with respect to $PSVs$, corresponding to $\sim35\%$ lumen diameter stenosis,\textsuperscript{21,22} or a narrowing of the lumen diameter in the longitudinal plane by $35\%$ was used as the cutoff point for stenosis. In 55\% of the cases, the degree of stenosis was $<50\%$, in 26\% of the cases the stenosis was $50\%$ to $69\%$, and $19\%$ of cases had stenosis $\geq 70\%$. In the case of bilateral stenosis or multiple plaques, the carotid artery or plaque with the highest degree of stenosis was selected for analysis.

At the baseline examination, measurements of height, weight, body mass index, blood pressure, nonfasting serum total cholesterol, HDL cholesterol, triglycerides, fibrinogen, and white blood cell count were done, and information about smoking habits was collected from self-administered questionnaires.\textsuperscript{17}

During the follow-up period, subjects with a stenosis of $\geq 70\%$ and incident ipsilateral transient ischemic attacks (TIAs) or nondisabling strokes ($n=9$) were referred to surgery, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) guidelines.\textsuperscript{23} Symptomatic cases with $<70\%$ stenosis and asymptomatic subjects with high-grade stenosis were given prophylactic antiplatelet treatment unless contraindicated, usually aspirin 160 mg/d. Endarterectomy was performed on an asymptomatic person with a rapidly progressing stenosis in 1 internal carotid artery (from 40\% to 90\% in 1 year) and contralateral occlusion and on 2 subjects with asymptomatic high-grade stenosis before renal transplantation. All other participants were given the best medical therapy available to lower cardiovascular risk factor levels.

At the 3-year follow-up examination, a detailed history of cerebrovascular events was recorded, and clinical neurological and ultrasound examinations were done in all subjects. All interviews and examinations were done by the same neurologist (E.B.M.), who was blinded to previous assessments of plaque echogenicity but not to whether the subject had stenosis or not. TIA was defined as a new-onset focal neurological abnormality lasting $<24$ hours, with no other apparent cause than cerebrovascular, and stroke likewise, except that the duration had to be $>24$ hours unless interrupted by death.\textsuperscript{23} Strokes were considered to be of ischemic origin when cerebral hemorrhage was excluded by CT or MR scans of the brain, which were performed in all subjects with a clinical diagnosis of stroke. Amaurosis fugax was defined as partial or complete uniocular vision of sudden onset lasting $<1$ hour. Deceased subjects ($27$ cases and $11$ controls) were identified by linkage to the National Population Register. Data on cerebrovascular events and details of all deaths were documented by hospital records (available in all but 2), death certificates (available in all), and autopsy records (available in 11 subjects).

Differences in mean values between groups were compared by ANOVA. Differences in proportions were tested by $\chi^2$ test and Fisher’s exact test. Significance of trends was tested by linear regression or by $\chi^2$ test for trend. Event rates were calculated by dividing number of events by observation-years. The Kaplan-Meier method was used for survival analysis, with censoring for nonstroke death, carotid endarterectomy, or at the time of the 3-year follow-up examination. Few ischemic events occurred in the echogenic group, and the proportion of survival was similar to the predominantly echogenic group; thus, the predominantly echogenic and echogenic groups were pooled in the life-table analysis (Figure). Cox proportional-hazards regression models were used to model the outcomes stroke and cerebrovascular event as a function of plaque echogenicity, degree of stenosis, and cardiovascular risk factors. Predictor variables were logarithmically transformed to achieve normal distribution when calculated properly, but because this had no significant influence on results, untransformed values were used. The SAS software package was used for the statistical analyses (SAS, release 6.12, 1996), except for $\chi^2$ tests for trend, which were calculated by the Epi Info software package (Epi Info, version 6.04, 1997). Two-sided probability values of $P<0.05$ were considered significant.

**Results**

Selected characteristics of the study population are shown in Table 1. Persons with echoluent plaques had a higher degree of stenosis, lower levels of HDL cholesterol, and higher levels of total cholesterol, fibrinogen, white blood cell count, and systolic blood pressure than others. A larger proportion of subjects with stenosis than subjects without stenosis were current smokers. There was a male preponderance and slightly lower age among subjects with echoluent plaques compared with subjects in the other plaque morphology groups and subjects without stenosis, but these differences were not significant. There were no significant differences in diastolic blood pressure or body mass index between groups.

