Eur J Vasc Endovasc Surg **23**, 519–523 (2002)
doi:10.1053/ejvs.2002.1649, available online at http://www.idealibrary.com on IDEAL®

Asymptomatic Carotid Stenosis in Patients on Medical Treatment Alone

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Objective: *the aim of this study was to investigate the effect of currently recommended medical treatment (MT) on changes in carotid stenosis in a group of asymptomatic patients taken from the Asymptomatic Carotid Surgery Trial (ACST).*
Method: *collaborators in ACST were given information on MT for stroke prevention (including antiplatelet agents, lipid-lowering drugs, diabetic and hypertension control). Patients underwent clinical examination and duplex scanning at entry, 4 months following randomisation and annually thereafter. The cohort of patients studied were those randomised to MT with complete follow up duplex datasets at four years* ($n = 219$). *None had undergone carotid endarterectomy (CEA) or developed ipsilateral carotid symptoms.*
Results: *there was no change in median carotid stenosis over four years (baseline 79% (IQR 10%) and 4 year median 79% (IQR 10%)) a median difference of 0 with* $Q1 = -5$ *and* $Q3 = +5$ ($p = 0.98$ *Wilcoxon one sample test), whilst in many patients' stenoses progressed and regressed during this time. No individual MT variable correlated with stenosis progression or regression.*
Conclusion: *in this group of ACST patients on MT, mean carotid stenosis was unchanged over 4 years. Individual patients' stenoses progressed (and regressed) without symptoms occurring. An increase in stenosis should not be the sole basis for deciding to operate on an asymptomatic patient.*

Key Words: Asymptomatic carotid stenosis; Carotid endarterectomy; Ultrasonography; Risk factors.

Introduction

The purpose of this study was to investigate carotid stenosis changes in patients from the ongoing Asymptomatic Carotid Surgery Trial (ACST). The natural history of carotid stenosis is very important, as severity of stenosis and stenosis progression are thought to be predictors of stroke risk.[1–4] Recent studies have demonstrated that aggressive use of statins can slow and regress carotid intima media thickness, but these studies have been conducted in patients with very early atherosclerosis.[5,6] The effect of currently recommended Medical Treatment (MT) in patients with moderate or advanced carotid stenosis is unclear. This study sought to investigate this in a group of patients who remained asymptomatic and who had been followed up for 4 years.

Patients and Methods

Patients were recruited into ACST if they were found to have an asymptomatic carotid stenosis, which might be suitable for carotid endarterectomy (CEA). Asymptomatic was defined as not having suffered from ipsilateral transient ischaemic attack (TIA), amaurosis fugax or stroke within the previous 6 months. After patients consented, they were randomised in equal numbers to either CEA and MT or MT alone.

At study entry vascular risk factors were assessed (blood pressure, total cholesterol level and diabetic status) and patients underwent neurological examination. Established coronary artery disease was assessed by history. Medication was noted by group (i.e. antihypertensive, antiplatelet, anticoagulants and lipid-lowering therapy). A history of previous (greater than 6 months) ipsilateral symptoms or brain scan evidence of cerebral infarction were noted. On entry current carotid stenosis was assessed by duplex scanning.

ACST subjects were followed up 4 months after entry and annually thereafter. At each follow-up they

This paper was presented at the ESVS 2001 in Lucerne, Switzerland.
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1078–5884/02/060519 + 05 $35.00/0

underwent duplex scanning and had their blood pressure measured. Current drug therapy was noted. History and examination were performed to assess for symptoms (stroke, TIA).

The aim of the present study was to assess change in carotid stenosis and the effect of MT on patients randomised to this arm of the study. In this paper, the ACST database was interrogated; only patients with complete duplex data sets for four years were included and only the carotid artery that had been considered for surgery was studied. Patients were excluded if they had any data missing, had a major event (death, stroke) or had carotid intervention during follow up.

Medical therapy (MT)

Centres participating in ACST were sent the trial protocol[7] which included guidelines for appropriate MT. These consisted of optimal and rigorous control of blood pressure (hypertension requiring treatment was defined as greater than 160/90 mmHg) and diabetes, advice regarding cessation of smoking and either antiplatelet or anticoagulation treatment. Cholesterol lowering was advised if total cholesterol was greater than five mmol/l at baseline. Ischaemic heart disease whether symptomatic or uncovered by investigation should have been appropriately treated and was not a reason for exclusion from ACST (however simultaneous CEA and coronary artery bypass was not allowed).

