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Pre-operative Carotid Plaque Echolucency Assessment has no Predictive Value for Long-Term Risk of Stroke or Cardiovascular Death in Patients Undergoing Carotid Endarterectomy

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WHAT THIS PAPER ADDS

In patients with asymptomatic carotid stenosis, plaque echolucency has been shown to predict the risk of ipsilateral stroke and could therefore aid patient selection for preventive surgery. However, carotid plaque echolucency is also thought to predict other cardiovascular events and the value of pre-operative echolucency assessment for post-operative cardiovascular risk is largely unknown. Long-term outcomes of patients undergoing CEA in the ACST-1 trial were assessed with respect to plaque echolucency in the randomised artery at baseline. No differences in risk of stroke or cardiovascular death were found between patients with echolucent and non-echolucent plaques.

Introduction: In patients with carotid stenosis receiving medical treatment, carotid plaque echolucency has been thought to predict risk of future stroke and of other cardiovascular events. This study evaluated the prognostic value of pre-operative plaque echolucency for future stroke and cardiovascular death in patients undergoing carotid endarterectomy in the first Asymptomatic Carotid Surgery Trial (ACST-1).

Methods: In ACST-1, 1832/3120 patients underwent carotid endarterectomy (CEA), of whom 894 had visual echolucency assessment according to the Gray-Weale classification. During follow-up patients were monitored both for peri-procedural (i.e. within 30 days) death, stroke, or MI, and for long-term risk of stroke or cardiovascular death. Unconditional maximum likelihood estimation was used to calculate odds ratios of peri-procedural risk and Kaplan-Meier statistics with log-rank test were used to compare cumulative long-term risks.

Results: Of 894 operated patients in whom echolucency was assessed, 458 plaques (51%) were rated as echolucent and peri-procedural risk of death/stroke/MI in these patients was non-significantly higher when compared with patients with non-echolucent plaques (OR 1.48 [95% CI 0.76–2.88], $p = .241$). No differences were found in the 10 year risk of any stroke (30/447 [11.6%] vs. 29/433 [11.0%], $p = .900$) or cardiovascular (non-stroke) death (85/447 [27.9%] vs. 93/433 [32.1%], $p = .301$).

Conclusion: In ACST-1, carotid plaque echolucency assessment in patients undergoing CEA offered no predictive value with regard to peri-operative or long-term stroke risk or of cardiovascular (non-stroke) death.

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INTRODUCTION

Ischaemic stroke and myocardial infarction (MI) are commonly caused by rupture of atherosclerotic plaques and this risk may be related to local plaque instability rather than to the extent of stenotic disease.[1,2] Several plaque characteristics have been shown to make carotid plaques more prone to rupture and these have been thought helpful in identifying patients at high risk of stroke. Previous studies have shown that carotid plaques with a lipid rich core, intraplaque haemorrhage, and a thin fibrous cap are positively associated with a past history of cerebrovascular events.[3–6] Lipid rich cores appear echolucent on B-mode duplex ultrasound (DUS) assessment, while plaques with "less risky" high fibrous content or calcification appear echogenic.

In patients with asymptomatic carotid stenosis not undergoing carotid revascularisation, carotid plaque echolucency has been associated with a higher risk of future stroke[7–10] and

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it has been suggested as a tool to help aid patient selection for prophylactic carotid endarterectomy (CEA).

Atherosclerosis is a systemic disease and carotid plaque echolucency may reflect plaque instability in other vascular beds as well. Carotid plaque echolucency has been associated with a higher risk of coronary events, even when patients received adequate lipid lowering therapy.[11–13] In a prospective study of 338 endarterectomies, the impact of carotid plaque echogenicity on restenosis, future cardiovascular events, and overall survival was studied. Echolucent carotid plaques (Gray-Weale type I or II) were associated with a significantly higher risk of carotid restenosis and a higher rate of cardiovascular events. However, no difference in overall survival was found, and the prognostic significance of pre-operative echolucency assessment with regard to cardiovascular risk remains largely unknown.[14]

The Asymptomatic Carotid Surgery Trial (ACST-1), the largest randomised controlled trial comparing CEA plus medical therapy versus medical therapy alone in patients with asymptomatic carotid stenosis, has uniquely long, reliable follow-up of both patient cohorts. The present study aimed to assess whether a positive pre-operative carotid plaque echolucency assessment would predict future cardio- and cerebrovascular risk in patients undergoing CEA in ACST-1.

