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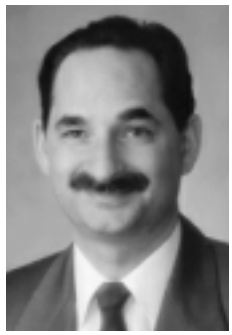
Endarterectomy for Preventing Stroke in Symptomatic and Asymptomatic Carotid Stenosis. Review of Clinical Trials and Recommendations for Surgical Therapy.



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ABSTRACT

Background: Multicenter, randomized trials have demonstrated advantages for surgery over medical therapy in both symptomatic and asymptomatic carotid stenosis of greater than 70%. Controversial interpretations of these trials are debated between medical and surgical camps. The goal of this review is to summarize the current state of knowledge in carotid stenosis and the role of surgery and several advances in operative management.

Methods: Summaries of seven major controlled trials of carotid endarterectomy versus medical therapy are presented along with supportive data from over 90 related publications. Criticisms, deficiencies as well as strengths are offered.

Results: All studies in which trial design, clinical variables, case selection, complication definition, and patient follow-up were well conceived and performed showed statistically significant advantages for surgical therapy within a remarkable short interval of follow-up (less than 3 years). Carotid endarterectomy demonstrated a two to four fold reduction in the late incidence of stroke when compared to optimum medical management (risk factor reduction and initiation of antiplatelet therapy). Reduction in stroke risk over time remains stable in surgically treated patients whereas medically treated patients clearly show progression of stenosis and evolution of new neurologic events with time. Several studies indicate that diabetes is a risk factor for stroke with medical therapy that is eliminated by surgical therapy. Advantages were more clearly demonstrated when symptomatic patients (TIAs, stroke, or amaurosis) were studied, but asymptomatic patients received significant benefit as well. The degree of benefit measured was in direct balance to the perioperative risk. Perioperative stroke and death rates must be low (less than 3% combined for asymptomatic patients) in order for statistically significant differences to be detected. However, most centers now can perform carotid endarterectomy within these outcome parameters.

Conclusions: Randomized trials support the safety and efficacy of carotid endarterectomy for stenosis greater than 70% (with or without symptoms). Advantages of surgery over medical therapy were found in less than three years and there is ample evidence to suggest that the differences between these groups would have been even more pronounced had longer follow-up been obtained. Thus for patients who face many years of risk after diagnosis of a carotid lesion, early surgery is the most important and effective intervention for preventing stroke. The results of these trials raised initial concern over increasing health care expenditures from rising surgical case volumes. However, studies of cost effectiveness confirmed that surgery saves health care dollars when compared to the long term care of stroke victims.

INTRODUCTION

Stroke remains the third leading cause of death in the United States, following heart disease and cancer. Endarterectomy for carotid atherosclerosis was first reported by Eastcott in 1954 [Eastcott 1954]. Forty-five years later, a wide schism still remains between certain camps of medical physicians and surgeons regarding the role of carotid endarterectomy (CEA) in stroke prevention.

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Table 1. Prospective Randomized Trials of CEA

Symptomatic Stenosis	Asymptomatic Stenosis
European Carotid Surgery Trial (ECST)	**Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin (CASANOVA)**
North American Symptomatic Carotid Endarterectomy Trial (NASCET)	**Mayo Asymptomatic Carotid Endarterectomy Trial**
Veterans Affairs Symptomatic Trial	**Veterans Affairs Asymptomatic Trial**
	Asymptomatic Carotid Atherosclerosis Study (ACAS)

Table 2. Comparative results of seven major prospective randomized trials

Trial	Study Group	Mean Follow-up	Rate of New Neurologic Events	
			Medical Rx	Surgical Rx
ECST	Symptomatic	3 years	16.8%	10.3%
NASCET	Symptomatic	2.7 years	26%	9%
Veterans Affairs	Symptomatic	1 year	19.45%	7.7%
CASANOVA	Asymptomatic	3.5 years	11.3%	10.7%
Mayo Clinic	Asymptomatic	2 years	11%	11%
Veterans Affairs	Asymptomatic	4 years	20.6%	8.0%
ACAS	Asymptomatic	2.7 years	11%	5.1%

Numerous clinical studies, both large and small, randomized and non-randomized, prospective and retrospective have accumulated in the literature in these past 4 decades. None-the-less, the controversy continues with strong opinions both for and against surgical therapy. Only the recent publication of large well-controlled multicenter prospective randomized trials has brought some clarification to the role of CEA in stroke management. It is timely to review the conclusions reached by these studies and to provide an overview of current indications and benefits obtained in both symptomatic and asymptomatic patients with extracranial vascular disease.

In the United States today, more than 500,000 new strokes are diagnosed each year. Multiple etiologies account for this vast problem, including cardiac embolism, valvular heart disease, intracardiac defects, paradoxical embolism, hypertension, intracranial stenosis, cerebral angiopathy, and of course, extracranial vascular disease. It is estimated that between 20% and 30% of these half million new events per year are due solely to extracranial carotid artery stenosis [Timsit 1992]. Narrowing of the carotid artery more than 50% is present in approximately 5% of the population over 65 years of age [ECST 1995].

Asymptomatic carotid bruits are known to carry an annual stroke risk of 2% to 5% [Hennerici 1987, Autret 1987, O'Holleran 1987, Norris 1991]. Although this first seems to be a small risk, over many years the cumulative risk becomes quite serious. Since carotid disease is often bilateral, there is additional risk from the contralateral lesion that further endangers the patient over prolonged follow-up.

