Ultrasonic Echolucent Carotid Plaques Predict Future Strokes

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Background—We tested prospectively the hypothesis that stroke development can be predicted by echolucency of carotid atherosclerotic plaques in previously symptomatic and asymptomatic patients.

Methods and Results—We followed incidence of ipsilateral ischemic strokes for 4.4 years in 111 asymptomatic and 135 symptomatic patients with ≥50% relevant carotid artery stenosis. At inclusion, echogenicity of carotid plaques and degree of stenosis were evaluated with high-resolution B-mode ultrasound with computer-assisted image processing and Doppler ultrasound, respectively. We observed 44 ipsilateral ischemic strokes. In symptomatic patients, relative risk of ipsilateral ischemic stroke for echolucent versus echorich plaques was 3.1 (95% CI, 1.3 to 7.3), whereas for 80% to 99% versus 50% to 79% stenosis, the relative risk was 1.4 (95% CI, 0.7 to 3.0). Relative to symptomatic patients with echorich 50% to 79% stenotic plaques, those with echolucent 80% to 99% stenotic plaques, echolucent 50% to 79% stenotic plaques, and echolucent 80% to 99% stenotic plaques had relative risks of ipsilateral ischemic strokes of 3.1 (95% CI, 0.7 to 14), 4.2 (95% CI, 1.2 to 15), and 7.9 (95% CI, 2.1 to 30), equivalent to absolute risk increases of 11%, 18%, and 28%. This was not observed in previously asymptomatic patients.

Conclusions—Echolucent plaques causing ≥50% diameter stenosis by Doppler ultrasound are associated with risk of future stroke in symptomatic but not asymptomatic individuals. This suggests that measurement of echolucency, together with degree of stenosis, may improve selection of patients for carotid endarterectomy. (Circulation. 2001;104:68-73.)

Key Words: arteriosclerosis ■ stroke ■ carotid arteries ■ ultrasonics ■ follow-up studies

Benefit of prophylactic carotid endarterectomy in patients with severe carotid stenoses and previous focal neurological symptoms has been demonstrated in 2 randomized multicenter trials1-2; however, ≥7 operations were performed to avoid 1 stroke. In the only similar trial studying previously asymptomatic patients with severe carotid stenoses, 20 operations were needed to prevent a single stroke.3

Most cerebrovascular events are associated with carotid stenoses <75%, indicating atheroembolic rather than low-flow genesis.4 Therefore, noninvasive identification of plaque types prone to rupturing and causing embolic stroke would help to improve the effectiveness of this operation. Ultrasonic measurement of plaque echolucency, indicating plaques with lipid-rich cores,5-12 is one such promising measurement; subjectively evaluated echolucency of carotid plaques on ultrasound B-mode imaging was associated with the presence or development of neurological events.4,13-17 The ability of objective computer-assisted ultrasound evaluation of plaque echolucency to predict stroke incidence, however, has not been reported in a prospective study.

We tested prospectively the hypothesis that stroke development can be predicted by echolucency of carotid atherosclerotic plaques in symptomatic and asymptomatic patients with ≥50% carotid stenosis.

Methods

Subjects

The study included 246 consecutive patients recruited from 1556 patients referred for carotid ultrasound examination at Rigshospitalet (Copenhagen University Hospital) from 1994 to 1996 (Table 1). Entry criterion was a degree of carotid stenosis ≥50% ipsilateral to previously symptomatic (n=135) or asymptomatic hemispheres (n=111).

Symptomatic patients had experienced ischemic strokes with moderate disabilities (n=31), minor ischemic strokes with no residual deficits (n=47), transient ischemic attacks (TIA; n=45), or amaurosis fugax (AF; n=12) on the side related to the relevant carotid stenosis. The reasons for including symptomatic carotid patients in this study and thereby renouncing from carotid endarterectomy were age >70 years (n=26), severe illness (n=10), patient refusal of operation (n=12), moderate neurological deficits remaining after stroke (n=31), symptoms >6 months ago (n=25), or degree of stenosis <70% (n=33).

