Carotid artery disease: From knife to stent

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A number of prospective randomized trials have examined the efficacy of carotid endarterectomy (CEA) in patients with carotid stenosis. This brief review surveys their findings, concluding with some observations that stem from this collective body of evidence.

TRIALS FOR ASYMPTOMATIC CAROTID STENOSIS

The **CASANOVA (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin) study**[1] randomized patients with asymptomatic carotid stenosis (> 50% but < 90%) to either immediate CEA (n = 206) or no immediate surgery, including some patients who underwent delayed surgery after developing ischemic symptoms, progressive severe stenosis, bilateral stenosis, or contralateral stenosis (n = 204). At 3-year follow-up, with death or new stroke as primary end points, there was no difference in the primary outcome (ipsilateral stroke or death) between the immediate-surgery group and the other group of patients (10.7% vs 11.3%). However, nearly half the patients in the "no immediate surgery" group eventually did have an endarterectomy for one of the reasons stated above. This study's unusual design lessens its statistical validity.

The **VA Asymptomatic Stenosis Trial**[2] randomized patients with asymptomatic carotid stenosis (> 50%) to operative (n = 211) or nonoperative (n = 233) therapy. At a mean follow-up of 4 years, the combined incidence of ipsilateral neurologic ischemic events (transient ischemic attack [TIA] and stroke) was reduced in the surgical group (8%) compared with the medical group (20.6%) ($P < .001$). However, the sample size was not large enough to show a statistically significant difference in rates of stroke alone. For the outcome of ipsilateral stroke, the incidence was 4.7% (including perioperative strokes) in the surgical group compared with 9.4% in the medical group ($P = .056$). However, when perioperative mortality (1.9%) was included with the surgical stroke rate, the difference between the two groups was not statistically significant.

The **Asymptomatic Carotid Atherosclerosis Study (ACAS)**[3] substantiated the hypothesis that CEA may prevent stroke in certain patients with asymptomatic carotid stenosis. This trial randomized 1,662 patients with high-grade carotid stenosis (> 60% diameter reduction by ultrasonography and/or angiography) to medical management alone or to medical management plus CEA. Over 5 years (mean follow-up = 2.7 years), the primary outcome measure, ipsilateral stroke, was reported in 5.1% of the patients who received CEA compared with 11.0% of the nonsurgical patients, for a projected overall 53% relative risk reduction. Although 9% of patients were not treated according to their randomization status, the stroke risk reduction was comparable whether analysis was done by intention to treat or by actual treatment received. Stroke risk reduction was more prominent in men and was apparently independent of the degree of stenosis or contralateral carotid artery disease. A substantial portion of the surgical risk was attributable to angiography (1.2% stroke rate), and the initial risk for surgery plus angiography was offset by a constant risk of ipsilateral stroke at approximately 2.2% per year in the nonsurgical group.[4] The surgical benefit was apparent by 10 months and was statistically significant at 3 years.

TRIALS FOR SYMPTOMATIC STENOSIS

The **European Carotid Surgery Trial (ECST)**[5] randomized patients with mild (defined as < 30%), moderate (30% to 69%), or severe (70% to 99%) carotid stenosis to surgical or nonsurgical treatment. Interim analysis among 2,200 patients (mean follow-up of 2.7 years) led to premature termination of the trial

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for patients in the mild and severe stenosis groups. Among the 374 patients with mild stenosis, there was no significant difference in ipsilateral stroke rates between the surgical and nonsurgical groups. There were more treatment failures in the surgery group, which was attributed to the 2.3% risk of death or disabling stroke during the first 30 days after surgery. Among patients with severe stenosis, however, surgery was shown to be beneficial in preventing stroke. There was a 7.5% risk of ipsilateral stroke or death within 30 days of surgery. At 3 years of follow-up, there was an additional 2.8% risk of stroke in the surgery group, for a total risk of 10.3%, compared with a 16.8% risk in the nonsurgery group ($P < .0001$). Importantly, the incidence of death or ipsilateral disabling stroke was reduced from 11% in the nonsurgery group to 6% in the surgery group. ECST used a different criterion for determining carotid stenosis than did the NASCET (see below), VASST (see below), or ACAS investigations. When re-analyzed using the NASCET criteria, patients in ECST with greater than 70% stenosis had a stroke risk and achieved benefit from surgery at rates comparable to those in NASCET or VASST.

The **North American Symptomatic Carotid Endarterectomy Trial (NASCET)**[6] prematurely stopped randomizing patients with carotid stenosis greater than 70% because of the overwhelming stroke risk reduction observed in the surgical group. A total of 659 patients in this stenosis category were randomized to surgical (n = 331) or nonsurgical (n = 328) therapy. At a mean follow-up of 24 months, the primary outcome measure, ipsilateral stroke, was noted in 26% of nonsurgical patients vs 9% of patients who had undergone endarterectomy, for an absolute risk reduction of 17% (relative risk reduction of 71%). The benefit for surgical patients was highly significant ($P < .001$) in a variety of outcome measures, including stroke in any territory, major stroke, and major stroke or death from any cause. A perioperative morbidity/mortality of 5.8% was rapidly surpassed in the nonsurgical group, such that surgical benefit was apparent by 3 months. Moreover, the protective effect of surgery was durable over time, with few strokes noted in the endarterectomy group beyond the perioperative period. A secondary outcome, functional disability (assessed by a standardized disability scale), was significantly less severe in the surgery group over time ($P < .001$).[7] Multivariate analysis demonstrated that surgical benefit was independent of a variety of demographic variables such as age, sex, or risk factors for stroke. There was a direct correlation between surgical benefit and the degree of angiographic stenosis.