What is more difficult to estimate is the disability, social and personal costs, including skilled nursing care and physical dependency caused by stroke. Just the financial burden to the family and society is considerable. The average cost of care for a major stroke victim is $34,000 plus $18,000 per year of disabled life [Cronenwett 1997]. These numbers do not in any way estimate the human suffering of the patient and family after loss of speech, vision, or motor function.

There is clearly an advantage to the patient, family and society for prevention of stroke. What had not been proven in past decades is the relative advantage of surgery as compared to medical therapy. Recent studies have attempted to address several important issues:

- Does carotid endarterectomy offer real advantages over medical treatment in prevention of future neurologic events?

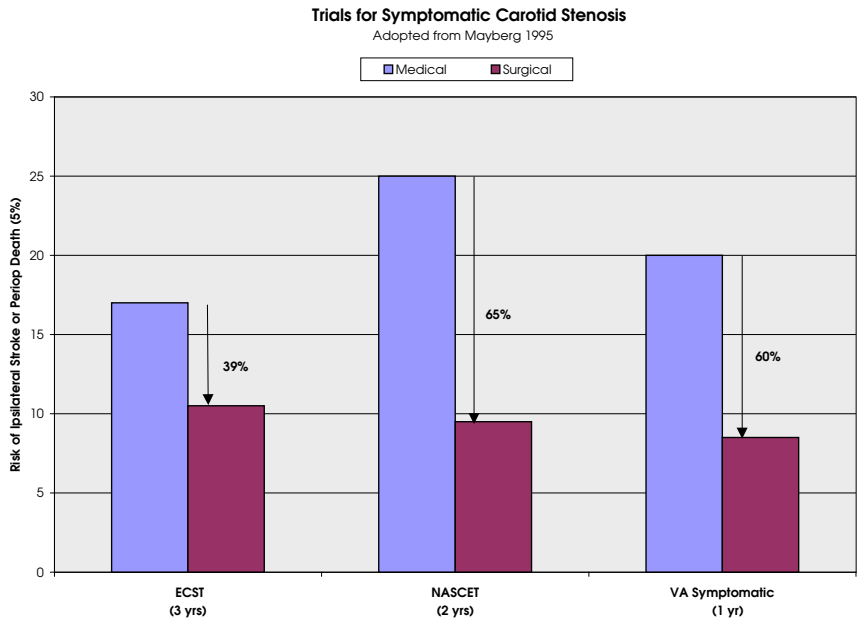

Figure 1. Symptomatic carotid stenosis: absolute and relative reductions in future neurologic events. Carotid endarterectomy versus medical therapy.

- Which patients receive benefit?
- What is an acceptable operative risk?
- Are symptomatic and asymptomatic patients different?

Well designed trials are now showing a clear advantage for surgery. Opponents of CEA have analyzed and criticized the published results, leading to blurring of the conclusions and further speculation. It is timely to summarize the composite information from these major studies and review the indications, results, and modern techniques of carotid endarterectomy with emphasis on the ability of surgery to prevent future neurologic events.

OVERVIEW OF RANDOMIZED TRIALS

Table 1 summarizes the major trials of the last decade that attempted to address the differences between surgical and medical therapy. Comparative results of each trial (for both symptomatic and asymptomatic patients) are listed in Table 2. Figure 1 illustrates the absolute and relative reductions in future neurologic events provided by surgery for symptomatic patients as published in the largest three multicenter trials of the last decade. Figure 2 illustrates the findings for the largest trials investigating asymptomatic high grade stenosis. Each trial illuminates part of the picture so that a summary of their individual findings will permit recommendations and treatment standards for current practice.

SYMPTOMATIC PATIENTS

1. North American Symptomatic Carotid Endarterectomy Trial (NASCET)

The definitive modern study for symptomatic carotid stenosis was the North American Symptomatic Carotid Endarterectomy Trial (NASCET) which enrolled 662 patients with > 70% stenosis and ipsilateral symptoms into medical and surgical treatment limbs [NASCET 1991]. The trial involved 50 centers in the USA and Canada. To qualify for enrollment, investigating centers must have performed at least 50 endarterectomies in the prior 24 months with a 6% combined stroke-death morbidity. Patients were restricted to age less than 80 years and must have suffered a hemispheric TIA, monocular blindness of less than 24 hours duration (amaurosis fugax), or a nondisabling stroke within 120 days prior to enrollment. A carotid stenosis of 30% to 99% was present on the side of the symptoms in all enrolled patients and the lesion must have been technically suitable for endarterectomy according to preoperative angiography. Patients were grouped into two categories based on lesion severity: 1) stenosis of 30% to 69%, and 2) stenosis of 70% to 99%, with all angiograms calibrated and measured by an independent neuroradiologist in a blinded fashion. There were multiple exclusion criteria, such as:

- Intracranial lesion more severe than the cervical lesion
- No angiographic confirmation of the lesion, the contralateral side or the intracranial circulation
- Mentally incompetent or unwilling to give informed consent
- Multiorgan failure
- Cancer
- Cerebral infarction on either side that deprived the patient of useful function in the affected territory
- Symptoms attributable to other disorders (fibromuscular dysplasia, aneurysm, tumor)
- Cardiac valve or rhythm disorder known to be associated with embolic stroke
- Previous ipsilateral carotid endarterectomy