Of the asymptomatic patients, 46 were duplex scanned for carotid bruit or various nonspecific, nonhemispheric symptoms such as dizziness and vertigo. The remaining 65 patients in the asymptomatic...
To calculate median gray-scale values, white and black (Media Cybernetics). Outlines of an area of plaque, blood, and adventitia at the level of the plaque were drawn on the B-mode image. In case of echolucency, corresponding color Doppler images or video sequences of the same plaque helped to detect the brightest adventitia at the level of the plaque were digitized with a Targa 2000 frame grabber, and processed with the software program Image-Pro Plus, version 1.2.01, for Windows (Media Cybernetics). Outlines of an area of plaque, blood, and adventitia at the level of the plaque were drawn on the B-mode image. In case of echolucency, corresponding color Doppler images or video sequences of the same plaque helped to detect the exact borders of the carotid artery plaque. The gray-scale value of each pixel in these 3 outlined regions (0 to 255; 0=black and 255=white) were used to calculate median gray-scale values. A standardization method of B-mode images was used; the median gray-scale value of the plaque was adjusted linearly so that the median value of blood was 0 and that of adventitia was 190. In case of acoustic shadowing from a plaque, the shadow region was not included in the outline. The mean of the standardized median gray-scale values of the plaque was used to divide plaques into echolucent (<74) and echorich (>74), respectively. The coefficient of variation for gray-scale measurements was 5.5% when 58 consecutively chosen images were reprocessed by the same ultrasonographer (M.-L.M.G.) to obtain a second set of gray-scale values. Ultrasound examinations and computer processing of images were performed by an experienced ultrasonographer (M.-L.M.G.) before end-point identification.

### Ultrasound Examination
At inclusion, echogenicity of carotid plaques was evaluated with high-resolution B-mode ultrasound and computer-assisted image processing. The B-mode and corresponding color Doppler images of the carotid artery plaques were recorded onto super-VHS videotape, digitized with a Targa 2000 frame grabber, and processed with the software program Image-Pro Plus, version 1.2.01, for Windows (Media Cybernetics). Outlines of an area of plaque, blood, and brightest adventitia at the level of the plaque were drawn on the B-mode image. In case of echolucency, corresponding color Doppler images or video sequences of the same plaque helped to detect the exact borders of the carotid artery plaque. The gray-scale value of each pixel in these 3 outlined regions (0 to 255; 0=black and 255=white) were used to calculate median gray-scale values. A standardization method of B-mode images was used; the median gray-scale value of the plaque was adjusted linearly so that the median value of blood was 0 and that of adventitia was 190. In case of acoustic shadowing from a plaque, the shadow region was not included in the outline. The mean of the standardized median gray-scale values of the plaque was used to divide plaques into echolucent (<74) and echorich (>74), respectively. The coefficient of variation for gray-scale measurements was 5.5% when 58 consecutively chosen images were reprocessed by the same ultrasonographer (M.-L.M.G.) to obtain a second set of gray-scale values.

Degree of stenosis was determined by routine Doppler criteria as <50%, 50% to 79%, 80% to 99%, or occlusion. A systolic velocity >120 cm/s equals ≥50% stenosis, and a diastolic velocity >135 cm/s equals ≥80% stenosis, validated by angiography as the gold standard. Ultrasound examinations and computer processing of images were performed by an experienced ultrasonographer (M.-L.M.G.) before end-point identification.

### End Points
Neurological and cardiac symptoms occurring during the 4.4-year observation period were noted by M.-L.M.G.) at each 6-month visit or during a final telephone interview. Subsequently, neurological symptoms were further evaluated by a neurological consultant (S.V.) on the basis of collected copies of medical reports from hospitals and/or general practitioners. The consultant was not aware of results from the ultrasound examinations.

The primary end point of the study was ischemic stroke developed ipsilateral to the relevant carotid stenosis. Secondary end points were ipsilateral AF and TIA. Tertiary end points were coronary events such as myocardial infarction, onset of angina pectoris, PTCA, or CABG and total mortality.

Ischemic strokes were defined as focal neurological symptoms lasting >24 hours (with or without persisting disabilities) for which CT showed corresponding ischemic infarction and ruled out cerebral hemorrhage. Hemorrhagic strokes (n=4) were excluded as events. Patients with bilateral hemispheric symptoms and those with known cardiac mural thrombus (as verified on echocardiography) were excluded from the analysis because of suspected cardioembolic origin (n=5). TIA was defined as ipsilateral focal neurological symptoms lasting <24 hours. AF was temporary monocular blindness ipsilateral to the relevant carotid artery stenosis.

Causes of death were obtained from the Danish Registry of Causes of Death. Follow-up was 100%.

### Statistical Analysis
Data were stratified a priori in symptomatic and asymptomatic patients but were also analyzed combined. Kaplan-Meier curves for event-free survival and log-rank tests evaluated the differences between 2 plaque types (echolucent versus echorich or 80% to 99% stenosis versus 50% to 79% stenosis) with the Statistica program (Statsoft). Relative risks (with 95% CIs) of primary, secondary, and tertiary end points for plaque type (echolucent versus echorich, 80% to 99% stenosis versus 50% to 79% stenosis, or combinations of these versus echorich 50% to 79% stenosis) were calculated with the Cox regression model with the use of SPSS (SPSS Inc). Cox regression models with plaque type as a predictor of end points.