Duplex scanning

At each follow-up, patients underwent further duplex scanning. Median carotid stenosis of the group was studied over time. Centres used their preferred scanning technique to calculate stenosis in keeping with the study protocol. Estimation of stenosis had to be expressed as percentage diameter reduction but no specified duplex scanning method was imposed on centres. We analysed actual reported change over the four year period (four year value minus baseline stenosis) and divided them into 10% categories. However in keeping with recent studies and for comparative purposes, we undertook a separate analysis using Strandness' criteria. Strandness categorised diameter reduction and stenoses into group (0%, 1–14%, 15–49%, 50–79%, 80–99%) using duplex ultrasound.[1,8] Progression, in this study was then defined as advancement to a higher category at any time during follow up. In patients who had progressed to a higher category we also recorded those who subsequently returned to the lower level.

Regression was similarly defined as a change to a lower category at 4 years compared to baseline value.

Statistical Methods and Analysis

Spearman's non-parametric correlation coefficients were calculated. One- and two-sample Wilcoxon and the Chi-squared tests were used to study gender, baseline cholesterol, patients on lipid-lowering treatment at baseline and four years, baseline blood pressure and change in blood pressure between baseline and four years. Median values and interquartile ranges were calculated. The tests were two sided and $p < 0.05$ was considered significant.

Results

Currently there are 1386 patients in the MT arm of ACST, and 853 have been followed up for four years. Two hundred and nineteen (16%) MT patients fulfilled all the entry criteria for this study (all 6 duplex scans reported and no major event or operation) representing 49 centres and 15 countries. The mean age of the group was 68 years. The mean cholesterol level at baseline was 6.0 mmol/l and 23% (51/219) were diabetic (see Table 1).

The median percentage carotid stenosis was plotted against time (Fig. 1). There was no change over the four years (baseline 79% (IQR 10%) and 4 year median 79% (IQR 10%), a median difference of 0% $Q1 = -5$, $Q3 = +5$, $p = 0.98$ one-sample Wilcoxon test). The change in percentage stenosis (in 10% increments) of individuals was analysed from baseline to 4 years (Fig. 2). There was no association between individual absolute change in stenosis and gender ($p = 0.9$ Chi-squared), baseline cholesterol or blood pressure ($p = 0.3$–0.8 two-sample Wilcoxon test). There was also no correlation between change in either blood

Table 1.

Baseline characteristics ($n = 219$)	
Male/female	151/68
Mean age (years)	68
No. of diabetics	51 (23%)
Mean cholesterol (mmol/l)	6.0 (IQR 5.3–6.8)
Mean systolic blood pressure (mmHg)	155 (IQR 140–170)
Mean diastolic blood pressure (mmHg)	83 (IQR 80–90)

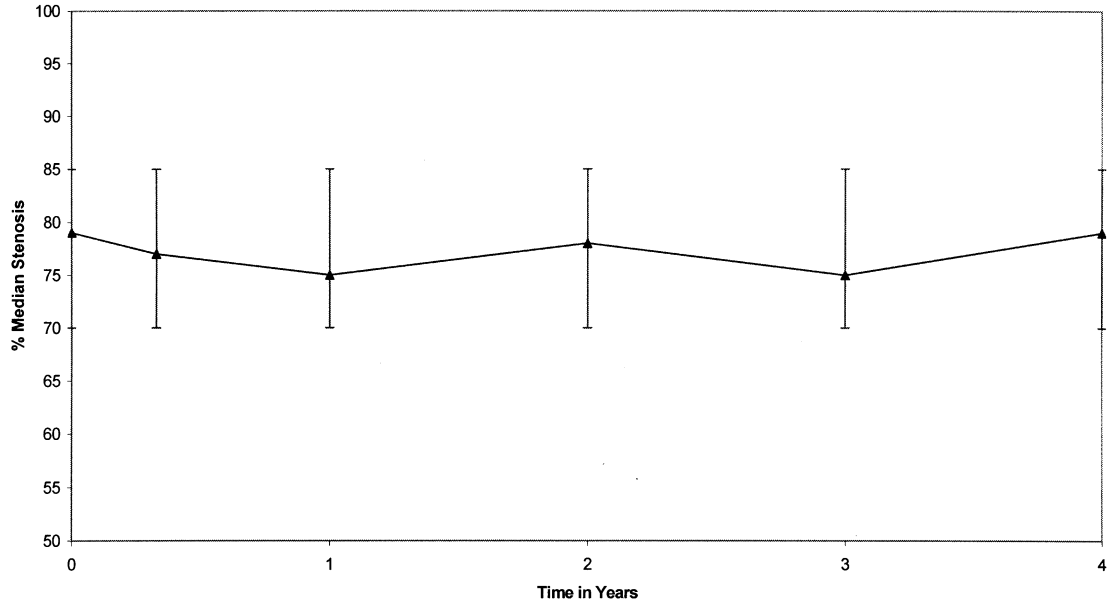

Fig. 1. Median carotid stenosis and the interquartile range of 219 patients randomised to currently recommended Medical Treatment followed for 4 years. There was no change in median carotid stenosis over 4 years (baseline 79% (IQR 10%)) and 4 year median 79% (IQR 10%), a median difference of 0 with Q1 = −5 and Q3 = +5 ($p = 0.98$ Wilcoxon one-sample test).