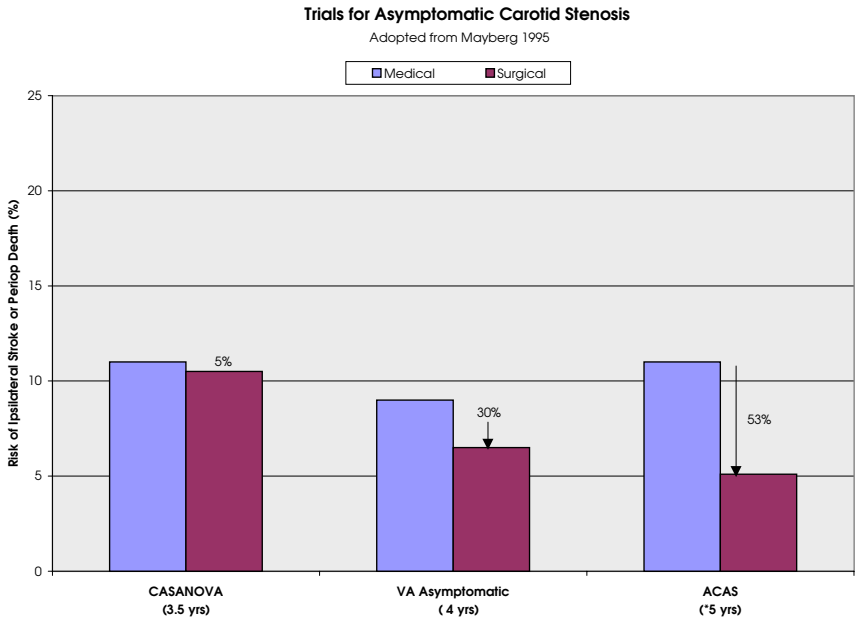

Figure 2. Asymptomatic carotid stenosis: absolute and relative reductions in future neurologic events. Carotid endarterectomy versus medical therapy.

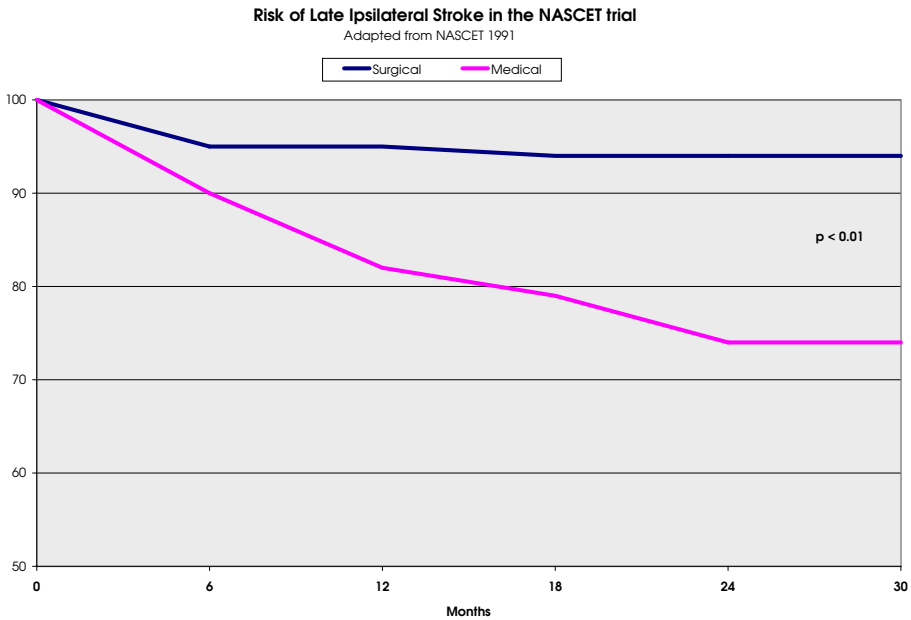

Figure 3. NASCET trial for symptomatic carotid stenosis. Event Free Kaplan-Meier curves of surgical versus medical therapy.

In addition, patients were temporarily ineligible if found to have uncontrolled hypertension, diabetes, angina, prior myocardial infarction (MI) within the preceding 6 months, declining neurologic function, contralateral CEA within the prior 4 months, or a major surgical procedure within the prior 30 days. If these conditions resolved within the 120 day window after the qualifying cerebrovascular event, the patients could then be enrolled.

All enrolled patients were treated with antihypertensive, antilipid, and antidiabetic therapy as indicated, plus 1,300 mg of aspirin daily. After randomization, surgical patients underwent standard endarterectomy within an average of 2 days after randomization including postoperative neurologic assessment by the surgeon for the first 30 days and by the study neurologist beginning at one month postoperatively and then every 3 months. Duplex was repeated one month after entry and subsequent to any neurologic event.

Table 3. NASCET Risk factors (studied prospectively)

1.	Age > 70 years
2.	Male gender
3.	Systolic BP > 160 mm Hg
4.	Diastolic BP > 90 mm Hg
5.	Recent symptoms (< 31 days)
6.	History of prior stroke
7.	Stenosis > 80%
8.	Plaque ulceration
9.	Prior smoking (any time)
10.	History of Hypertension
11.	History of Myocardial Infarction
12.	History of Congestive Heart Failure
13.	Diabetes
14.	Claudication
15.	Elevated lipids

Enrollment began January 1, 1988 and there was 100% follow-up for an average of 18 months. By the third year (February 1991) the differences between surgical and medical therapy were so marked for patients with higher grade stenosis (70% to 99%) that randomization was halted prematurely and the treating physicians notified. Randomization continued for patients with less severe stenosis (30% to 69%).