### TABLE 1. Characteristics of 246 Patients With ≥50% Carotid Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic (n=111)</th>
<th>Symptomatic (n=135)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>64 (37–78)</td>
<td>66 (41–82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Other risk factors for stroke, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>59</td>
<td>65</td>
<td>0.36</td>
</tr>
<tr>
<td>Smoking</td>
<td>62</td>
<td>49</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
<td>48</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
<td>15</td>
<td>0.24</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
<td>4</td>
<td>0.37</td>
</tr>
<tr>
<td>Previous focal neurological symptoms, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Lipids and lipoproteins, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma cholesterol</td>
<td>6.8</td>
<td>6.4</td>
<td>0.05</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>4.1</td>
<td>3.8</td>
<td>0.09</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.5</td>
<td>1.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Plasma triglycerides</td>
<td>1.8</td>
<td>1.9</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Mann-Whitney U test compared age and lipids and lipoproteins between groups; χ² tests compared other characteristics between groups.
adjusted for either age or age and other risk factors (sex, hypertension, smoking, diabetes mellitus, and atrial fibrillation). Censorship was as follows: (1) for the primary end point ipsilateral ischemic stroke, it was death, ipsilateral endarterectomy, or ipsilateral ischemic stroke; (2) for the secondary end point ipsilateral TIA and AF, it was death, ipsilateral endarterectomy, ipsilateral ischemic stroke, or ipsilateral TIA or AF; (3) for the tertiary end point cardiac event, it was death or cardiac event; and (4) for the tertiary end point death, it was death only. Interaction between plaque type and symptomatic/asymptomatic status was tested in a Cox model in which both these factors, the 2-way interaction term between these 2 factors, and age were entered; the likelihood ratio test determined statistical significance. Values of $P \leq 0.05$ were considered significant.

**Results**

The 246 patients were followed up for an average of 4.4 years; those surviving were followed up from 3.0 to 5.8 years. Risk factors for stroke, previous focal neurological symptoms, and lipid profiles of participants are shown in Table 1. Risk factor and lipid profiles were similar in previously symptomatic and asymptomatic patients.

We observed 44 ipsilateral ischemic strokes, 35 ipsilateral TIA or AF, 36 coronary events, and 64 deaths (Table 2). Seventeen patients underwent carotid endarterectomy.

**Stroke Predicted by Plaque Echolucency or Stenosis**

Patients with echolucent plaques experienced more ipsilateral ischemic strokes compared with those with echorich plaques (Figure 1; log-rank $P=0.02$). This was found in previously symptomatic patients (Figure 2, top right; log-rank $P=0.005$; at 4.4 years, 29% versus 12%) but not in previously asymptomatic patients (Figure 2, top left; log-rank $P=0.85$). On Cox regression adjusted for age, symptomatic patients with echolucent plaques versus echorich plaques had a 3.1-fold (95% CI, 1.3 to 7.3) risk of ipsilateral ischemic stroke (Table 3). When the analysis also was adjusted for other risk factors for stroke, the results were similar.

![Figure 1](http://circ.ahajournals.org/figure1.png)

**Figure 1.** Survival free of ipsilateral ischemic strokes as a function of carotid plaque echogenicity or severity of stenosis. Echolucent is gray-scale median <74. Echorich is gray-scale median ≥74. Numbers at risk are listed below each graph.

There was a weak trend suggesting that those with 80% to 99% versus 50% to 79% carotid stenosis experienced more ipsilateral ischemic strokes (Figure 1; log-rank $P=0.18$). In previously symptomatic patients, there was a similar trend (Figure 2, bottom right; log-rank $P=0.11$; at 4.4 years, 28% versus 18%) but not in previously asymptomatic patients (Figure 2, bottom left; log-rank $P=0.93$). On Cox regression, symptomatic patients with 80% to 99% versus 50% to 79% carotid stenosis had a nonsignificant 1.4-fold (95% CI, 0.7 to 3.0) risk of ipsilateral ischemic stroke (Table 3).