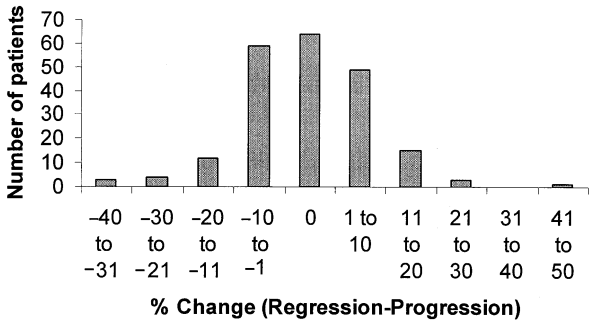

Fig. 2. Changes in individual carotid stenosis from baseline to 4 years (− values represent regression and + values represent progression in stenosis) grouped by 10% categories.

pressure or carotid stenosis between baseline and 4 years ($p = 0.25$ Spearman), nor was there an association between stenosis change and whether patients were taking lipid-lowering treatment ($p = 0.9$ two-sample Wilcoxon test).

Patients' stenoses were also classified by Strandness' criteria: 15–49%: ($n = 2$), 50–79%: ($n = 110$), 80–99%: ($n = 107$). When comparing only the baseline and 4 year stenosis values; 31 patients regressed to a lower group, 148 patients remained in the same group, 37 patients progressed by one group and 3 by two categories. However by defining progression as an increase of stenosis to a higher category at any time during follow-up, 51 patients progressed (123 patients remained in the same group and 45 patients regressed). Ten of the 51 who progressed subsequently "regressed" to their original category at a later follow-up.

Those patients whose stenosis progressed at any stage to a higher category (by Strandness' criteria) were compared with the rest. There were no significant differences by gender, baseline cholesterol, blood pressure (and change in mean blood pressure) and lipid-lowering treatment between those who progressed ($n = 51$) and those who did not ($n = 168$) (p values > 0.5).

Discussion

This study analysed changes in carotid stenosis in a group of patients from the ACST randomised to MT. None of these had major events and none had CEA. Patients who were symptomatic had been excluded as ACST is still ongoing and the current findings are blinded to all except the data monitoring committee. This group represents those patients who have been followed for four years and who fulfilled the inclusion/exclusion criteria; none were specifically or individually selected. Many of those followed for four years were excluded because of incomplete duplex reporting. This is because whilst overall follow up is excellent, many centres do not have the resources to perform annual duplex scanning. However when those patients with incomplete

duplex follow-up were included in the analysis there was still no change in carotid stenosis over 4 years.

The results in this selected group demonstrate that mean carotid stenosis did not change over 4 years. This may be surprising, as some might expect to see overall progression in a group such as this who have moderate to severe carotid stenosis,[8] even though we have excluded those who were symptomatic. It is also difficult to attribute this result to individual components of the MT as none of the analyses performed demonstrated differences between patients who progressed and those that did not. Other studies have grouped stenoses by Strandness' criteria and defined progression by advancement into a higher group.[8,9] In ACST many centres do not use this method and therefore it may be inappropriate to categorise the data by these criteria. To compare with other studies this analysis was performed and none of the specific variables were associated with progression or regression.

Muluk *et al*. studied the natural history of carotid stenosis in a large number of patients; the majority of whom had negligible or only very mild stenosis at the beginning of the study.[8] They demonstrated that a systolic blood pressure of greater than 160 mmHg at baseline was associated with a greater risk of progression of carotid stenosis. Our study did not confirm this even though our patients had tighter carotid stenosis.

McMahon, in the LIPID study of 552 patients with early (non-stenotic) atherosclerosis demonstrated that 4 years of pravastatin therapy resulted in a decrease in carotid wall thickness.[5] Smilde demonstrated a similar regression in carotid intima media thickness in patients with (non-stenotic) early atherosclerosis with familial hypercholesterolaemia who were treated with aggressive atorvastatin therapy for 2 years.[6] However, Liapis studied patients with mild stenosis (mean stenosis 45%) and found that hypercholesterolaemia did not correlate with stenosis progression.[10] The findings from our study are similar.