In the high grade stenosis subset, 328 patients underwent CEA with 18 neurologic events (5.5%) including 12 minor events, 5 major events, and 1 fatal stroke. The combined stroke-death rate was 5.8% for all events and 2.1% if only major neurologic events were considered. The mortality rate (separate from stroke) was 0.6%. Cranial nerve injury occurred in 7.6%, wound hematoma 5.5%, wound infection 3.4%, myocardial infarction 0.9%, congestive heart failure 0.6%, and arrhythmia 1.2%.

In the medical cohort, there were 11 neurologic events within the first 30 days (8 minor, 2 major and 1 fatal). Thus, the early medical stroke-death rate (in the first 30 day time window) was already 3.3%.

During late follow-up, new neurologic events were more numerous in the non-surgical group. The risk of an ipsilateral stroke within the first 2 years following randomization was 26% for medically treated patients and 9% for surgical patients (including the 5.5% perioperative events). The absolute risk reduction was 17% and the relative risk reduction 65%. Kaplan-Meier event free curves revealed that the early disadvantage of surgical perioperative morbidity was rapidly overcome by progressing events in the medically treated subset, so that surgery was superior after only 3 months (see Figure 3 ◉).

For patients who did not die or have a stroke in the first 30 days, there was a 12.2% risk of a major stroke in the medically treated subset over the first 2 years of follow-up whereas the risk for the surgically treated cohort was only 1.6% ($p < .00001$). There was no difference in early or late

Table 4. NASCET Risk factors identified at enrollment into the study and associated with an increased incidence of late stroke at 2 years of follow-up with medical management. The comparative surgical late risk was 1.6% over 2 years and did not change over time or by risk factor association.

Ipsilateral Amaurosis	17%
Hemispheric TIA	44%
Stenosis 70-79%	12%
Stenosis 80% to 89%	18%
Stenosis 90 to 99%	26%
More than 5 medical comorbid conditions	17%
More than 6 medical comorbid conditions	23%
More than 7 medical comorbid conditions	39%

results between small medical centers and large medical centers participating in the study.

When patients were stratified according to medical risk factors for stroke (see Table 3 ◎), there was a marked increased risk for medically treated patients with multiple risk factors, but no increased risk in surgically treated patients. The NASCET investigators found that medically treated patients with 0 to 5 of these risk factors suffered a 2 year post randomization risk of ipsilateral stroke of 17%, which rose to 23% in the presence of 6 risk factors and 39% for 7 or more risk factors. This compares with an overall 9% two year risk in the surgically treated cohort with no differences found regardless of the number of risk factors present.

Symptom classification at presentation also influenced the risk of late stroke (see Table 4 ◎). Patients entering the trial because of ipsilateral amaurosis experienced a late stroke rate of 17% at 2 years with medical therapy while those presenting with hemispheric TIAs demonstrated a late stroke rate of 44% at 2 years [Easton 1994]. More importantly, 95% of the neurologic events in medically treated patients occurred on the same side as the randomized artery, confirming a cause and effect relationship between high grade (>70%) stenosis and future stroke [Easton 1994].

The degree of stenosis at randomization also correlated with benefit from surgery. The risk of stroke at two years following randomization in the medically treated patients was directly related to the severity of stenosis. The risk was 12% for stenosis of 70% to 79%, 18% for stenosis of 80% to 89%, and 26% for stenosis of 90% to 99%.

The benefits of carotid endarterectomy persisted even if minor or non-disabling neurologic events were removed from analysis. The benefits obtained by surgery were also durable, with a cumulative 4 year risk of stroke of 9.5% (versus 9.0% at 2 years) for an additional risk of only 0.5% from year 2 to year 4 of follow-up [Easton 1994]. This data indicates that the risk of ipsilateral stroke following surgery is very, very low in future years.

2. European Carotid Surgery Trial (ECST)

Further evidence to support endarterectomy in symptomatic patients was obtained by the European Carotid Surgery Trial (ECST) which began in 1981. A total of 2,518 patients were enrolled over 10 years. Symptoms considered for enrollment included TIA, retinal infarction or non-disabling stroke within the previous 6 months. Patients were randomized to medical therapy (aspirin) or medications plus surgery. At 3 years, the risk of ipsilateral stroke was 16.8% for the medical cohort and 10.3% (including a 7.5% perioperative stroke-death risk) for the surgical group (see Table 2 ◎) [ECST 1991]. If perioperative events are excluded from analysis, the late risk in surgical patients was 2.8% over 3 years, or less than 1% per year compared with a 5.6% annualized rate of late stroke in the medically treated cohort.

3. Veterans Affairs Symptomatic Trial

This trial involved 16 academic medical centers in the Veterans Affairs hospital system beginning in 1988. Enrollees were males with 50% or greater ipsilateral carotid stenosis and symptoms of TIA, stroke or retinal ischemia within 120 days of enrollment [Mayberg 1991]. Multiple exclusion criteria limited the comorbidity permitted in study patients (exclusion of ventricular ectopy more than 10 per minute, evidence of cardiac ischemia by Thallium, severe hypertension, renal failure, emergent medical conditions requiring intensive care treatment, etc.) Over 5,000 patients were screened before enrolling 193 participants. Over 60% of patients had experienced a prior TIA and 28% had experienced a prior stroke before the index event which lead to randomization. Three quarters of index events were part of a pattern of repetitive symptoms [Mayberg 1991]. Calibrated angiography revealed a stenosis greater than 70% in two thirds of randomized patients. After randomization, half received medical therapy with 325 mg of aspirin daily and the other half underwent CEA within 3 days of randomization. After 193 patients, the trial was halted prematurely because of the results of the NASCET and ECST.