Compared with subjects with no stenosis, subjects with stenosis had an increased risk for stroke (RR 2.72, 95\% CI 1.06 to 7.03) and any cerebrovascular event (6.95, 95\% CI
There were trends toward increasing incidence of both TIA and stroke with increasing degree of echolucency (Table 2). For amaurosis fugax, the trend was less clear, because of lack of events in 3 of the groups. Although the absolute number of ipsilateral events was low (n=22), there was a significant linear trend toward higher number of events with increasing echolucency (P=0.017) (Table 2). When adjusted for age, sex, and degree of stenosis, the relative risk of ipsilateral events in the predominantly echolucent group was 3.52 (95% CI 1.0 to 12.42), and in the echolucent group, 3.64 (95% CI 0.79 to 16.75). In this model, the combined group of echogenic and predominantly echogenic plaques was treated as the reference, because there were no incidents in the echogenic group.

There was a significant linear trend toward higher risk for cerebrovascular events with more echolucent plaques (Table 3, Figure). The unadjusted relative risk for cerebrovascular events was >12 times higher in subjects with echolucent plaques than in subjects without stenosis. When adjustments were made for age, sex, and degree of stenosis, there was still a significant linear trend toward higher risk with increasing echolucency (Table 3). The exclusion of persons with previous cerebrovascular events did not alter the results (data not shown). The adjusted relative risk for each 10% increase in degree of stenosis was 1.19 (95% CI 1.04 to 1.37).

White blood cell count, fibrinogen, and smoking were significant predictors of events in univariate analysis, whereas there were no significant associations between risk of cerebrovascular events and age, sex, total cholesterol, HDL cholesterol, triglycerides, systolic or diastolic blood pressure, or body mass index (data not shown). In a multivariate Cox regression in which age, sex, degree of stenosis, fibrinogen,

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<tr>
<th>Table 1. Risk Factors in Subjects Without and With Carotid Stenosis, Stratified by Plaque Echogenicity: The Tromsø Study</th>
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<tbody>
<tr>
<td><strong>No Stenosis</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Male sex*</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Degree of stenosis, %</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
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<tr>
<td>HDL cholesterol, mmol/L</td>
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<tr>
<td>Triglycerides, mmol/L</td>
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<tr>
<td>Fibrinogen, mmol/L</td>
</tr>
<tr>
<td>White blood cell count</td>
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<tr>
<td>Current smoking*</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>History of ischemic cerebrovascular disease*</td>
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<th>Table 2. Incidence of Cerebrovascular Ischemic Events During a Median of 3.0 Years of Follow-Up in Subjects With No Carotid Stenosis and Subjects With Stenosis, According to Plaque Echogenicity: The Tromsø Study</th>
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<tbody>
<tr>
<td><strong>Stenosis</strong></td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>TIA</td>
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<tr>
<td>Amaurosis fugax</td>
</tr>
<tr>
<td>Ischemic stroke</td>
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<tr>
<td>Any cerebrovascular event*</td>
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<tr>
<td>Any ipsilateral cerebrovascular event†</td>
</tr>
</tbody>
</table>

Values are percentages (n).

*χ² test for linear trend 26.9, P = 0.000001.
†χ² test for linear trend 5.65, P = 0.017.
white blood cell count, smoking, and plaque echogenicity were included in the model, only white blood cell count ($P=0.004$), degree of stenosis ($P=0.019$), and plaque echogenicity ($P=0.026$) were independent predictors of cerebrovascular events. Inclusion in the multivariate model of other cardiovascular risk factors, such as systolic blood pressure and HDL cholesterol, did not change the results.

### Discussion

In the present study, subjects with echolucent stenotic plaques had a much higher risk of stroke and cerebrovascular events than subjects with other plaque types. The increased risk was independent of degree of stenosis, age, sex, and other cardiovascular risk factors. Thus, the present study supports the existence of a higher risk of stroke in subjects with echolucent plaques.