Enrollment in the **VA Symptomatic Stenosis Trial (VASST)**[8] was discontinued in early 1991 on the basis of preliminary data consistent with the NASCET findings. Subsequent analysis showed a statistically significant reduction in the primary outcome measures of ipsilateral stroke or crescendo TIA for patients with carotid stenosis greater than 50%. A total of 189 men aged 35 to 82 years (mean = 64.2 years) were randomized to surgical (n = 91) or nonsurgical (n = 98) treatment. The rate of cerebral angiography complications was low, with no permanent residual deficits and transient complications in 5% (2% local vascular, 2% transient neurologic, 1% minor allergic). Two thirds of randomized patients demonstrated angiographic internal carotid artery stenosis greater than 70%. Secondary outcomes involving complications of surgery were relatively infrequent, including respiratory insufficiency requiring extended intensive care monitoring (5%), minor to moderate wound hematoma (5%), cranial nerve deficit (5%), myocardial infarction (2%), and pulmonary embolism (1%).

At a mean follow-up of 11.9 months, there was a significant 11.7% absolute risk reduction for stroke or crescendo TIA in patients receiving CEA (7.7%) compared with nonsurgical patients (19.4%) (relative risk reduction of 60%; $P = .028$). Among stratified subgroups, the benefit of surgery was more prominent in TIA patients relative to patients with transient monocular blindness or stroke, although these differences were not statistically significant. The benefit of surgery was apparent as early as 2 months after randomization and persisted over the entire period of follow-up. The efficacy of CEA was durable, with only one ipsilateral stroke occurring beyond the 30-day perioperative period. Discounting one preoperative stroke, a perioperative morbidity of 2.2% and mortality of 3.3% (total = 5.5%) was achieved over multiple centers among relatively high-risk patients.

■ META-ANALYSIS OF SYMPTOMATIC STENOSIS TRIALS

To determine the long-term risk of stroke following CEA, and to identify risk factors, Kaplan-Meier analysis was used to calculate ipsilateral carotid territory ischemic stroke risk starting on the 30th day after CEA in 1,728 patients who underwent surgery in the ECST investigation.[9] The risks of disabling ipsilater-

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al ischemic stroke and any ipsilateral ischemic stroke were constant after CEA, reaching 4.4% (95% CI = 3.0% to 5.8%) and 9.7% (95% CI = 7.6% to 11.7%), respectively, by 10 years. Presentation with cerebral symptoms, diabetes, peripheral vascular disease, and elevated systolic blood pressure were associated with an increased risk of late stroke following CEA, but severity of preoperative stenosis, plaque morphology, and use of a patch graft were not.

A recent meta-analysis of pooled data from the ECST, NASCET, and VASST investigations was derived from the trials' original electronic data files, with outcome events redefined, if necessary, to achieve comparability.[10] Data for 6,092 patients, with 35,000 patient-years of follow-up, were pooled. The risks of the main outcomes in both treatment groups did not differ among trials, and neither did the effects of surgery. Surgery increased the 5-year risk of ipsilateral ischemic stroke in patients with less than 30% stenosis (n = 1,746, absolute risk reduction of –2.2%, P = .05), had no effect in patients with 30% to 49% stenosis (n = 1,429, absolute risk reduction of 3.2%, P = .6), was of marginal benefit in those with 50% to 69% stenosis (n = 1,549, absolute risk reduction of 4.6%, P = .04), and was highly beneficial in those with 70% or greater stenosis without near-occlusion (n = 1,095, absolute risk reduction of 16.0%, P < .001). There was a trend toward benefit from surgery in patients with near-occlusion at 2 years' follow-up (n = 262, absolute risk reduction of 5.6%, P = .19), but no benefit at 5 years (absolute risk reduction of –1.7%, P = .9).

■ SUMMARY AND OBSERVATIONS

Several notable features are common to these trials examining the efficacy of CEA for symptomatic stenosis.

First, CEA provided profound protection against subsequent ipsilateral stroke in patients with high-grade symptomatic stenosis. A lesser but significant degree of protection was observed in asymptomatic high-grade or symptomatic intermediate-grade stenosis. The stroke risk reduction was realized early after surgery, persisted over extended periods of time, and was independent of other risk factors.

Second, stroke rates in the nonsurgical high-grade symptomatic patient cohort considerably exceeded those reported from prior prospective and retrospective studies. Symptomatic patients receiving aspirin in prior prospective multicenter trials had annual stroke rates ranging from 3% to 7%, compared with rates between 15% and 20% in nonsurgical patients (mostly receiving aspirin) from NASCET and VASST.

The efficacy of CEA depends in part on an acceptable level of perioperative morbidity and mortality. The risk of late ipsilateral ischemic stroke following CEA for symptomatic stenosis is only about 1% per year, and it remains low for at least 10 years after CEA. Several risk factors may be useful in identifying patients at particularly high risk for late postoperative stroke. Meta-analysis of the trials with the same measurements and definitions yielded highly consistent results. Surgery is of some benefit for patients with 50% to 69% symptomatic stenosis and is highly beneficial for those with 70% or greater symptomatic stenosis but without near-occlusion. Benefit in patients with carotid near-occlusion is marginal in the short term and uncertain in the long term. These are the standards against which alternative treatments should be judged.

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