

# Stroke

American Stroke  
Association<sup>SM</sup>

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American  
Heart Association



## **Carotid Endarterectomy for Asymptomatic Carotid Stenosis: Asymptomatic Carotid Surgery Trial**

P.M. Rothwell and L.B. Goldstein

*Stroke* 2004;35;2425-2427; originally published online Aug 26, 2004;

DOI: 10.1161/01.STR.0000141706.50170.a7

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214  
Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online  
ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/35/10/2425>

Subscriptions: Information about subscribing to *Stroke* is online at  
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

Section Editors: Marc Fisher, MD, and Antoni Dávalos, MD

## Carotid Endarterectomy for Asymptomatic Carotid Stenosis Asymptomatic Carotid Surgery Trial

P.M. Rothwell, MD, PhD, FRCP; L.B. Goldstein, MD

Effective prevention is inarguably the best option for reducing the individual and societal burden of stroke. For each patient, clinicians balance the benefits of a given preventive therapy against its associated risks and costs. Where possible, these assessments should be based on the results of randomized clinical trials. Carotid endarterectomy (CEA), the most-commonly used surgical procedure to prevent stroke, has been subjected to several randomized trials. These underlie evidence-based guideline and consensus statements providing recommendations for its use.<sup>1-7</sup> The evidence base for endarterectomy for symptomatic stenosis is considerable,<sup>8,9</sup> but guidelines on surgery for asymptomatic stenosis have been largely based on the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS)<sup>10</sup> in conjunction with other smaller trials.<sup>11,12</sup> Guidance differs from endorsement of the operation for selected patients (eg, based on patient age, life expectancy, concomitant illnesses, etc.) with varying degrees of asymptomatic stenosis (generally either 60% to 99% or 80% to 99%) in whom the procedure can be performed with low (ie, <3%) complication rates to advising that endarterectomy not be performed in patients without referable symptoms.

ACAS reported a 47% relative reduction in the risk of ipsilateral stroke and perioperative death in patients randomized to surgery despite a 5-year risk of ipsilateral stroke without the operation of only 11%.<sup>10</sup> The results led to major increases in rates of endarterectomy for asymptomatic stenosis in some countries, most notably the United States. Of the approximate 150 000 endarterectomies performed in the United States each year, at least half are done for stenoses that have never been symptomatic.<sup>13</sup> In contrast, the ACAS results had little effect on endarterectomy rates in other countries such as the United Kingdom, where it was felt that the benefit (it was estimated that 40 operations were needed to prevent 1 disabling or fatal stroke after 5 years) did not justify the cost.

There was also concern that the very low operative risks in ACAS (excluding complications of angiography: 1.5%, 95% CI, 0.6% to 2.4% for stroke and death; and 0.14%, 95% CI, 0% to 0.4%, for death) could not be matched in routine clinical practice. ACAS only accepted surgeons with an excellent safety record, rejecting 40% of initial applicants and subsequently barring from further participation some surgeons who had adverse operative outcomes during the trial.<sup>14</sup> Figure 1 compares the operative risks in ACAS with the results of a meta-analysis of the 46 surgical case series that published operative risks for asymptomatic stenosis during ACAS and the 5 years after publication.<sup>15</sup> Operative mortality was 8× higher than in ACAS (1.11% versus 0.14%;  $P=0.01$ ), and the risk of stroke and death was ≈3× higher among comparable studies in which outcome was assessed by a neurologist (4.3% versus 1.5%;  $P<0.001$ ). Even after community-wide performance measurement and feedback, the overall risk for stroke or death after endarterectomy performed for asymptomatic stenosis in 10 US states was 3.8% (including 1% mortality).<sup>16</sup> Therefore, the degree to which the ACAS results can be generalized to routine clinical practice remained uncertain. Results of the largest randomized trial of endarterectomy for asymptomatic stenosis, the Medical Research Council Asymptomatic Carotid Surgery Trial (ACST), have now been published.<sup>17</sup> How will these results affect current practice recommendations?