At a mean follow-up of only 11.9 months (just under one year), a strong difference was already demonstrated in favor of surgery. Stroke or crescendo TIAs were present in only 7.7% of CEA patients versus 19.4% of medically treated patients [Mayberg 1991]. For those with preoperative stenosis > 70%, the differences were more marked (7.9% versus 25.6%, see Figure 4 ◎). There was no significant differences found when comparing patients with stenosis of 50% to 69%.

The results also indicated a marked risk of crescendo TIAs (12.2%) in the medical cohort during follow-up while there were none in the surgically treated group (0%) [Mayberg 1991]. The cumulative risk reduction for new events was 11.7% in favor of surgery.

ASYMPTOMATIC PATIENTS

1. Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin (CASANOVA)

The CASANOVA study attempted to answer the dilemma surrounding the asymptomatic patient, but confused matters instead due to poor study design and noncompliance with the protocol [CASANOVA 1991].

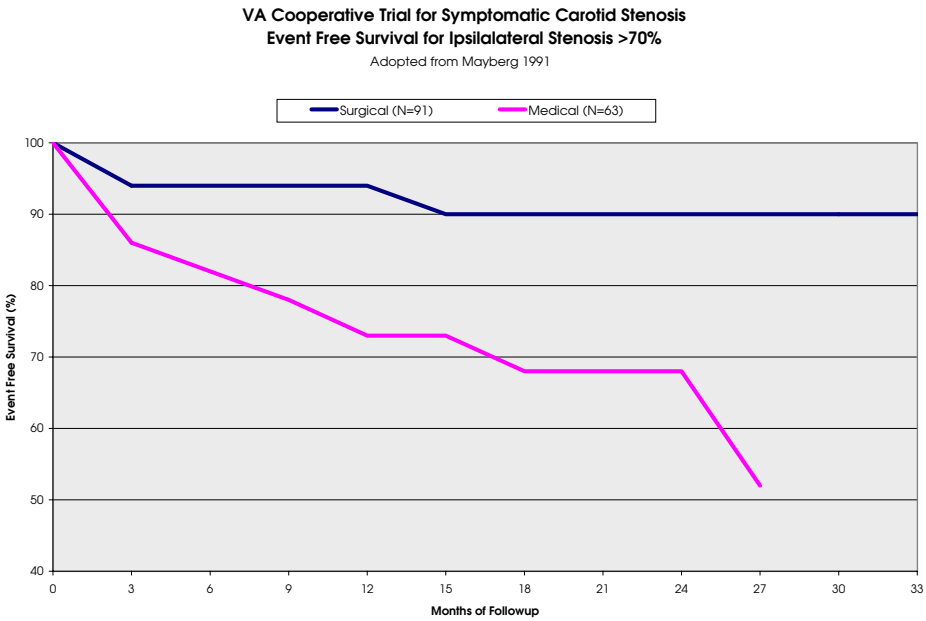

Figure 4. Veterans Affairs trial for symptomatic carotid stenosis. Event Free Kaplan-Meier curves of surgical versus medical therapy for patients with > 70% stenosis.

CASANOVA investigators enrolled 410 asymptomatic patients with 50% to 90% stenosis at 10 different German centers [CASANOVA 1991]. The protocol dictated that medical and surgical groups were to receive both aspirin and dipyridamole, but unfortunately only 69% actually received aspirin and only 89% received both protocol drugs [Easton 1994]. There were many other protocol deviations as well, such as 20% of the medically assigned patients undergoing early CEA with another 26% crossing over to surgery for the late development of TIAs, stenosis progression, or development of bilateral stenosis. The statistical conclusions were thus invalidated by crossover of almost half of the medical patients [Mayberg 1995]. In the surgical cohort, 27% underwent CEA before randomization, 17% never received the assigned operation, and 11% underwent bilateral endarterectomy.

At a mean follow-up of 3.5 years, the risk of stroke in the CASANOVA study was 11.3% for the medically treated group and 10.7% for the surgical group (not significant). However, the conclusions were not supportable because of small numbers in subsets, large standard deviations, multiple protocol deviations, and exclusion of stenosis greater than 90%.

2. Mayo Asymptomatic Carotid Endarterectomy Study

Another incomplete attempt to address the question of the asymptomatic patient was the Mayo Asymptomatic Carotid Endarterectomy Study. This trial randomized only 71 patients involving a surgical group that was excluded from aspirin therapy while the medical group received 80 mg of aspirin per day [Mayo 1992]. The trial was halted prematurely because of a high incidence of myocardial infarction (22%) in the 36 surgically assigned patients. This included 4 myocardial infarcts occurring after randomization and before surgery, 2 on the day of surgery, and 2 postoperatively. The high incidence of myocardial infarction was attributed to withholding aspirin from the surgically assigned patients. The incidence of stroke was 11% in both groups, but the small number of enrollees and the presence of confounding variables and protocol deviations did not permit any statistically valid conclusion regarding the differences between medicine and surgery. The authors also erred when attributing preoperative strokes to the surgical morbidity. The trial investigators did not take into account that two of the three strokes accredited to surgical therapy took place before the operation (during the waiting period after randomization and before CEA) [Mayo 1992]. If these two events are removed from analysis, the stroke risk for surgery was indeed lower than with medical therapy.

