A recent issue of Stroke contained descriptions of two more direction signals along the misty road that has been travelled by those seeking the rightful place for carotid endarterectomy in stroke prevention. One was described by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators in their report of the design and ongoing execution of the North American multicenter randomized trial funded by the National Institutes of Health to evaluate this procedure as applied to symptomatic disease. The other was represented by a reprinting of the Clinical Alert issued by the National Institute of Neurological Diseases and Stroke (NINDS) advising all medical practitioners that patients with symptoms appropriate to a severely (more than 70%) stenotic artery are less likely to suffer stroke in that territory at 18 months after endarterectomy than identical patients who receive only the best of known medical care.

Some surgeons and physicians did not feel that this trial was necessary and could claim now that their position, biased in favor of these results, has been vindicated. Other practitioners were less enthusiastic and felt that we did not know enough in the era of declining stroke to continue submitting patients to a procedure with a real risk of immediate stroke or death in the perioperative period without harder evidence of its worth. Enthusiasts, skeptics, and the patients of both will be comforted to know that, for the first time since the operation was introduced in 1954, it has been subjected to two scientifically credible and parallel trials and declared beneficial in one denned group of patients: those with symptoms related to severe (70-99%) extracranial stenosis.

We should caution that the good news contained in the Clinical Alert must be received by those who care for stroke-threatened patients with full awareness of exactly how this conclusion was reached and what it is that the investigators in NASCET have shown. First, these good results for surgery came from a trial in which the surgeons were carefully selected and attained a 30-day perioperative stroke and mortality rate of 2.3% for permanent disabling stroke and death. Hospitals and surgical departments must ensure that those who perform the procedure do so with a skill comparable to this.

The entry criteria excluded patients with serious complicating illnesses such as myocardial infarction within 6 months, unstable angina, congestive heart failure, and uncontrolled hypertension, as well as those whose cerebral ischemic events had not recurred for 4 months. It would be wrong to extrapolate NASCET's results to the population of patients that were excluded for the reasons listed in the methods article. A clinical trial selects the patients who are hypothesized to be benefited by the treatment under study. Those patients whose inclusion appears likely to diminish the possibility of identifying any benefit are excluded. The results must not be generalized to embrace patients of a type that was never studied.

Furthermore, stringent measurements were employed by the NASCET investigators to define a 70-99% stenosis. The percentage of narrowing was calculated using the narrowest portion of the diseased artery selected from at least two planes and compared to the normal artery beyond the carotid bulb. The more common method of using the widest part of the bulb as the denominator would have placed an additional 20% of NASCET patients in the "severe" category inappropriately. The results of this trial cannot yet be applied to patients evaluated by the more liberal mode of measurement of stenosis. Indeed, the investigators report that there is a distinct downward gradient in the benefit obtained as the degree of stenosis diminishes from 99% to 70%; for patients below 80% at 18 months of follow-up, benefit is detectable only when other important risk factors are present (NASCET Principal Investigators, personal communication). With longer follow-up, benefit may be detectable for all patients with moderate (30-69%) or moderately severe stenosis. Only time will tell.

In the same week in which NINDS sent out its Clinical Alert, the European Carotid Surgery Trial (ECST) investigators advised their participants that symptomatic patients with a narrowing of 70-99% benefit from surgery (C. Warlow, personal communication). By a remarkable coincidence, the Monitoring Committees of both NASCET and ECST came independently and simultaneously to the same conclusion. In addition, both committees advised their
investigators that the data on patients with symptoms related to a stenosis of 30-69% did not allow any conclusion as yet about the efficacy of carotid endarterectomy. Both NASCET and the European Trial are obliged to continue to randomize and follow patients with stenosis of less than 70%. A smaller Veterans Administration trial in the United States had been randomizing symptomatic patients with 50-99% stenosis. Because the majority of their patients were comparable to the severe group of NASCET patients, they have discontinued randomization and soon will be publishing their results (M. Mayberg, personal communication).

Previous multicenter randomized trials have looked for benefit of surgery in the prevention of stroke. The Joint Study of Carotid Endarterectomy failed to prove the value of the procedure because they encountered an 11% perioperative rate of stroke and death, less than half the patients had symptoms clearly of carotid origin, and only 316 patients with carotid stenosis were studied. The procedure of anastomosis between the extracranial and intracranial arteries failed to prevent stroke when submitted to a multicenter international trial (EC/IC Bypass Study). Critics suggested that the "best patients for the procedure" had been deviated from the trial. In the end, this criticism did not remain a substantive issue. To obviate its repetition at the conclusion of NASCET, the investigators were careful to record, in a prospective manner, the characteristics of patients at the participating centers who were eligible for the trial, but who received endarterectomy without being randomized into the study. In those who were treated outside the trial, there was no particular, peculiar, or unique group of patients more likely than the patients in the trial to benefit from the procedure. The conclusions about the patients with severe stenosis in NASCET will be generalizable to the populations of patients with similarly measured degrees of stenosis due to arteriosclerotic disease and appropriate accompanying symptoms.

Patients and medical practitioners will want to help the investigators conclude these trials quickly by joining with the 4,000 patients and 120 centers committed already to the evaluation of symptomatic carotid disease in NASCET and the ECST.

The need for trials evaluating carotid endarterectomy in asymptomatic patients is not influenced by the early conclusions from NASCET or the ECST. The trials must continue. At the conclusion of all ongoing studies on symptomatic and asymptomatic patients, the answer to the 35-year-old question of which patients should and which patients should not be submitted to carotid endarterectomy will be definitively answered once and for all.

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References


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