![Figure 2](http://circ.ahajournals.org/figure2.png)

**Figure 2.** Survival free of ipsilateral ischemic strokes as a function of carotid plaque echogenicity or severity of stenosis, stratified for presence or absence of previous focal neurological symptoms. Echolucent is gray-scale median <74. Echorich is gray-scale median ≥74.
Symptomatic/asymptomatic status did not interact statistically with echogenicity or stenosis severity on ipsilateral ischemic strokes (Cox regression, $P = 0.13$ and $P = 0.42$). Neither plaque echolucency nor percent stenosis was associated with incidence of ipsilateral TIA/AF, cardiac events, or total deaths (Table 3).

**Stroke Predicted by Plaque Echolucency and Stenosis**

Among previously symptomatic patients and relative to those with echorich 50% to 79% stenotic plaques, those with echorich 80% to 99%, echolucent 50% to 79%, and echolucent 80% to 99% stenotic plaques had relative risks of ipsilateral ischemic strokes of 3.1 (95% CI, 0.7 to 14), 4.2 (95% CI, 1.2 to 15), and 7.9 (95% CI, 2.1 to 30), respectively (Table 4). This is equivalent to absolute risk increases in the 3 latter groups of 11%, 18%, and 28%, respectively. This was not observed among previously asymptomatic patients (Table 4).

**Discussion**

Important new results from this prospective study include the following: (1) objectively measured echolucent carotid plaques compared with echorich plaques predict a 3.1-fold risk of ipsilateral ischemic strokes (equivalent to 17% absolute risk increase) in previously symptomatic but not in previously asymptomatic patients, and (2) among previously symptomatic patients, echolucent 80% to 99% stenotic plaques predict an 8-fold risk compared with echorich 50% to 79% stenotic plaques (equivalent to 28% absolute risk increase). Our data suggest that if computer-assisted measurement of echolucency is used selectively in symptomatic patients, this ultrasound evaluation may improve the selection of patients for carotid endarterectomy.

Supporting our findings, the only other follow-up study investigating 4886 asymptomatic individuals found that subjectively evaluated echoluent plaques compared with echorich plaques conferred a relative risk for ischemic stroke of 2.5 (95% CI, 1.4 to 4.5). After adjustment for conven-
The presence of thrombosis is probably intermittent, although it may be found in as many as 80% of asymptomatic patients. The presence of thrombosis is probably intermittent, although it may be found in as many as 80% of asymptomatic patients.

TABLE 4. Relative Risk of Ipsilateral Ischemic Stroke as a Function of Carotid Plaque Echogenicity and Severity of Stenosis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Echogenicity</th>
<th>Stenosis, %</th>
<th>Patients, n</th>
<th>Relative Risk (95% CI)</th>
<th>Absolute Risk at 4.4 Years, %</th>
<th>Absolute Risk Increase, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=246)</td>
<td>Echorich</td>
<td>50–79</td>
<td>77</td>
<td>1</td>
<td>12</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Echorich</td>
<td>80–99</td>
<td>31</td>
<td>1.1 (0.3–3.6)</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Echoricent</td>
<td>50–79</td>
<td>96</td>
<td>1.7 (0.8–3.8)</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Echoricent</td>
<td>80–99</td>
<td>42</td>
<td>3.1 (1.3–7.4)</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Asymptomatic (n=111)</td>
<td>Echorich</td>
<td>50–79</td>
<td>38</td>
<td>1</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echorich</td>
<td>80–99</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>–16</td>
</tr>
<tr>
<td></td>
<td>Echoricent</td>
<td>50–79</td>
<td>43</td>
<td>0.6 (0.2–1.8)</td>
<td>12</td>
<td>–4</td>
</tr>
<tr>
<td></td>
<td>Echoricent</td>
<td>80–99</td>
<td>20</td>
<td>1.4 (0.4–4.9)</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Symptomatic (n=135)</td>
<td>Echorich</td>
<td>50–79</td>
<td>39</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echorich</td>
<td>80–99</td>
<td>21</td>
<td>3.1 (0.7–14)</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Echoricent</td>
<td>50–79</td>
<td>53</td>
<td>4.2 (1.2–15)</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Echoricent</td>
<td>80–99</td>
<td>22</td>
<td>7.9 (2.1–30)</td>
<td>36</td>
<td>28</td>
</tr>
</tbody>
</table>

Relative risks are based on Cox regression analysis adjusted for age. Echoricent is gray-scale median $\geq 74$.

Echorich is gray-scale median $\leq 74$.

The mechanism behind the association between plaque echolucency and increased stroke incidence is not completely resolved. El-Barghouty et al. found that the content of soft tissue (ie, lipid and hemorrhage) in the plaque was associated with plaque echolucency. Conversely, a highly fibrous tissue content was associated with echorich plaques. We and others have confirmed these findings. Thus, because echolucency is associated with lipid-rich carotid plaque and coronary plaques rich in lipid are thought to be most prone to rupturing and causing clinical events, it seems possible that carotid echolucency plaques are those most prone to rupture and thus cause embolic stroke.