3. Veterans Affairs Asymptomatic Trial

The Veterans Affairs Cooperative Study group included a limb for asymptomatic patients at 11 centers [Hobson 1993]. Enrollees were all males with 50% or greater carotid stenosis but without symptoms. Exclusion criteria included: 1) prior cerebral infarction, 2) prior CEA, 3) prior extracranial to intracranial (EC-IC) bypass, 4) high surgical risk due to associated medical illness, 5) long-term anticoagulant therapy, 6) life expectancy under 5 years, and 7) surgically inaccessible lesion. Patients received optimum medical therapy, including 1,300 mg aspirin daily with half randomized to CEA. The perioperative stroke-death rate was 4.9%. At a mean follow-up of 4 years, the incidence of ipsilateral neurologic events was 20.6% in the medical group and only 8.0% in the surgical group (which included all perioperative events as well as three strokes due to arteriography). This difference was highly significant at $p < .0001$. Kaplan-Meier event free curves are depicted in Figure 5

In discussion of their results, the authors reported that statistical significance between medical and surgical therapy

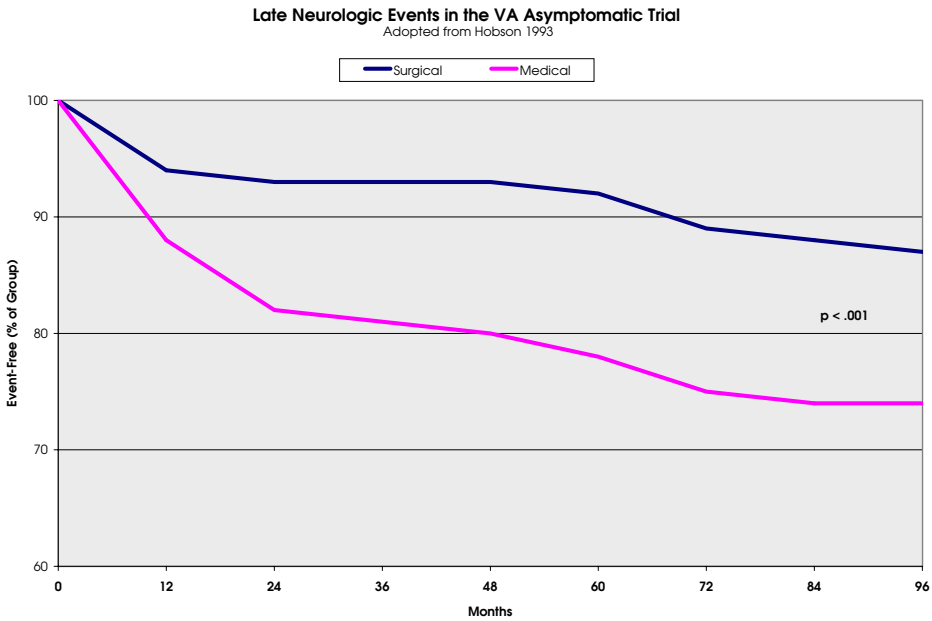

Figure 5. Veterans Affairs trial for asymptomatic carotid stenosis. Event Free Kaplan-Meier curves of surgical versus medical therapy for patients with > 70% stenosis.

Table 5. ACAS Investigators

	Center	Location	Patients (N)
1.	Lehigh Valley Hospital	Allentown, Pennsylvania	142
2.	Marshfield Clinic	Marshfield Wisconsin	121
3.	Columbia University	New York City, New York	91
4.	University of Kentucky Chandler Medical Center	Lexington, Kentucky	88
5.	Hôpital de l'Enfant Jesus	Québec City, Québec, Canada	86
6.	University of California	San Diego, California	78
7.	Loyola University Medical Center	Maywood, Illinois	77
8.	Univerisity of Tennessee	Memphis, Tennessee	74
9.	University Hospital, London	Ontario, Canada	63
10.	Victoria Hospital, London	Ontario, Canada	61
11.	Virginia Mason Clinic	Seattle, Washington	57
12.	University of Cincinatti	Cincinnati, Ohio	55
13.	Bowman Gray School of Medicine	Winston-Salem, North Carolina	52
14.	University of Iowa Hospital and Clinics	Iowa City, Iowa	49
15.	Johns Hopkins Bayview Medical Center	Baltimore, Maryland	46
16.	St. John's Mercy Medical Center	St. Louis, Missouri	44
17.	University of Arizona Health Sciences Center	Tucson, Arizona	42
18.	University of Mississippi Medical Center	Jackson, Mississippi	39
19.	Milton S. Hershey Medical Center	Hershey, Pennsylvania	35
20.	University of Texas Southwestern Medical Center	Dallas, Texas	35
21.	University of California	Los Angeles, California	35
22.	Oregon health Sciences University	Portland, Oregon	34
23.	Yale University	New Haven, Conneticut	34
24.	University of Arkansas for Medical Sciences	Little Rock, Arkansas	32
25.	Medical College of Virginia (VCU)	Richmond, Virginia	27
26.	Barrows Neurological Institute	Phoenix, Arizona	26
27.	Oschner Clinic	New Orleans, Louisiana	21
28.	University of Medicine and Dentistry	Newark, New Jersey	20
29.	New England Medical Center	Boston, Massachussets	19
30.	Henry Ford Hospital	Detroit, Michigan	17
31.	University of New Mexico	Albuquerque, New Mexico	13
32.	Sunnybrook Health Science Centre, University of Toronto	New York, Ontario, Canada	11
33.	Harbin Clinic	Rome, Georgia	10
34.	Roanoke Neurological Associates	Roanoke, Virginia	10
35.	Singing River Hospital	Pasagoula, Mississippi	6
36.	California Pacific Medical Center	San Francisco, California	4
37.	Northwestern University Medical School	Chicago, Illinois	4
38.	University of Rochester	Rochestor, New York	3
39.	Cleveland Clinic	Cleveland, Ohio	1
	Total		**1,662**

was lost when perioperative deaths in addition to neurologic events secondary to angiography were added to the surgical event rates. The analysis was also skewed by an unusually high late fatality rate. In the medically assigned group, there was a 12.4% risk of TIAs and 9.4% risk of stroke at 4 years, but also a fatality rate of 33.5% [Hobson 1993]. The late mortality in the surgical limb was 33.2% despite withholding entry to 380 patients who were felt to be too sick for surgery and 48 referrals judged to have a life expectancy of less than 5 years. The high fatality rate appears to have been associated with multiple comorbid conditions in the entrants, and probably reduced the number of patients in whom late stroke could have occurred, thus blunting the power of the trial. None-theless, the neurologic event rates were impressively lower in surgically treated patients (see Figure 5 ◎).

