Plaque Echolucency and the Risk of Ischaemic Stroke in Patients with Asymptomatic Carotid Stenosis Within the First Asymptomatic Carotid Surgery Trial (ACST-1)

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INTRODUCTION

Patients with a severe asymptomatic (> 70%) atherosclerotic stenosis of the internal carotid artery are at increased risk of future stroke.1-3 Two large randomized trials have shown that carotid endarterectomy (CEA) reduces long-term stroke risk in such patients when compared with medical treatment alone.4,5 While triple medical therapy (i.e., statins, and antiplatelet and antihypertensive drugs) reduces stroke risk, carotid intervention confers an additional 6—7% absolute stroke risk reduction and is appropriate for patients considered to be at high risk of stroke. In

Keywords: Carotid artery stenosis, Carotid echolucency, Carotid ultrasound, Randomized trial, Stroke

WHAT THIS PAPER ADDS

Carotid artery plaque characteristics may help identify patients at risk of stroke. On ultrasound, potential “high risk” carotid plaques appear echolucent. Long term follow-up studies on the natural course of echolucent plaques are scarce. Whether definite plaque echolucency (> 25% soft plaque) predicted future stroke risk in patients with severe asymptomatic carotid stenosis randomized within the first Asymptomatic Carotid Surgery Trial (ACST-1) was assessed in this study. Although the number of events was low, definite plaque echolucency was associated with a higher 5-year ipsilateral risk of stroke and might therefore be a predictor of ipsilateral stroke.

Objective/Background: On ultrasound, potentially “high risk” carotid plaques may appear echolucent. In this study, whether a confident classification of echolucent plaque was a predictor of future ipsilateral ischaemic stroke in asymptomatic patients randomized to medical therapy in the Asymptomatic Carotid Surgery Trial-1 (ACST-1) was assessed.

Methods: We performed a post-hoc analysis of 814 ACST-1 patients randomized to medical therapy alone with baseline plaque assessment classified as definitely echolucent (> 25% soft plaque) or nonecholucent (< 25% soft plaque). Kaplan—Meier survival curves were used to compare cumulative rates of ipsilateral ischaemic stroke in both groups.

Results: In the first 5 years after randomization, a significantly higher risk of ipsilateral stroke was observed in patients with definitely echolucent plaques (8.0%; 95% confidence interval [CI] 6.4—9.6) when compared with patients with definitely nonecholucent plaques (3.1%; 95% CI 2.1—4.1; p = .009). After adjustments for other risk factors, plaque echolucency was associated with a 2.5-times increased risk of ipsilateral ischaemic stroke (hazard ratio 2.52; 95% CI 1.20—5.25; p = .014). Use of lipid-lowering therapy was low in both groups during the first 5 years after randomization but rose sharply during years 5—10 of follow-up, and was significantly more likely to be prescribed for patients with echolucent plaques (p = .001). The risk of ipsilateral ischaemic stroke at 10 years was similar for both groups of patients (p = .233).

Conclusion: Although the numbers of events in this study was low, definite plaque echolucency (> 25% soft plaque) was associated with a higher 5-year ipsilateral stroke risk in ACST-1 and may therefore help to identify patients at increased risk of stroke for whom carotid intervention may be particularly beneficial.

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patients with asymptomatic carotid stenosis, age, systolic blood pressure, increased serum creatinine, history of smoking, and previous ipsilateral and contralateral symptoms are all associated with an increased risk of future stroke. Furthermore, if noninvasively assessed, several plaque characteristics, such as a thin fibrous cap, a lipid necrotic core and intraplaque haemorrhage have been suggested as potential markers for selecting patients at high risk of stroke. On ultrasound, “high-risk” plaques can appear echolucent and several observational studies have found a positive association between plaque echolucency and stroke risk, raising the possibility that plaque echolucency could be used to select patients at markedly increased stroke risk for asymptomatic intervention. However, these were nonrandomized studies and lacked long-term follow-up. The Asymptomatic Carotid Surgery Trial-1 (ACST-1) is a large randomized controlled trial with prolonged follow-up, which compared the use of early “preventative” CEA with deferral of surgery in patients with severe asymptomatic carotid stenosis. In the deferred surgery arm of the trial, 814 patients with definite echolucent or definite nonecholucent imaging at baseline were followed-up for 10 years. This allowed comparison of any differences between stroke risk in both groups. This study sought to determine whether definite baseline plaque echogenicity is a reliable predictor of increased future stroke risk in ACST-1 patients randomized to receive medical therapy alone.