It is known from autopsy studies of coronary heart disease that lipid-rich plaques are unstable and prone to rupture and thrombus formation and are associated with unstable angina, myocardial infarction, and sudden death.\(^{24,25}\) On B-mode ultrasound assessments, lips, thrombi, and hemorrhage all will appear as echolucent structures. Hemorrhage seldom occupies $>2\%$ of total plaque size,\(^{26}\) however; thus, it seems unlikely that hemorrhage contributes substantially to the observed echolucency. The association between plaque morphology in carotid arteries and cerebrovascular disease in the present prospective study may therefore be analogous to the relationship between lipid-rich plaques and coronary events. Because many clinical ischemic events occurred in a vascular territory different from the one supplied by the artery with the echolucent plaque, however, we cannot assume the same causal relationship between plaque morphology and events as seen in studies of coronary heart disease, although it seems clear that plaque echolucency is a marker of higher risk.

Our results are in line with the findings from previous studies. In the Cardiovascular Health Study (CHS),\(^{16}\) a cohort of 4886 persons $\geq 65$ years old were followed up for a mean of 3.3 years. Plaque echogenicity was characterized as hypoechoic, isoechoic, or hyperechoic. The relative risk of ipsilateral stroke for hypoechoic plaques was 2.78 (95% CI 1.36 to 5.69). The hypoechoic group probably corresponds to our echolucent group and perhaps partly to the predominantly echolucent group. The older study population probably explains why the stroke rate was higher in the CHS than in the present study. Sterpetti et al\(^{8}\) examined prospectively 214 consecutive patients referred to a vascular laboratory and found that degree of stenosis $\geq 50\%$ and heterogeneous plaques were independent predictors of new cerebrovascular events. The term heterogenic in the Sterpetti study referred to plaques with mixed high-, medium-, and low-level echoes and probably included plaques containing zones with echolucency, whereas the term homogenic was used to characterize all plaques that gave uniformly high-level echoes and probably corresponds to what we have called echogenic.

Known cardiovascular risk factors such as sex, blood pressure, total cholesterol, and HDL cholesterol were not significant predictors of cerebrovascular events in the present study. This is not surprising, because these risk factors are associated with both presence of stenosis and plaque echogenicity, which will attenuate the effect of the cardiovascular risk factors on cerebrovascular events. Also, the effects of age will be difficult to detect in a matched design. Smoking, fibrinogen, and white blood cell count were the only risk factors that were significant predictors of events in univariate analysis. Both fibrinogen and leukocyte count correlate with smoking. Interestingly, in multivariate analysis, only white blood cell count was a significant predictor of cerebrovascular events (along with degree of stenosis and plaque echolucency). This might reflect inflammatory processes related to the atherosclerotic lesion.\(^{27}\)

The low number of events in each echogenicity group in our study calls for a cautious interpretation of the results. Although a significant linear trend was found, the confidence intervals were wide. A similar trend was observed for ipsilateral events, but the study did not have enough power to assess the independent effect of plaque morphology on ipsilateral events. Conclusions about whether plaque echolucency plays a causal role in the development of cerebrovascular ischemic events or merely acts as a marker of higher risk cannot be made on the basis of data from an observa-
The fact that the examiner knew whether a participant in the study had stenosis or not may have biased the results toward a greater difference between subjects with and without stenosis when it comes to clinical events, especially events like TIAs and amaurosis fugax, which are more susceptible to the subjective evaluation of the observer than stroke. We do not think, however, that this has led to substantial impact on the results. More importantly, the observer was blinded to plaque morphology, which makes it unlikely that any serious observation errors have biased the results in this respect. It is likely that the present study underestimates the true relationship between plaque morphology and risk of clinical disease because of random misclassification of plaque morphology.

TIA and amaurosis fugax are by definition transient, benign symptoms, which in themselves are no threat to the patient’s health. They do, however, represent “warning signs” and as such are important predictors of stroke. Evaluation of plaque morphology in addition to the grade of stenosis might improve clinical decision-making and differential treatment for individual patients. Computer-quantified plaque morphology assessment, which is a more objective method of ultrasonic plaque characterization, may further improve this. It has been suggested that plaque echolucency should be used to select patients with asymptomatic stenosis for carotid surgery, but it is not known whether surgery is of greater benefit than medical treatment in subjects with echoluent stenotic plaques compared with subjects with echogenic plaques.

We conclude that plaque echolucency and degree of stenosis are independent predictors of stroke and cerebrovascular events. The present population-based study provides support for the concept that echoluent plaques are more likely to produce clinical cerebrovascular events.

Acknowledgments

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References

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