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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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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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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

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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.[6] 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.[7–10] On ultrasound, "high-risk" plaques can appear echolucent and several observational studies have found a positive association between plaque echolucency and stroke risk,[11,12] 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.[11,12] 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.[5] 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.[13] 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.[13,14]

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).[5] 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