Carotid Endarterectomy
Where Do We Draw the Line?

Philip B. Gorelick, MD, MPH

In March 1951, Fisher’s report on occlusion of the internal carotid artery characterized basic clinical and pathological features of an important disease syndrome.1 Fisher described fleeting neurological symptoms attributable to atherosclerotic narrowing, thrombosis, and cerebral embolism that might arise from thrombotic material lying in the carotid sinus. He suggested that vascular surgical bypass of the occluded portion of the artery by anastomosis of the external carotid artery above the area of narrowing might be feasible. In October 1951, Carrea et al2-3 of Buenos Aires, Argentina, who were aware of Fisher’s work,4 performed the first successful carotid reconstruction. This included partial ablation of the atherosclerotic plaque and end-to-end anastomosis of the proximal portion of the external carotid to the distal portion of the internal carotid. In May 1954, Eascott et al4 performed resection and reconstruction of the common and internal carotid arteries by direct end-to-end anastomosis, an operation that gave impetus to the development of extracranial carotid surgery.5 However, in 1953, DeBakey5 was credited with performing the first successful carotid endarterectomy (CEA), the procedure that has dominated surgery for extracranial carotid occlusive disease for the past 4 to 5 decades.3

These pioneers1-5 helped to usher in the modern era of CEA. Early attempts at surgical correction of extracranial carotid artery occlusive disease led to the Joint Study of Extracranial Arterial Occlusion in 1959.6 The Joint Study was designed to assess the efficacy of carotid surgery and included 6535 patients (69% men). In 1961, 5 and later 13 of the centers agreed to a controlled trial whereby patients would be randomly assigned to surgical or nonsurgical therapy. The main finding of the trial was that there was no statistically significant difference in stroke or death between the 2 treatment groups. The study had shortcomings and was criticized for being inconclusive. The trial, however, was the only major randomized and controlled study until the 1980s.

The 1980s were punctuated by cautionary notes concerning CEA.7-9 Concern was fueled by startling reports of high complication rates,10,11 yet there was exponential growth in the performance of the procedure based largely on anecdotal evidence. It was estimated that only 35% of CEAs were being performed for appropriate indications.12 By the mid-1980s, dissemination of such sobering news may have led to a decline in the number of CEAs.13

CEA had become a topic of emotional debate and uncertainty since rigorous scientific investigation was wanting.14,15 Finally, in the 1990s the main results of large-scale clinical trials were published.16-25 At last, the debate would end—or would it? The National Institute of Neurological Disorders and Stroke supported 3 of these major trials.17,18,22,23

What have we learned from these clinical trials? The main results for symptomatic and asymptomatic patients are summarized in Table 1. CEA is beneficial in symptomatic patients with high-grade carotid stenosis (70% to 99%). This was a main conclusion of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Medical Research Council European Carotid Surgery Trial (ECST).17,19 Furthermore, within the range of 70% to 99% carotid diameter stenosis as defined by cerebral arteriography, NASCET showed a stenosis-dependent effect for degree of carotid stenosis (70% to 79%, 80% to 89%, and 90% to 99%) and degree of risk reduction after CEA in a secondary analysis.17 The final results of ECST20 suggested that the cutoff point for major benefit with CEA in arteriography-determined stenosis was approximately 80%, which correlated with approximately 60% stenosis in NASCET (ECST and NASCET used different methods for measuring carotid stenosis26; an arteriographic stenosis equivalence scale is shown below Table 1). ECST showed a downward trend in the benefit of surgery for carotid stenosis from a range of 90% to 100% to a range of 80% to 89%. Overall, men had more benefit than women, and younger patients had more benefit over a narrow range of severe stenosis than older patients.20 The Veterans Affairs Cooperative Study21 was halted when results of NASCET and ECST became available. The results of this study of 193 participants supported a stenosis-dependent effect that favored CEA and showed the benefit of CEA when there was high-grade stenosis (>70%).

Less severe carotid stenosis (0% to 29%) was studied in ECST.19 In this group the risk of ipsilateral ischemic stroke was low, even in the absence of surgery, and any benefits of CEA were outweighed by early operative risks.