An association between plaque echolucency and stroke incidence was observed in previously symptomatic but not in asymptomatic individuals. Because statistical evidence of an interaction between echolucency and symptomatic/asymptomatic status on stroke incidence was not found, a possible explanation for the absence of association in asymptomatic patients is lack of power. Alternatively, echolucency could reflect different pathogeneses in the 2 types of patients: a previous plaque rupture with thrombus formation and intraplaque hemorrhage leading to embolization in asymptomatic patients but relatively stable lipid-rich plaque content in asymptomatic patients. B-mode ultrasound imaging cannot reliably determine whether hypoechoic/echoluculent material represents lipid, hemorrhage, or thrombus. However, the latter 2 possibilities are not very likely because plaque hemorrhage (including thrombus and constituting $<1\%$ of the plaque) was not associated with plaque echolucency, as was “lipid,” an eosinophilic, amorphous substance histochemically identical with cholesterol and its esters (constituting 40% of the plaque). Moreover, thrombus is not always present in plaques from patients with recent symptoms, although it may be found in as many as 80% of asymptomatic patients. The presence of thrombosis is probably intermittent, reflecting the dynamic process of rupture, thrombus formation, healing, and remodeling of the plaque.

The absence of a significant association between severity of stenosis and stroke incidence in the present study was unexpected and probably due to a lack of power because several previous studies have indicated such findings. Both the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial found stroke incidences in symptomatic patients resembling our incidence rate of 21% at 4.4 years: 17% cumulative risk of ipsilateral stroke in 3 years and 26% risk in 2 years of follow-up in medically treated patients with $>70\%$ stenosis, respectively. Correspondingly, in the Asymptomatic Carotid Atherosclerosis Study, the 5-year cumulative risk of ipsilateral stroke was 11% in in asymptomatic patients with $\geq 60\%$ stenosis.

In the present study, 26% of carotid stenosis patients died during 4.4 years of follow-up. This demonstrates that we studied a very sick population of patients, which has the advantage that a large number of end points accumulated over a relatively short period of time. Nevertheless, it would also have been interesting to study a younger, less diseased population of patients in whom the strength of echo as a noninvasive procedure in predicting first-time stroke could be tested.

Potential study limitations include the fact that we were not able to exclude ischemic strokes of origins other than the carotid plaques, ie, strokes occurring as a result of lesions in the aorta or intracranial vessels; however, strokes thought to be of cardioembolic origin and hemorrhagic strokes were excluded. Reproducibility of the ultrasound evaluation could be another limitation. Few results have been published on reproducibility of computer-assisted ultrasound imaging, but those existing are very promising. Elatrozy et al. found coefficients of variation among 4 observers of $\pm 4.7\%$. The coefficient of variation in this study for intraobserver variation was 5.5%. A high degree of agreement on repeated examinations. Furthermore, ultrasound B-mode imaging suf-
fers from limitations like acoustic shadowing resulting from calcifications in the plaque, speckle diffraction, and angle dependence. These problems might be reduced with a newly available technique, multangle spatial compound imaging. This technique combines images from multiple different scanning angles, thereby reducing speckle and angle dependence and improving image quality. The ultrasound procedure is fast and relatively inexpensive and includes both measurement of degree of stenosis and gray-scale level in the plaque. MRI may also be a good discriminator of vulnerable carotid plaque features in vitro and probably in vivo. This method has a higher spatial resolution than ultrasound B-mode and does not suffer from acoustical shadows. However, this method is still very expensive, and its use in plaque characterization is limited mainly to research. Furthermore, MRI has to overcome flow and motion artifacts and overestimation of degree of stenosis.

In conclusion, the present results suggest that measurement of carotid plaque echoluency, together with severity of stenosis, may improve patient selection for carotid endarterectomy. Because definite benefit for surgery applies to all symptomatic individuals with a stenosis of ≥50%, plaque texture or echogenicity might be particularly useful to inform patients of an excess risk. Furthermore, in countries where not all symptomatic patients with ≥50% stenosis are offered an operation, additional information on plaque echolucency may help doctors offer a limited number of operations to those with potentially the most benefit. Finally, ultrasound echolucency can also add to the strength of operation indication in cases of “borderline” severity of stenosis (≈50%), single neurological events as opposed to multiple events, and AF, which does not carry the same high risk as hemispheric symptoms, TIA, or stroke.

Acknowledgments

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References


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