4. Asymptomatic Carotid Atherosclerosis Study (ACAS).

The role of endarterectomy for the treatment of asymptomatic patients was further addressed by the Asymptomatic Carotid Atherosclerosis Study (ACAS). Multiple investigators participated in a rigorous protocol for preoperative evaluation, randomization, and defined treatment limbs [ACAS 1989]. This study is likely the most extensive and well coordinated multicenter protocol executed in modern medicine, involving 39 different institutions of various surgical backgrounds including private, community, neurosurgical as well as vascular specialty and university based practices (see Table 5 ◎) [ACAS 1995]. A total of 117 surgeons were credentialed to participate as study investigators by a pre-trial screening of surgeon and institutional conformity to morbidity and mortality endpoints, thus eliminating surgeons with a poor track record for this operation [Moore 1991]. The quality of the neurological expertise and ultrasound diagnostics was also prescreened. During the 6 years of this study, more than

12,080 carotid endarterectomies were performed at these same institutions, indicating a significant case volume and level of experience. After screening of more than 42,000 eligible patients from the referral pool, a total of 1,662 patients who met the inclusion criteria were randomized between medical and surgical therapy for asymptomatic unilateral stenosis. All patients were treated identically, except for the addition of carotid endarterectomy in the surgical cohort. Preoperative management in all patients included risk factor reduction and aspirin. The primary objective was the impact on 5 year ipsilateral stroke rate provided solely by carotid endarterectomy. Additional endpoints of the study included:

- Surgical success ratios for the primary carotid lesion
- Rate of progression (or regression) of carotid stenosis in the medically treated cohort
- Incidence of recurrent carotid stenosis following adequate endarterectomy
- Incidence of all other vascular events (TIAs, MI, death) during a 5 year follow-up

Recruitment of patients followed the same pattern as seen in common practice, including referrals from primary care physicians who detected a bruit during routine exam, or those found during workup for other vascular disease, the contralateral carotid, or those located during screening duplex exams. Inclusion age was restricted to the range of 40 to 79 years. Patients were excluded if they could (or would) not complete the anticipated 5 year follow-up, had contraindications to aspirin therapy, suffered a neurologic event on the same side as the study lesion, or suffered a contralateral event within 45 days of enrollment. Other exclusion criteria included:

- Unstable angina
- Uncontrolled atrial fibrillation
- Severe diabetes
- Uncontrolled hypertension
- Renal insufficiency
- Hepatic disease
- Cancer

All patients entered must have a proven carotid stenosis of 60% or greater by angiography or screening doppler evaluation within 2 months of enrollment [ACAS 1995]. Patients with bilateral asymptomatic stenosis were accepted, but only one vessel was enrolled for the purposes of the study (the vessel with the greater stenosis, or the left (dominant) carotid in the case of equal severity). For the purposes of quality control, all patients randomized to surgery were required to undergo a confirmation angiography if only screening dopplers were used during enrollment [ACAS 1995]. If the post-randomization angiogram demonstrated a higher degree of stenosis on the opposite side, then this vessel became the study vessel. The non-study vessel continued as a medically treated lesion unless a stroke or TIA occurred at which time the patient could cross over to surgery for symptomatic disease [ACAS 1995]. Joint approval for entry was required from both the study neurologist and study surgeon. All randomized patients were treated with aspirin 325 mg per day from a single pharmaceutical supplier and were aggressively counseled on risk factor reduction including smoking, hypertension and diabetes management, lipid levels, etc. Surgical patients were operated on an elective schedule within 2 weeks of randomization. All patients were examined for neurologic deficits by both the study neurologist and surgeon following the surgery and for 30 days post-operatively. This methodology ensured against bias and missed events. Intense postoperative follow-up with symptom surveillance took place every 3 months.

Individual surgeons wishing to participate were screened and approved by the Surgical Management Com-