Between 1993 and 2003, ACST randomized 3120 patients with >60% mainly asymptomatic carotid stenosis (12% had symptoms at least 6 months previously) to immediate endarterectomy plus medical treatment versus medical treatment alone or until the operation became necessary.<sup>17</sup> Surgeons were required to provide evidence of an operative risk of ≤6% for their last 50 patients having an endarterectomy for asymptomatic stenosis, but none were excluded on the basis of his/her operative risk during the trial. Selection of patients was based on the "Uncertainty Principle," with very few

Received July 26, 2004; accepted July 27, 2004.

From the Stroke Prevention Research Unit (P.M.R.), University Department of Clinical Neurology, Radcliffe Infirmary, Oxford, UK; and the Department of Medicine (Neurology) (L.B.G.), Duke Center for Cerebrovascular Disease, Center for Clinical Health Policy Research, Duke University and Veterans Administration Medical Center, Durham, NC.

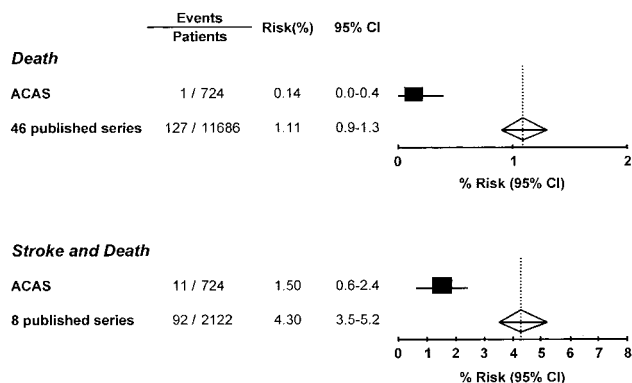
Correspondence to Professor P.M. Rothwell, Stroke Prevention Research Unit, University Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Rd, Oxford OX2 6HE. E-mail peter.rothwell@clneuro.ox.ac.uk

(*Stroke*. 2004;35:2425-2427.)

© 2004 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000141706.50170.a7



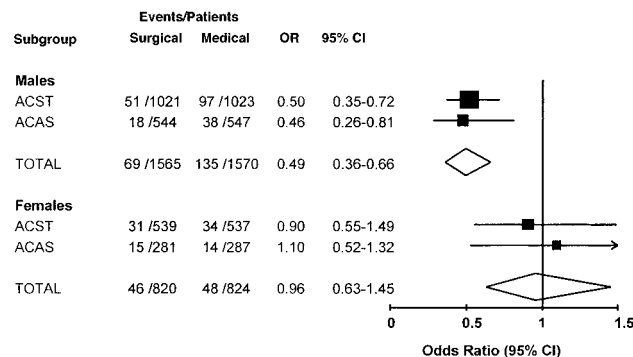
**Figure 1.** The overall results of a meta-analysis of the operative risk of death (top) from all studies published between 1990 and 2000 inclusive that reported risks of CEA for asymptomatic stenosis<sup>15</sup> and the operative risk of stroke and death in those studies in which outcome was assessed by a neurologist (bottom) compared with the same risks in ACAS.<sup>10</sup>

exclusion criteria and with stenosis assessed by Doppler ultrasonography. There was neither an evaluation of the ultrasonographer's training nor a centralized audit of his/her performance.<sup>17,18</sup>

Despite the differences in methods, the results of ACST and ACAS were quite similar. Although the 5-year risk of any stroke or perioperative death in the nonsurgical group was lower in ACST (11.8%) than in ACAS (17.5%), the absolute reductions in 5-year risk with surgery were not substantially different (5.3%, 95% CI, 3.0% to 7.8% versus 5.1%, 95% CI, 0.9% to 9.1%, respectively). The main differences between the trials were in the 30-day operative risks of death (0.14%, 95% CI, 0% to 0.4% in ACAS versus 1.11%, 95% CI, 0.6% to 1.8% in ACST;  $P=0.02$ ) and stroke and death combined (1.5%, 95% CI, 0.6% to 2.4% in ACAS versus 3.0%, 95% CI, 2.1% to 4.0% in ACST;  $P=0.04$ ).