What are the results when there is moderate stenosis (eg, 30% to 69%)? In NASCET, when there was <50% stenosis, the failure rate did not differ significantly in the surgically treated and medically treated groups.18 Among those with 50% to 69% stenosis, however, there was a “moderate”
## TABLE 1. Summary of Major Carotid Endarterectomy Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Severity of Carotid Stenosis</th>
<th>No. of Participants</th>
<th>Perioperative Stroke and Death Rate</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsurgical</td>
<td>Surgical</td>
<td>Nonsurgical</td>
<td>Surgical</td>
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<tr>
<td>Symptomatic patients</td>
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<tr>
<td>NASCET(^\text{17})</td>
<td>70–99%</td>
<td>331</td>
<td>328</td>
<td>3.3%</td>
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<tr>
<td>NASCET(^\text{18})</td>
<td>&lt;50%</td>
<td>690</td>
<td>678</td>
<td>2.4%</td>
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<tr>
<td></td>
<td>50–69%</td>
<td>428</td>
<td>430</td>
<td>(combined rate for &lt;50%, 50–69% stenosis)</td>
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<tr>
<td>ECST(^\text{19*})</td>
<td>0–29%</td>
<td>155</td>
<td>219</td>
<td>...</td>
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<tr>
<td></td>
<td>70–99%</td>
<td>323</td>
<td>455</td>
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<tr>
<td>ECST(^\text{20})</td>
<td>0–99%</td>
<td>1211</td>
<td>1807</td>
<td>...</td>
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<tr>
<td></td>
<td>(0.5% and 0.4% occluded in surgery and control groups, respectively)</td>
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<tr>
<td>Veteran Affairs Cooperative Study(^\text{21})</td>
<td>&gt;50%</td>
<td>101</td>
<td>92</td>
<td>2.0%</td>
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benefit of ipsilateral stroke reduction for CEA over medical therapy alone during a 5-year period. Risk factors for perioperative stroke or death were contralateral carotid occlusion, left-sided carotid disease, taking 650 mg aspirin per day, absence of a history of myocardial infarction or angina, lesion present on CT or MRI that was ipsilateral to the symptomatic stenosed artery, history of diabetes mellitus, and diastolic blood pressure 90 mm Hg. CEA was associated with greater long-term benefit in men, those with a recent stroke, recent hemispheric symptoms, and those taking 650 mg of aspirin per day. Prospective study of the relationship between aspirin dose and CEA clarified results from post hoc subgroup analysis in NASCET. The Aspirin Carotid Endarterectomy (ACE) Trial showed that the risk of stroke, myocardial infarction, and death within 30 days and 3 months of CEA was lower for patients taking 81 or 325 mg of aspirin before surgery compared with those taking 650 or 1300 mg of aspirin per day (written communication, H.J.M. Barnett, MD, 1999). Finally, patients with 70% stenosis had a durable benefit from CEA at 8 years of follow-up.

Two large-scale trials of CEA for asymptomatic carotid stenosis have been published. The Asymptomatic Carotid Atherosclerosis Study (ACAS) showed a modest benefit projected over 5 years that favored surgery in those with 60% stenosis.22 Risk of ipsilateral stroke and any perioperative stroke or death was less for CEA by an estimated average annual absolute difference of approximately 1.2% (P=0.004). In subgroup analysis, men had a 66% 5-year reduction in stroke risk (95% CI, 0.36 to 0.82), whereas women had an event rate reduction of only 17% (95% CI, −0.96 to 0.65). The difference between men and women, however, was not statistically significant (P=0.10). Possibly, women did not derive benefit from CEA because they had more perioperative complications (3.6% versus 1.7%). In addition, there was a trend for greater risk reduction for CEA in younger patients (P=0.50) but no stenosis-dependent effect by degree of carotid stenosis (60% to 69%, 70% to 79%, 80% to 99%). Finally, there was no statistically significant difference in favor of CEA for reduction of major ipsilateral stroke or any perioperative major stroke or death (P=0.12). Overall, there were relatively small numbers of events in the various subgroups under study, which limits statistical power to draw more firm conclusions about subgroup results.

Another trial, the Veterans Affairs Cooperative Study, included patients with asymptomatic carotid stenosis of 50% diagnosed by arteriography.24 Ipsilateral neurological end points were reduced when stroke was combined with transient ischemic attack (TIA) and transient monocular blindness. There was no significant difference between groups, however, in an analysis of all stroke and death (P=0.12). Overall, there were relatively small numbers of events in the various subgroups under study, which limits statistical power to draw more firm conclusions about subgroup results.

The Mayo Asymptomatic Carotid Endarterectomy Study23 was halted prematurely because there was an excess of myocardial infarction in the surgical group. The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA) study25 included 410 patients...
with 50% to 90% stenosis. The investigators concluded that CEA was not beneficial; however, interpretation of data were confounded by a complex study design and exclusion of patients with >90% carotid stenosis.