There is no standardised technique of duplex scanning, but because ACST is very large, individual centres' variations are less important. Furthermore the individual patient is followed at the same centre each visit and centres are asked to validate their own techniques. By not imposing a standard technique, the patients entered represent normal day to day practice of the trial collaborators, and reflect the stenosis values on which their decisions are based. Recently a study has been performed in patients from ACST centres that perform angiography and duplex ultrasound; this showed good correlation between angiography and duplex ultrasound in one hundred patients (unpublished).

The use of x-ray contrast angiography is becoming more selective with many centres now relying on duplex ultrasound alone or in conjunction with magnetic resonance imaging. All methods of assessment have scope for error whether overestimating or underestimating stenosis values. All clinicians will have encountered these difficulties when following up patients who are asymptomatic with significant carotid stenoses especially as stenosis progression and severe baseline stenosis are thought to be associated with subsequent neurological events.[1–4]

The only reported large trial supporting prophylactic CEA for asymptomatic carotid stenosis is the Asymptomatic Carotid Atherosclerosis Study (ACAS). ACAS demonstrated that patients who had an asymptomatic carotid stenosis of greater than 60% (measured by angiography) did better with CEA than conservative treatment in preventing stroke.[11] Since ACAS was published in 1995 there has been a large increase in the number of prophylactic CEAs performed.[12] However ACAS failed to demonstrate any increased benefit in operating on patients with very tight (80–99%) stenosis, when compared with the overall group. Despite this, others have advised patients with duplex Doppler ultrasound stenoses of greater than 70% that are asymptomatic to undergo CEA.[8,10] The results of our study have highlighted the difficulty of relying on the value of "actual" stenosis to decide on when to operate on aysmptomatic patients. If decisions are made purely on the basis of 'progression' then many patients would have undergone CEA even though they remained asymptomatic and some if left would have "regressed" by the following visit. The mortality and morbidity from CEA in asymptomatic patients is significant and probably much higher than the very low rate of morbidity and mortality found in ACAS (less than 3%). Rothwell, Wong and Kucey separately investigated outcomes of carotid endarterectomy for asymptomatic carotid stenosis and found overall combined stroke and death rates varied from 3.35–5.1%.[13–15] These results may mean that there is no benefit in prophylactic CEA; at present many believe surgery is not cost effective and that much stronger evidence of stroke prevention is needed.

The only ongoing trial, which should help to answer these questions is the ACST. After analysis and, if appropriate metanalysis, it should be possible to determine whether operation is justified for patients with asymptomatic carotid stenosis. This study demonstrates that appropriate MT, without

operation, is not associated with increasing carotid stenosis in this group of otherwise asymptomatic patients.

Acknowledgements

The Asymptomatic Carotid Surgery Trial is supported by the U.K. Medical Research Council and the Stroke Association.