Apart from replicating the results of ACAS in a more pragmatic setting, what else have the results of ACST added? In ACAS, there was a nonsignificant ( $P=0.26$ ) 2.7% reduction in the absolute risk of disabling or fatal stroke with surgery. ACST reported a statistically significant ( $P=0.004$ ) 2.5% (95% CI, 0.8 to 4.3%) absolute reduction. This observation is important because CEA is a potentially dangerous intervention, and having a precise assessment of its benefits in terms of those outcomes that are of most importance to patients is essential before surgery is recommended to otherwise healthy asymptomatic individuals. ACST has provided this evidence (although the number needed to treat to prevent 1 disabling or fatal stroke after 5 years remains  $\approx 40$ ).

In contrast to the results of randomized trials of endarterectomy for symptomatic stenosis,<sup>8,19</sup> neither ACST nor ACAS showed increasing benefit from surgery with increasing degree of stenosis within the 60% to 99% range.<sup>10,17</sup> This counterintuitive observation was assumed to be attributable to a lack of statistical power in ACAS but cannot be dismissed with the additional data provided by ACST. Part of the explanation may be that measurement of the exact degree of stenosis is less accurate with Doppler ultrasound scanning than with catheter angiography. For example, neither ACAS nor ACST identified near-occlusions (situations where there



**Figure 2.** The effect of endarterectomy for asymptomatic carotid stenosis on the risk of any stroke and operative death by sex in ACST<sup>17</sup> and ACAS.<sup>10</sup>

is very low poststenotic flow associated with distal narrowing or collapse of the ICA).<sup>8,20</sup> This situation is paradoxically associated with a low risk of stroke during medical treatment in symptomatic<sup>8,20</sup> and asymptomatic<sup>21</sup> patients and no clear benefit from endarterectomy (at least in symptomatic cases).<sup>8</sup> The prevalence of near-occlusions during angiography increases with degree of stenosis, as determined by the method used in the European Carotid Surgery Trial (ECST); the North American Symptomatic Carotid Endarterectomy Trial method is not applicable.<sup>20</sup> In the ECST, the proportion of near-occlusions was 0.6% at 60% to 69% stenosis, 2.3% at 70% to 79% stenosis, 9.2% at 80% to 89% stenosis, and 29.5% at 90% to 99% stenosis.<sup>11</sup> In the pooled analysis of the randomized trials of endarterectomy for symptomatic carotid stenosis, the higher proportion of near-occlusions in the upper deciles of stenoses diluted the benefit of endarterectomy, and a clear increase in benefit with degrees of stenosis between 70% and 99% was only apparent when near-occlusions were analyzed separately.<sup>8</sup>

Although some subgroup analyses were reported in ACAS, the trial had insufficient power to reliably analyze subgroup-treatment effect interactions. Because of its larger sample size, ACST had greater power to evaluate subgroups, although no analyses were prespecified in any detail in the trial protocol.<sup>18</sup> ACST did perform some subgroup analyses, but only reported results for the reduction in risk of nonperioperative stroke (ie, the benefit) and the perioperative risk (ie, the harm) separately.<sup>17</sup> The overall balance of hazard and benefit, which is of most importance to patients and clinicians, was not reported, although the data can be extracted from the Web tables that accompanied the ACST report. Sex-based differences in the overall results of endarterectomy are of particular interest. Because of a higher operative risk in women and a lower risk of stroke without surgery, CEA for symptomatic stenosis is less beneficial for 70% to 99% stenosis in women than in men and of no benefit in women with 50% to 69% stenosis (overall interaction  $P=0.003$ ).<sup>9</sup> The same trend was found in ACAS, with a statistically borderline sex-treatment effect interaction.<sup>10</sup> Figure 2 shows a meta-analysis of the effect of endarterectomy on the 5-year risk of any stroke and perioperative death in ACAS and ACST. Surgical benefit is greater in men than in women (pooled interaction  $P=0.01$ ), and it remains uncertain

whether there is any worthwhile benefit at all in women. Subgroup analyses can be unreliable, and overall benefit from surgery might well accrue in women with longer follow-up, as is planned for the ACST, but current evidence does not appear to justify the high rates of CEA for asymptomatic stenosis in women in some countries.