In this issue of Stroke, Paciaroni et al \(^\text{27}\) and Ferguson et al \(^\text{28}\) share with us results of final primary data from NASCET. These articles focus on 2 key topics: medical complications of CEA and a detailed review of surgical results. Medical complications that occurred within 30 days after CEA were reported in 1415 patients with symptomatic internal carotid artery stenosis (30% to 99%) and were compared with those in 1433 patients who received medical care alone. Overall, medical complications occurred in 8.1% who underwent CEA. Most were of short duration (69.7%), and cardiovascular disorders were common (14 myocardial infarction, 22 arrhythmia, 14 congestive heart failure, 19 angina pectoris, 20 hypertension, 24 hypotension, and 2 sudden death). There were 5 deaths; 3 were from myocardial infarction and 2 were sudden. In the medical treatment arm, complications occurred with approximately one third the frequency (3.4% versus 10.0%). Predictors of medical complications in the CEA group were history of myocardial infarction or angina and hypertension. Overall, there was a low rate of serious perioperative medical complications, and perioperative myocardial infarction (1.0%) was uncommon. It must be kept in mind, however, that patients with recent history of myocardial infarction, unstable angina pectoris, or recent congestive heart failure were excluded from NASCET.

The NASCET surgical results study detailed rates of perioperative stroke and death at 30 days, stroke severity at 30 days, and stroke and death at 90 days, variables that influenced perioperative risk, and durability of CEA. \(^\text{28}\) Among 1415 patients, there were 92 perioperative outcome events, for an overall rate of 6.5% (death, 1.0%; disabling stroke, 1.8%; non-disabling stroke, 3.7%; 4.5% at 30 and 90 days, respectively). Approximately one third of the perioperative events occurred intraoperatively, and most strokes were attributed to thromboembolism. Baseline predictors of surgical risk were hemispheric TIA as qualifying event (versus retinal TIA), left-sided procedure, contralateral carotid occlusion, ipsilateral ischemic lesion on CT scan, and irregular or ulcerated ipsilateral plaque. History of coronary artery disease with prior cardiac procedure was a protective factor. Other baseline variables that did not increase or decrease perioperative risk were age (<65 versus ≥65 years); sex; hemispheric TIA versus stroke; surgery within 30 days of the qualifying event; hyperlipidemia; intraoperative monitoring, a shunt, or both; and geographic location or type of surgeon (neurosurgeon versus vascular surgeon). These 2 studies \(^\text{27,28}\) sharpen our focus for perioperative medical and surgical complications associated with CEA and their predictors.

What possible effect has recent publication of these major CEA trials had on the rate of CEA? As mentioned previously, the substantial increase in use of CEA between 1980 and 1985 was followed by a marked fall between 1985 and 1988 and a plateau effect until approximately 1992. \(^\text{29–33}\) Rates of CEA, however, increased sharply after publication of ECST and NASCET in 1991. \(^\text{29,30}\) There have also been reports of substantial increase in the number of CEAs since the ACAS Clinical Advisory in September 1994. \(^\text{34,35}\) Asymptomatic patients constitute approximately 40% to 50% of those who undergo CEA. \(^\text{34,36,37}\) Women and blacks have considerably lower rates. \(^\text{29}\)

With the performance of CEA on the rise again, we are reminded of the potential for inappropriate use \(^\text{36–39}\) and community complication rates \(^\text{40–45}\) that may exceed acceptable levels established in recent clinical trials. \(^\text{16–24}\) Factors such as perceived availability of cerebral angiography and physician specialty may influence the frequency of use of CEA. \(^\text{46}\) Lack of use or inappropriate use may be partially addressed through targeted educational programs. Of concern, however, are past reports of substantially higher perioperative complication rates in the community than reported in recent trials. \(^\text{40}\) Combined morbidity and mortality that exceed the expected 3% for patients with asymptomatic carotid stenosis and 6% for patients with symptomatic stenosis could eliminate the benefit gained from surgery. \(^\text{47}\) This has led to a call to action for mandatory audits of surgical complications. \(^\text{48,49}\) Physicians who refer patients for CEA must be knowledgeable of acceptable surgical morbidity and mortality rates. Factual, objective information on complications should be recorded for individual surgeons, who can then share these results with their patients and local physicians.

Surgical skill is critical to the success of CEA. High-volume surgeons and hospitals seem to have better results. \(^\text{42,43}\) Furthermore, as shown in this issue of Stroke by the NASCET collaborators \(^\text{27,28}\) and by others, \(^\text{47,48}\) complications of CEA may be predicted by clinical data that may be used to stratify operative risk. \(^\text{47,48}\) Risk factors for postoperative complications in asymptomatic carotid stenosis, for example, may include age ≥75 years, history of congestive heart failure, combined CEA and coronary surgery, and sex (women). \(^\text{49}\)