METHODS

Patient selection

The methods of ACST-1 (ISRCTN 26156392) have been described previously. Briefly, in ACST-1, 3,120 patients with tight carotid artery stenosis were randomized to receive immediate CEA or deferral of operation until it seemed more necessary (e.g., symptoms developed). Patients were eligible for randomization if they had severe unilateral or bilateral atheromatous carotid artery disease appropriate for operation and if the stenosis being randomized had not caused any recent transient ischaemic attack or stroke in the preceding 6 months. Patients were expected to be available for long-term follow-up. Patients randomized to immediate CEA (n = 1,560) were excluded from the present report, leaving 1,560 patients with deferral of CEA potentially eligible for inclusion in this study, 814 of whom had a definite assessment of echolucent or nonecholucent at baseline. The use of appropriate medical treatment (i.e., antithrombotic, antihypertensive, and lipid-lowering therapy) was similar in both treatment groups.

Ultrasound assessment

In ACST-1, carotid stenosis was assessed by duplex ultrasound following local protocols. Sonographers were asked to assess plaque echogenicity at baseline and to score it as follows: > 25% soft plaque (echolucent) or <25% soft plaque (nonecholucent) for both carotid arteries.

Classification of plaques as definitely echolucent or nonecholucent was according to the Gray—Weale classification, where echolucent meant Gray—Weale type I or II.

Outcome events

The main outcomes in ACST-1 were perioperative (i.e., within 30 days) mortality and morbidity (stroke and myocardial infarction) and the long-term incidence and outcome of nonperioperative stroke. In the trial, strokes and other major outcome events were adjudicated by an independent end-point committee blinded to treatment allocation. Wherever possible, strokes were further classified by type (i.e., ischaemic, haemorrhagic), laterality (i.e., ipsilateral, contralateral, vertebrobasilar), and disability (i.e., nondisabling, disabling, fatal). In the current report, ipsilateral ischaemic stroke (disabling and nondisabling) was chosen as the primary end point. Secondary end points were any ischaemic stroke, death, and ipsilateral occlusion.

Statistical analysis

The frequencies of baseline characteristics between patients with echolucent- and nonecholucent plaques were compared using a chi-square test, and Kaplan—Meier survival statistics were used to calculate cumulative rates of primary and secondary end points. Patients were studied from the time of randomization and were censored in case of ipsilateral stroke, surgery, death, or if lost to follow-up. All analyses were performed on first strokes (although the final trial report also included the outcome for all strokes, as second and subsequent events were recorded and assessed during long-term follow-up). The p-values for comparison of survival curves were determined by the log-rank test (pooled over strata). Where p-values appeared statistically significant (< .05) a pairwise comparison was performed to determine the difference between the intercepts. Cox proportional hazards regression models were used to model the outcome of ipsilateral ischaemic stroke as a function of plaque echogenicity and cardiovascular risk factors. For each of these possible risk factors, hazard ratios (HR) and 95% confidence intervals (CI) were determined. Multivariate analysis was performed with variables with a p-value of < .30 in univariate analysis.

RESULTS

Study population

In total, 1,560 patients were randomized to medical therapy alone (i.e., deferral of CEA) in ACST-1. Patients were enrolled from 117 participating centres. One-third of centres confidently assessed echolucency in all patients (37/117 [32%], centres), just over half did so selectively (67/117 [57%]), and about 10% of centres did not assess echolucency in any patient enrolled (13/117 [11%] centres); hence, baseline plaque echogenicity was assessed in a total of 814 patients (52%). In 403/814 patients (49%), a substantial component of the plaque (> 25% of the total) appeared echolucent on ultrasound. Baseline characteristics of...
patients with and without definite echolucent features are compared in Table 1. Patients with echolucent plaques were significantly younger and had more severe stenosis than patients with nonecholucent plaques (chi-square \( p = .019 \) and \( p < .001 \), respectively).

**Follow-up and events**

The median duration of follow up for the 814 patients studied was 78 months (interquartile range [IQR] 49–112 months). Ischaemic stroke in any territory occurred in 78 patients, 42/403 (10%) from the echolucent group, and 36/411 (9%) from the nonecholucent group. In patients without baseline echolucent assessment, the total number of strokes was 73/747 (10%).