Science is based on replication, and ACST largely supports and extends the results of ACAS, showing a small but definite reduction in the risk of disabling or fatal stroke with surgery. The study adds to the body of data on which clinical and policy decisions regarding the potential usefulness of the procedure can be based. Clinicians and policy makers will need to determine whether or not changes in practices and recommendations are warranted.

### References

1. Biller J, Feinberg WM, Castaldo JE, Whittemore AD, Harbaugh RE, Dempsey RJ, Caplan LR, Kresowik TF, Matchar DB, Toole JF, Easton JD, Adams HPJ, Brass LM, Hobson RWI, Brott TG, Sternau L. Guidelines for carotid endarterectomy. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Stroke*. 1998;29:554–562.
2. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, Ross JL, Raps E, Ozer MN, Brass LM, Malone ME, Goldberg S, Booss J, Hanley DF, Toole JF, Greengold NL, Rhew DC. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *J Am Med Assoc*. 1999; 281:1112–1120.
3. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, Hill M, Howard G, Howard VJ, Jacobs B, Levine SR, Mosca L, Sacco RL, Sherman DG, Wolf PA, del Zoppo GJ. Primary prevention of ischemic stroke. *Circulation*. 2001;103:163–182.
4. The Intercollegiate Working Party for Stroke. *National Clinical Guidelines for Stroke*. London: Royal College of Physicians; 2002.
5. National Health and Medical Research Council. *Clinical Practice Guidelines: Prevention of Stroke: The Role of Anticoagulants, Antiplatelet Agents and Carotid Endarterectomy*. Canberra, Australia: National Health and Medical Research Council; 1997.
6. Swedenborg J, Rothwell PM, Jogestrand T, Bergqvist D. Consensus statement: carotid endarterectomy. In: Wahlgren NG, Ahmed N, Hardemark H-G, eds. *Update on Stroke 2002/2003*. Stockholm: Karolinska Stroke Update; 2003.
7. Perry JR, Szalai JP, Norris JW. Consensus against both endarterectomy and routine screening for asymptomatic carotid artery stenosis. *Arch Neurol*. 1997;54:25–28.
8. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–116.
9. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Effect of endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and to the timing of surgery. *Lancet*. 2004;363: 915–924.
10. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *J Am Med Assoc*. 1995;273:1421–1428.
11. Hobson RW, Weiss DG, Fields, Goldstone J, Moore WS, Towne JB, Wright CB, and the Veterans Affairs Cooperative study group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med*. 1993;328:221–227.
12. Mayo Asymptomatic Carotid Endarterectomy Study Group. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. *Mayo Clin Proc*. 1992;67:513–518.
13. Tu JV, Hannan EL, Anderson GM, Iron K, Wu K, Vranizan K, Popp AJ, Grumbach K. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med*. 1998;339:1441–1447.
14. Moore WS, Vesceera CL, Robertson JT, Baker WH, Howard VJ, Toole JF. Selection process for surgeons in the Asymptomatic Carotid Atherosclerosis Study. *Stroke*. 1991;22:1353–1357.
15. Bond R, Rerkasem K, Rothwell PM. High morbidity due to endarterectomy for asymptomatic carotid stenosis. *Cerebrovasc Dis*. 2003; 16(suppl):65.
16. Kresowik TF, Bratzler DW, Kresowik RA, Hendel ME, Grund SL, Brown KR, Nilasena DS. Multistate improvement in process and outcomes of carotid endarterectomy. *J Vasc Surg*. 2004;39:372–380.
17. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.
18. Halliday AW, Thomas D, Mansfield A. The Asymptomatic Carotid Surgery Trial (ACST). Rationale and design. *Eur J Vasc Surg*. 1994;8: 703–710.
19. Goldstein LB. Extracranial carotid artery stenosis. *Stroke*. 2003;34: 2767–2773.
20. Rothwell PM, Warlow CP. Low risk of ischaemic stroke in patients with collapse of the internal carotid artery distal to severe carotid stenosis: cerebral protection due to low post-stenotic flow? *Stroke*. 2000;31: 622–630.
21. Norris JW, Zhu CZ. Stroke risk and critical carotid stenosis. *J Neurol Neurosurg Psychiatry*. 1990;53:235–237.