So then, where do we draw the line? I am convinced that medical therapy (ie, antiplatelet agents and cardiovascular risk factor control/prevention) \(^\text{50}\) is the treatment of choice for those with symptomatic (TIA or minor stroke) lower-grade carotid stenosis (<50% by NASCET criteria). For high-grade symptomatic carotid stenosis (70% to 99% by NASCET criteria), CEA plus antiplatelet therapy and cardiovascular risk factor control/prevention is the treatment of choice. Those with moderate-grade symptomatic carotid stenosis (50% to 69% by NASCET criteria) walk a finer line. Absolute risk reductions for CEA in this case are more modest than for high-grade carotid stenosis. Thus, as major surgical perioperative complication rates exceed 6%, any benefit gained from surgery is soon lost. Chassin \(^\text{50}\) estimates that for every increase in 2 percentage points in the CEA complication rate above 6% to 7%, the 5-year benefit will be reduced by 20%. This is in contradistinction to high-grade carotid stenosis (70% to 99%), in which a modest increase in surgical morbidity and mortality may not negate benefit from CEA. In addition, before committing to CEA for symptomatic carotid stenosis, one must consider the patient’s risk factor profile and comorbid conditions. As shown by the NASCET investigators, such factors as contralateral carotid occlusion, appropriate lesion on CT scan, history of diabetes mellitus, and elevated diastolic blood pressure (>90 mm Hg) may double the perioperative risk of stroke or death, whereas men and those with recent stroke or hemispheric symptoms may derive greater long-term benefit from CEA. \(^\text{18}\) These
criteria may be useful to decide whether CEA should be recommended for those with 50% to 69% symptomatic stenosis.

The patient with ≥60% asymptomatic carotid stenosis (NASCET criteria) walks the finest line. There is little room for additional major surgical morbidity and mortality beyond the 3% standard, in view of the modest benefit of surgery. An increase of 2 percentage points in the complication rate could reduce the surgical benefit by ≥30% and render CEA ineffective and possibly harmful. If CEA for asymptomatic carotid stenosis is performed at higher than the accepted 3% surgical morbidity and mortality rate, as could potentially occur in the community on the basis of past studies, the public health impact in terms of dollars spent and morbidity and mortality could be substantial. Thus, with approximately one half of an estimated 130,000 CEAs performed in asymptomatic patients, wholesale application of CEA in less than optimal surgical circumstances could have adverse implications. Concerns over reproducibility of low clinical trial surgical morbidity by community surgeons and the ACAS finding that CEA may not reduce the risk of major stroke have led to nonuniform support of CEA in asymptomatic patients. There is a need to replicate the ≥60% asymptomatic carotid stenosis cut point and to have additional information about CEA in women, especially perioperative complication rates. We await results of the Asymptomatic Carotid Surgery Trial (ACST) for confirmatory evidence.

Mass screening for high-grade asymptomatic carotid artery stenosis is not recommended because it is not cost-effective. The prevalence of higher grades of asymptomatic carotid stenosis is low in the population at large, screening tests may lead to false-positive and false-negative results, and conventional cerebral angiography is associated with risks. Furthermore, the application of noninvasive blood flow measures to supplant conventional cerebral angiography remains a focus of debate that is unsettled. I continue to recommend cerebral angiography for patients who are being evaluated for CEA at centers with competent and experienced angiographers. Cerebral angiography remains the standard by which we determine degree of carotid stenosis for CEA. Further improvement in noninvasive carotid blood flow and imaging techniques to overcome inaccuracies and supplant conventional angiography with its inherent risks is a welcome advance that will lead to appropriate use of CEA with lower morbidity and mortality.

Summary

CEA is an important component of our arsenal for stroke prevention. Table 2 summarizes the number needed to treat to prevent 1 stroke in 2 years by CEA compared with medical therapy alone, according to Barnett et al. Patients with symptomatic high-grade carotid stenosis (70% to 99% by NASCET criteria) benefit most from CEA, whereas those with minimal degrees of stenosis (<50% by NASCET criteria) do not benefit from CEA. When there is moderate symptomatic carotid stenosis (eg, 50% to 69% by NASCET criteria), best results for CEA may be predicted by certain baseline characteristics and negated by certain operative risk predictors. The number needed to treat to prevent 1 stroke in 2 years in asymptomatic patients is relatively high, and additional clinical trial information is needed to confirm efficacy, safety, and subgroup results for these patients. CEA has been shown to be durable in symptomatic patients with high-grade stenosis (>70% by NASCET criteria). A national system of mandatory audits should be established for surgical and angiographic complications so that patients and physicians can make informed and intelligent decisions regarding use of CEA. Relatively small increases in major surgical and angiographic complication rates may tip the balance against CEA, especially in asymptomatic patients and those with moderate symptomatic carotid stenosis.

CEA is likely to continue to stir controversy and debate. Some of this will abate as we dynamically build on and refine important CEA guidelines and continue to perform important CEA studies that may prove contrary to hypothetical beliefs. With open minds, we will be able to advance the science and practice of CEA.

**References**


KEY WORDS: carotid endarterectomy • complications • editorials • stroke
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Stroke. 1999;30:1745-1750
doi: 10.1161/01.STR.30.9.1745

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