Nearing the Finish Line?
The Asymptomatic Carotid Atherosclerosis Study

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More than 1,200 patients have been randomized into the Asymptomatic Carotid Atherosclerosis Study (ACAS), and recruitment continues at a rate of about 30 per month. Fifteen hundred is the calculated sample size needed to answer the question, "Does endarterectomy in addition to best medical management and 325 mg aspirin daily significantly reduce the incidence of transient ischemic attack and stroke on the side of the randomized artery?" The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) have demonstrated convincingly that the surgical management of patients with documented transient ischemic attacks (TIAs) or minor strokes is beneficial for those who have a tight stenosis. In these studies, aspirin even in high doses did not substitute for endarterectomy. This adds particular urgency to the determination of whether the results in this "asymptomatic" population can also be translated to those who are "asymptomatic."

Two multicenter asymptomatic endarterectomy trials have closed recruitment. The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA) study completed randomization of 410 patients in December 1985. No significant difference in the number of neurological deficits and deaths was noted between the treatment groups, but the study design was not really a direct comparison of carotid endarterectomy plus medical management versus medical management alone. The surgical group could have either unilateral or bilateral endarterectomy; those patients having unilateral operation were to have a second operation if the contralateral side progressed to more than 50% stenosis. Patients in the medical group were not operated on for unilateral stenosis, but if the stenoses were bilateral, patients had surgery on the more stenosed side. Patients in the medical group had an endarterectomy if the stenosis progressed to more than 90%, or progressed bilaterally to greater than 50% stenoses. This design greatly reduced the likelihood of achieving a difference in event rates. Furthermore, patients with more than 90% stenosis were not eligible, so patients with the greatest risk of neurological events were excluded. Consequently, results from the CASANOVA trial cannot be considered conclusive regarding the efficacy of carotid endarterectomy for asymptomatic stenosis.

The Veterans Administration Cooperative Trial on Asymptomatic Carotid Stenosis was initiated in April 1983 and completed randomization of 444 adult male patients (mean age, 64 years) in October 1987. During a subsequent clinical follow-up that now extends to a mean of 48.9 months, these investigators reported a combined stroke and mortality rate of 4.3% for the medically managed groups. Final analysis of the medically and surgically treated patients with regard to anticipated differences in the incidence of TIA and stroke is a subject of ongoing follow-up. However, because of the VA trial's smaller sample size as well as its limitation to males, reaching the goals of the ACAS trial is all the more necessary. ACAS is projected to have approximately 91% power for detecting a 35% difference in ipsilateral TIA or stroke rates (two-sided testing, α=0.05) between the aspirin and aspirin-plus-endarterectomy groups.

The NASCET and ECST results have shown that TIA is an even greater risk factor for stroke in the presence of high-grade stenosis. Thus, the combination of TIA (in the presence of 70–99% stenosis) and stroke as the primary outcome event in ACAS and the VA trials becomes critically important. A separate secondary analysis in ACAS will be stroke alone. Although this is a firmer end point, the estimate of a 1% stroke rate per year makes treatment difference harder to detect. Moreover, determination of treatment effect from analysis of stroke alone is complicated because more than 80% of patients randomized to medical management in the ACAS and VA trials have had an endarterectomy after experiencing a TIA. This would appear to be the appropriate therapy in view of the results of the NASCET and ECST trials for those who have 70–99% stenosis of the symptomatic carotid artery.

A fundamental and potentially important difference between the asymptomatic carotid stenosis clinical trials and the symptomatic trials is the use of data from noninvasive tests in the asymptomatic clinical trials. Although the technique for measuring percent stenosis by angiogram is comparable between the...
asymptomatic and symptomatic carotid stenosis trials, the
definition of a threshold stenosis for randomization
in the asymptomatic trials (60% for ACAS and 50% for
the VA trial) is supplemented by inclusion of noninva-
sive hemodynamic data from Doppler sonography. Ran-
domization of a stenosis >50% required a positive
OPG-Gee in the VA trial.\textsuperscript{2} From the results of our
validation studies,\textsuperscript{8} we assume the calculated reductions
in luminal areas in both trials exceed 75% and are
comparable to the higher-grade stenoses reported in
NASCET and ECST. These differences must be consid-
ered in the analysis of the designs of these clinical trials.

This is not a time to relax our efforts or apply results
of other smaller trials to this definitive one. The place of
endarterectomy in the management of asymptomatic
carotid stenosis is not yet known. Only 300 more pa-
tients are needed to give ACAS sufficient power to
settle this vexing question. This goal is easily achievable
by 1993 if centers maintain the current pace of
recruitment.

Appendix

\textbf{ACAS Participating Clinical Centers}

Listed below are the clinical centers participating in ACAS.
Call the ACAS Operations Center at (919) 748-2161 for phone
numbers or addresses of contact persons at each center for
referral of potential patients.

University of Arizona Health Science Center, University of
Arkansas for Medical Sciences, Barrow Neurological Institute,
Bowman Gray School of Medicine of Wake Forest University,
University of California at Los Angeles School of Medicine,
University of California at San Diego, California Pacific
Medical Center, University of Cincinnati, Columbia Univer-
sity, Francis Scott Key Medical Center, Harbin Clinic, Henry
Ford Hospital, Milton S. Hershey Medical Center, Hopital de
L'Enfant Jesus, University of Iowa Hospitals and Clinics,
University of Kentucky Chandler Medical Center, Lehigh
Valley Hospital Center, Loyola University Medical Center,
Marshfield Clinic, Medical College of Virginia, University of
Medicine and Dentistry of New Jersey, University of Missis-
sippi, New England Medical Center, University of New Mex-
ico School of Medicine, Northwestern University Medical
School, Ochsner Clinic, Oregon Health Sciences University,
Roanoke Neurological Associates, St. John's Mercy Medical
Center, Singing River Hospital, Sunnybrook Medical Centre,
University of Tennessee, University of Texas Southwestern
Medical Center, Victoria Hospital, Virginia Mason Clinic,
University of Western Ontario, Yale University.

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