The ACST Collaborators are: M. Adiseshiah, London; R. Adovasio, Trieste; R.S. Akchurin, Moscow; M.I. Aldoori, Huddersfield; A.G. Alfageme, Galdakao; F.P. Alò, Ancona; P. Andziak, Warsaw; N.S. Angelides, Nicosia; O. Arena, Milan; S. Ashley, Plymouth; R.N. Baird, Bristol; D. Baker, London; K. Balzer, Mülheim an der Ruhr; A.A.B. Barros D'Sa, Belfast; G. Becchi, Genova; V. Benes, Prague; D. Bergqvist, Uppsala; D. Berridge, Leeds; F. Beyersdorf, Freiburg; C.C.R. Bishop, London; R. Blair, Hamilton; S. Bonardelli, Brescia; A.W. Bradbury, Edinburgh; G. Brown, Wakefield; J. Budd, Bath; P. Burke, London; K.G. Burnand, London; D.C. Busman, Leeuwarden; O. Busse, Minden; J. Buth, Eindhoven; P. Caiazzo, Caserta; M. Cairols, Barcelona; W.B. Campbell, Exeter; P.G. Cao, Perugia; J.M. Capdevila, Barcelona; J.M. Cardon, Nimes; A. Cavallaro, Rome; A.D.B. Chant, Southampton; S. Chaturvedi, Detroit; J.F. Clegg, Cheshire; M. Collice, Milan; C. Corominas, Mallorca; P. Curley, Wakefield; T. Dahl, Trondheim; A.H. Davies, London; J. Dayantas, Athens L. De Cossart, Liverpool G. Deriu, Padua; F. Diaz, Detroit; B.C. Eikelboom, Utrecht; L. Entz, Budapest; I. Flessenkämper, Berlin; V. Flis, Maribor; C. Forssell, Linköping; G. Fraedrich, Innsbruck; S. Franke, Würzburg; J.C. Garcia-Monco, Galdakao; A.E.B. Giddings, London; S.M. Giulini, Brescia; J. Gniadek, Katowice; A. Gottsäter, Malmö; E.C. Grocott, Hereford; Grönniger, Minden; G. Gurgel, Natal; G. Hamilton, London; R. Hannon, Belfast; P. Harris, Liverpool; C. Holdaway, Hamilton; R. Holdsworth, Stirling; J. Holm, Göteborg; R. Holness, Halifax; J.M. Hood, Belfast; M. Horrocks, Bath; W. Howes, Halifax; Iglesias-Negreia, La Coruna; J. Julia, Mallorca; Z. Jàrànyi, Budapest; R. Karmeli, Haifa; P.J. Kirkpatrick, Cambridge; D. Kiskinis, Thessaloniki; B. Klumpp, Berlin; H.W. Kniemeyer, Bern; H.-G. Knoob, Mülheim an der Ruhr; R. Kolvenbach, Dusseldorf; P. Konrad, Stockholm; G. Kretschmer, Vienna; A. Kroese, Oslo; P. Lamont, Bristol; R. Langille, Halifax; B. Lee, Belfast; M.J.A. Lepäntalo, Helsinki; P. Lozano, Mallorca; F. Lundgren, Norrköping; G. MacKean, Halifax; N. Maeder, Heidlberg; A.K. Malek, Warsaw; A.O. Mansfield, London; J. Marsch, Berlin; F. Mascoli, Ferrara; E. Mattsson, Göteborg; C.N. McCollum, Manchester; P.T. McCollum, Hull; D. Mehigan, Dublin; A.D. Mendelow, Newcastle upon Tyne; K. Miksic, Maribor; D. Mitchell, Bristol; I. Mogan, Budapest; L. Moggi, Perugia; L. Mozzon, Udine; J. Murie, Edinburgh; H.O. Myhre, Trondheim; L. Mátyás, Miskolc; T. Mätzsch, Malmö; R. Naylor, Leicester; A. Nicolaides, London; L. Norgren, Lund; W. Noszczyk, Warsaw; P. Olofsson, Stockholm; D. Palombo, Aosta; M. Caetano Pereira, Porto; S.J. Phillips, Halifax; G. Plate, Helsingborg; R.M. Porta, San Sebastian; A. Potemkowski, Kalmar; E. Pozzati, Bologna; M. Puttini, Milan; H. Pärsson, Uppsala; P. Qvarfordt, Helsingborg; D. Radak, Belgrade; G. Regina, Bari; V. Riambau, Barcelona; G. Roedig, Mülheim an der Ruhr; A. Rosendo Carrera, Vigo; C.V. Ruckley, Edinburgh; W. Sandmann, Düsseldorf; J. Schneider, Würzburg; J. Scott, Leeds; M.N. Sechas, Athens; D. Sege, St. Gallen; R.J. Segura Iglesias, Coruna; C.P. Shearman, Southampton; Simaná, Pilsen. M. Simms, Birmingham; C. Skiöldebrand, Kalmar; G. Slabakov, Sofia; F.C.T. Smith, Bristol; C.V. Soong, Belfast; T. Sosa, Zagreb; C. Spartera, L'Aquila; F. Spigonardo, Pescara; T. Sraïeb, Montfleury; G. Stansby, Newcastle upon Tyne; J. Streifler, Petach Tikva; J. Swedenborg, Stockholm; M. Szostek, Warsaw; R. Takolander, Stockholm; P. Taylor, London; J.F. Thompson, Exeter; P.R. Todorovic, Belgrade; A. Tovar-Pardo, La Coruna; N. Tusini, Modena; P. Van Schil, Antwerp; E. Vecchiati, Modena; R. Vila-Coll, Barcelona; L. Virreira, Mülheim an der Ruhr; S. Weimann, Innsbruck; G. Welch, Glasgow; D.C. Wilkins, Plymouth; A.R. Wilkinson, Hull; J.H.N. Wolfe, London; K. Woodburn, Truro; K.D. Wölfle, Augsburg; T.I. Yo, Rotterdam; B. Yoffe, Ashkelon; A. Zelikovski, Petach Tikva; N. Zinicola, Peitra-Ligure; J. de Nie, Goes; R.W.H. van Reedt Dortland, Utrecht; F. van der Linden, Geldrop.

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Accepted 26 March 2002