METHODS

Study design and patient selection

The trial protocol of ACST-1 has been published previously.[15] Patients were eligible for ACST-1 if they had tight unilateral or bilateral carotid stenosis and no ipsilateral neurological symptoms in the past 6 months. Patients were expected to be available for long-term follow-up. Between 1993 and 2003 a total of 3120 patients were randomised to either immediate CEA or deferral of surgery until it was considered necessary. Both groups received appropriate preventive cardiovascular medical therapy (antithrombotic, antihypertensive and lipid lowering therapy).

The present report includes all patients treated with CEA during the study period, regardless of their initial treatment allocation, and compares those with a randomisation assessment of echolucent versus non-echolucent plaque.

Plaque echolucency

The grade of stenosis of both carotid arteries was measured with DUS according to local centre protocol and participating centres were asked to assess plaque echolucency of the ipsilateral carotid artery. Plaques were considered to be definitely echolucent when >25% of carotid plaque content was soft (Gray-Weale type 1 or 2) and non-echolucent if soft plaque was uncommon (<25%) or absent (Gray-Weale type 3 or 4).[16]

Outcome events

The main trial outcomes of ACST-1 were peri-operative mortality and morbidity (stroke and myocardial infarction) and the incidence of non-peri-operative stroke (particularly in the carotid territory of the brain). An independent endpoint review committee, blinded for treatment allocation, adjudicated all major events and further classified strokes wherever possible. Cause specific mortality was ascertained for those participants who died during follow-up.

In the present study, primary endpoints were any stroke occurring after the procedural period (>30 days) and, separately, vascular (non-stroke) death. The secondary endpoint was peri-procedural stroke, MI, and death.

Statistical analysis

Baseline characteristics of patients with echolucent and non-echolucent plaques were compared using chi-square statistics. A separate analysis of baseline characteristics was performed comparing patients in whom echolucency was assessed with those in whom it was not assessed. For the analysis of non-peri-procedural stroke, patients were censored after their first stroke (i.e. subsequent strokes were not counted). For the analyses of vascular death, all previous events (i.e. non-fatal strokes) were ignored. Kaplan-Meier survival statistics were used to calculate the cumulative risk of primary endpoints and a p value was calculated using a log-rank test (pooled over strata). Analysis of peri-procedural events was limited to a patient's first CEA. Unconditional maximum likelihood estimation was used to calculate odds ratios with confidence intervals for the occurrence of peri-procedural events. All analyses were also separately performed for patients allocated immediate CEA. A p value of $<.05$ was considered to be statistically significant for all analyses.

RESULTS

Study population

CEA was performed on a total of 1832/3120 (59%) participants. The majority of those allocated immediate CEA had this surgery (1425/1,560, 91%) and usually did so within 1 month (median 27 days). Of those allocated deferral, a total of 407/1560 (26%) underwent surgery over the next decade. Median follow-up after surgery was 75 months for patients allocated to CEA and 45 months for the deferred cohort. Echolucency was assessed in 894/1832 (49%) and in just over half of those a substantial part of the plaque (>25%) appeared echolucent on ultrasound (458/894, 51%). Baseline patient characteristics are summarized in Table 1. Patients with echolucent plaques were slightly younger ($p = .043$) and were more often male ($p \leq .001$) than patients with non-echolucent plaques. Patients with echolucency assessment had a somewhat tighter ipsilateral stenosis and were more often treated with antihypertensive and lipid lowering therapy at trial entry.

Peri-procedural risk

The risk of peri-procedural events according to echolucency status is shown in Table 2. Twenty patients had a fatal peri-

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