The absolute number of ipsilateral strokes was higher in the echolucent group (77/27; 10-year risk 10.0% [95% CI 7.9–12.1]) when compared with the nonecholucent group (n = 19; 10-year risk 9.4% [95% CI 7.0–11.8]), but this difference was not significant (\( p = .421 \)). Most ipsilateral strokes in the patients with echolucent plaque occurred within the first 5 years (25/27 [93%]), in contrast to the group with nonecholucent plaques, where only half of the ipsilateral strokes occurred in the first 5 years (10/19 [53%]). Of those patients with ipsilateral ischaemic stroke, 5/27 (19%) patients with echolucent plaques and 4/19 (21%) patients with nonecholucent plaques underwent CEA after their stroke. The total number of patients that underwent CEA was 204/814 (25%), of whom 127 underwent surgery for reasons other than ipsilateral carotid symptoms. Cross-over rates were similar between those with definite echolucent plaques and nonecholucent plaques (\( p = .754 \)).

Table 2 shows the 5- and 10-year cumulative stroke risks among the three groups. Kaplan–Meier life table analysis showed a significantly higher 5-year risk of ipsilateral ischaemic stroke in patients with echolucent plaques compared with patients with nonecholucent plaques (\( p = .009 \)). However, ipsilateral ischaemic stroke risk at 10 years was similar between both groups (\( p = .233 \) (Fig. 1A)).

The average annual risk of ipsilateral stroke in the first 5 years after randomization (0–5 years) was 1.60% for patients with echolucent plaques and 0.62% for patients with nonecholucent plaques. Annual ipsilateral stroke risk in the 5 years thereafter (5–10 years) was 0.40% for patients with echolucent plaques and 1.26% for patients with nonecholucent plaques. The risk of any ischaemic stroke was similar at 5 years (\( p = .130 \)) and 10 years (\( p = .420 \) (Fig. 1B), as was cumulative survival (\( p = .947 \)). Adjusted for baseline severity of stenosis, cumulative risks of ipsilateral occlusion during follow-up were similar between both groups (\( p = .318 \)).

Statin use rose during the course of ACST-1, from 28% at baseline to 53% at 5 years to 78% during the final 5 years of follow-up. A significant difference in statin use between patients with echolucent and nonecholucent plaques was seen at 7 and 10 years postrandomization, with lipid-lowering therapy being more commonly prescribed for patients with echolucent plaques (chi-square \( p = .001 \) and \( p = .001 \))

**Risk factor analysis**

Univariate Cox proportional hazards model analysis of risk factors showed that carotid plaque echolucency was a significant predictor of future ipsilateral ischaemic stroke (\( p = .011 \)). Multivariate analysis was performed with factors with a \( p \)-value \( < .30 \) in univariate analysis: sex, cholesterol \( \geq 6.5 \) mmol, diabetes, ischaemic heart disease, antiplatelet therapy, previous symptoms, and echolucency. After adjustments for these risk factors, plaque echolucency was significantly related to a 2.5-times increase in ipsilateral ischaemic stroke risk in the first 5 years (25/403 [6.2%] vs. 10/411 [2.4%]; HR 2.52, 95% CI 1.20–5.25; \( p = .014 \) (Table 3).

**DISCUSSION**

In this study, whether ultrasound characterization of plaque ecchogenicity can predict future stroke risk in patients with
severe asymptomatic carotid artery disease was assessed. The study has demonstrated that plaque echolucency was independently related to risk of future ipsilateral stroke by 5 years, but no overall association was found between plaque echolucency and the development of an ipsilateral stroke during the 5–10-year follow-up. Several factors may explain why an association between plaque echolucency and ipsilateral stroke at 5 years but not at 10 years was found.

### Table 2. Cumulative 5- and 10-year risk of stroke by plaque echolucency (including number of patients).

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral stroke</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strokes (n)</td>
<td>% Cumulative 5-y risk of stroke (95% CI)</td>
<td>p</td>
<td>Strokes (n)</td>
</tr>
<tr>
<td>Patients with echolucent plaques (n = 403)</td>
<td>25</td>
<td>8.0 (6.4–9.6)</td>
<td>.009</td>
<td>27</td>
</tr>
<tr>
<td>Patients with nonecholucent plaques (n = 411)</td>
<td>10</td>
<td>3.1 (2.1–4.1)</td>
<td>.94</td>
<td>9.4 (7.0–11.8)</td>
</tr>
<tr>
<td>Patients with echolucency not assessed (n = 747)</td>
<td>31</td>
<td>5.3 (4.4–6.2)</td>
<td>.014</td>
<td>36</td>
</tr>
</tbody>
</table>

### Any stroke

<table>
<thead>
<tr>
<th></th>
<th>Strokes (n)</th>
<th>% Cumulative 5-y risk of stroke (95% CI)</th>
<th>p</th>
<th>Strokes (n)</th>
<th>% Cumulative 10-y risk of stroke (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with echolucent plaques (n = 403)</td>
<td>36</td>
<td>11.3 (9.5–13.1)</td>
<td>.130</td>
<td>42</td>
<td>15.4 (12.9–17.9)</td>
<td>.420</td>
</tr>
<tr>
<td>Patients with nonecholucent plaques (n = 411)</td>
<td>25</td>
<td>7.8 (6.3–9.3)</td>
<td>.36</td>
<td>14.4 (11.8–17.0)</td>
<td>.233</td>
<td></td>
</tr>
<tr>
<td>Patients with echolucency not assessed (n = 747)</td>
<td>56</td>
<td>9.3 (8.1–10.5)</td>
<td>.07</td>
<td>73</td>
<td>16.7 (14.6–18.8)</td>
<td>.415</td>
</tr>
</tbody>
</table>

Note. CI = confidence interval.

*p-Values derived by log-rank test (pairwise comparison between echolucent and nonecholucent plaques).

### Figure 1. Kaplan–Meier life table analysis of (A) risk of ipsilateral ischaemic stroke; (B) risk of any ischaemic stroke. * p-Value derived by log-rank test (pairwise comparison).

In Table 3, we present the results of our univariate and multivariate analyses of patient-related factors and their association with ipsilateral 5-year stroke risk.

### Table 3. Uni- and multivariate analysis of patient-related factors and ipsilateral 5-year stroke risk.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR (95% CI)</th>
<th>p</th>
<th>Adjusted HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization &gt; 65 y</td>
<td>1.12 (0.55–2.30)</td>
<td>.752</td>
<td>1.47 (0.66–3.33)</td>
<td>.341</td>
</tr>
<tr>
<td>Ipsilateral stenosis &gt; 90%</td>
<td>0.70 (0.32–1.50)</td>
<td>.356</td>
<td>1.43 (0.68–3.33)</td>
<td>.330</td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.57 (0.71–3.45)</td>
<td>.266</td>
<td>1.56 (0.79–3.03)</td>
<td>.196</td>
</tr>
<tr>
<td>Prerandomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol ≥ 6.5</td>
<td>1.79 (0.91–3.51)</td>
<td>.093</td>
<td>1.75 (0.89–3.45)</td>
<td>.103</td>
</tr>
<tr>
<td>Blood pressure ≥ 160</td>
<td>0.78 (0.39–1.57)</td>
<td>.485</td>
<td>1.43 (0.68–3.03)</td>
<td>.340</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64 (0.79–3.43)</td>
<td>.185</td>
<td>1.56 (0.79–3.03)</td>
<td>.196</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.65 (0.85–3.21)</td>
<td>.142</td>
<td>1.56 (0.79–3.03)</td>
<td>.196</td>
</tr>
<tr>
<td>Treatment recorded at entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1.03 (0.52–2.05)</td>
<td>.932</td>
<td>4.35 (0.59–33.3)</td>
<td>.150</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>4.78 (0.65–34.93)</td>
<td>.123</td>
<td>1.23 (0.21–7.39)</td>
<td>.687</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>0.89 (0.21–3.69)</td>
<td>.867</td>
<td>1.43 (0.68–3.03)</td>
<td>.340</td>
</tr>
<tr>
<td>Lipid-lowering</td>
<td>0.77 (0.35–1.70)</td>
<td>.517</td>
<td>1.43 (0.68–3.03)</td>
<td>.340</td>
</tr>
<tr>
<td>Previous symptoms</td>
<td>1.44 (0.74–2.81)</td>
<td>.285</td>
<td>1.36 (0.69–2.68)</td>
<td>.382</td>
</tr>
<tr>
<td>Echolucency</td>
<td>2.58 (1.24–5.36)</td>
<td>.011</td>
<td>2.52 (1.20–5.25)</td>
<td>.014</td>
</tr>
</tbody>
</table>

Note. HR = hazard ratio; CI = confidence interval.

*p-Values derived by log-rank test (pairwise comparison).

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*p-Values derived by log-rank test (pairwise comparison).
at 10 years was observed. First, these findings are based on a relatively small number of events, and the positive association seen at 5 years could simply be a chance finding. Second, the use of lipid-lowering therapy was low in both groups during the first 5 years after randomization but rose significantly thereafter, and particularly in those patients with echolucent plaques, which might explain the reduction in stroke risk seen in this group between 5 and 10 years. Third, “high-risk” patients with echolucent plaques who had their stroke in the first 5 years after randomization were no longer at risk as part of the 5–10-year cohort, which may have made the echolucent group relatively “low risk” beyond 5 years. Finally, the results (which stratify patients based on a single scan at baseline) could reflect the natural history of a relatively “stable” nonecholucent plaque that progressed from a low-risk lesion to an “unstable” echolucent plaque over time, leading to a subsequent ipsilateral ischaemic stroke. Consequently, it is possible to hypothesize that patients with an echolucent plaque assessed at baseline would consequently be more likely to suffer from stroke in the first years after randomization, whereas patients with nonecholucent plaques at randomization might develop an echolucent plaque in the first years after randomization. However, it was not possible to test this hypothesis as echolucent was only available at randomization in the study.

Previous studies have examined associations between plaque echolucency and stroke risk in patients with asymptomatic carotid stenosis. Some studies, such as ACSRS (Asymptomatic Carotid Stenosis and Risk of Stroke), report a positive association between plaque echolucency and stroke risk (but all have a relatively short follow-up), while one study did not show any significant association.

It seems possible that different definitions and techniques for measuring plaque echogenicity might be important, thereby limiting the comparability of previously published data.

The Gray–Scale Median is often proposed as a measurement of plaque echogenicity. Although this method is computerized, and therefore relatively objective, studies use different software packages and different thresholds to differentiate echolucent from nonecholucent plaques. Although some of these studies were large, none was randomized and follow-up was relatively short. Patients with asymptomatic carotid disease were only enrolled into these studies when the physician was willing to treat patients medically, and hence they were a highly selected population at low risk for stroke, and therefore prone to selection bias. The current report, including data from 1,560 patients with asymptomatic carotid disease randomly allocated to medical therapy alone in ACST-1, should help to eliminate this bias, as all trial patients were thought suitable for surgery prior to randomization.

Different pathophysiological mechanisms could explain the increased risk of stroke in patients with echolucent plaques. The rupture-prone “vulnerable” plaque, containing a thin fibrous cap, thrombus, and intraplaque haemorrhage will appear echolucent on ultrasound. Echolucent plaques may therefore rupture and provoke acute thromboembolization in the territory supplied by the carotid artery. Plaque echolucency could reflect a state of progressive atherosclerotic disease throughout the cardiovascular system, placing patients at higher risk for adverse events of atherosclerosis. The present results showed a significant association between plaque echolucency and ipsilateral events, but no association between echolucency and overall stroke risk was found, suggesting that vulnerable plaques rather than generalized atherosclerosis are the trigger for stroke.

This study has several limitations. First, ACST-1 was a large streamlined trial, so echolucency was not assessed or reported for all patients, and > 25% echolucency was a subjective assessment of the carotid plaque and hence operator dependent. Second, between 1993 and 2003, medical therapy improved (statins were being used more frequently and at higher doses), which may reduce the long-term risk of carotid-related stroke. Third, data on echolucency of the carotid plaque were only available in half of the patients randomized to medical treatment. However, stroke risk in those patients with and without echolucency assessed was similar, making it less likely that this is a potential source of bias. Finally, the analysis does not take into account histological analysis of the carotid plaque. However, this would not enable a clinical choice for, or against surgery, to influence patient treatment.

CONCLUSION
In conclusion, definite plaque echolucency (> 25% soft plaque) might be a predictor of ipsilateral stroke and is associated with a higher 5-year ipsilateral stroke risk in these trial patients with asymptomatic carotid disease. At this point it is too early to use plaque echolucency routinely as a tool in clinical decision making. In order to make recommendations, further large studies would be needed in patients receiving current medical treatment with standardized imaging protocols and long-term follow-up to allow reliable assessment of the utility of plaque echolucency as a predictor of stroke risk in patients with asymptomatic carotid stenosis.

CONFLICT OF INTEREST
None.

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REFERENCES