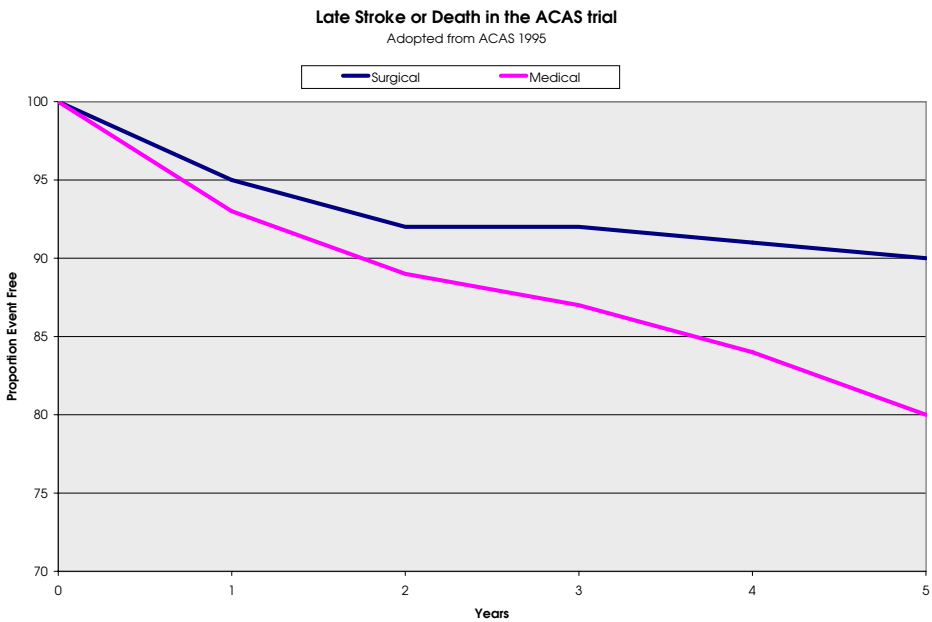

Figure 6. ACAS trial for asymptomatic carotid stenosis. Event Free Kaplan-Meier curves of surgical versus medical therapy.

mittee of the ACAS investigators in order to eliminate potential bias introduced by substandard surgical results [Moore 1991]. Criteria for acceptance of an applying surgeon were:

- Minimum performance of at least 12 carotid endarterectomies per year
- At least 50 consecutive endarterectomies performed with a minimum combined morbidity (stroke plus death) of 3% for asymptomatic patients and 5% for symptomatic patients.

Of the 164 surgeons applying to be ACAS investigators, 117 (71.4%) were approved. The combined morbidity and mortality rate of the approved surgeons for 5,641 endarterectomies preceding ACAS was 2.3% (1.7% for asymptomatic patients), well below the minimum criteria [Moore 1996]. This selection method offered the study patients the best surgical results to compare with the medical limb of the trial and favorably influencing the outcome in favor of CEA.

In the 6 years of the study, only 3 patients were lost to follow-up. The remaining patients were followed up every 3 months with alternating clinic exams and phone interviews, supported with doppler studies at 3, 6, 12, 18, and 24 months post randomization [ACAS 1995]. Compliance with aspirin therapy was verified by pill counts.

Two-thirds of the patients were male with a mean age of 67 years. Almost half (48%) were between the ages of 60 and 69 years and 95% were caucasian. Approximately 75% had an audible bruit in the study vessel and 43% had an audible bruit in the contralateral vessel [ACAS 1995]. Hypertension was present in 64%, cigarette smoking in 26% and diabetes in 23%. A fourth of enrollees (25%) had suffered a neurologic event in the contralateral hemisphere (and thus were not asymptomatic in general, just for the side in question).

A total of 828 patients were randomized to the surgical arm of the study, of which 721 patients underwent carotid endarterectomy by one of the study surgeons. There was only one death for a 30 day mortality of only 0.139% [Young 1997]. Ten patients suffered a post-operative stroke within the first 30 days for an incidence of 1.5%. The incidence of stroke or TIA during preoperative confirmatory angiography was nearly the same (1.2%) [Young 1997] indicating that elimination of routine angiography would favorably impact the advantage of prophylactic endarterectomy in the asymptomatic population.

The conclusion drawn by ACAS is that stroke risk reduction (immediate, short term, and long term) by carotid endarterectomy is superior to medical therapy (see Figure 6 ◉). Although the trial design called for a 5 year follow-up, the independent monitoring board terminated the study when differences reached statistical significance at only 2.7 years of follow-up [ACAS 1994]. In the surgical arm, the aggregate risk of stroke over 5 years was 5.1% while the risk for the medical cohort was 11%. Thus, surgery offered a relative risk reduction of 53%. Also, the yearly risk of future stroke was significantly less following surgery than with continued medical therapy. The 5.1% stroke risk encountered with surgery is an aggregate figure, including both perioperative and postoperative events. As mentioned, the perioperative risk of stroke was 1.5%, leaving a late incidence of 3.6% spread over 5 years for an annualized risk of 0.72% per year. However, in the medical cohort, the annualized risk of stroke during late follow-up was 2.2% per year, nearly three times the rate observed in surgical patients. The perioperative complication rate was higher in women and this reduced the protective benefit of surgery in females. The relative risk reduction in late stroke was 69% overall whereas it was only 16% in women [ACAS 1994].

Barnett comments that major disabling strokes were not decreased in ACAS [Barnett 1995]. However, in the same issue of the Annals of Internal Medicine, Brott and Toole (two principal ACAS organizers) made the point that the number of major strokes was so small that the sample size was below the threshold for statistical validity [Brott 1995]. However, ACAS did show a favorable trend in preventing late major, disabling strokes since 6.0% of the medical group were so affected after a mean of 2.7 years while only 3.4% of the surgical group were so affected [Brott 1995].

The ACAS investigators performed routine preoperative brain CAT scanning and found silent infarcts in 15% of "asymptomatic" patients [Brott 1994]. The infarcts were generally small in size and evenly distributed between the ipsilateral and contralateral hemispheres [Brott 1994]. This phenomenon raises the question as to whether all patients in the ACAS study were really asymptomatic or just not having detectable symptoms of their events. For those with silent strokes, they would probably have best been considered symptomatic and the results of the NASCET trial more applicable to their situation.

PLAQUE ULCERATION

Certain studies have suggested that ulcerated, nonstenotic plaques are associated with neurologic symptoms, particularly amaurosis fugax and the presence of opthalmic infarcts or Hollenhorst plaques [Moore 1978, Dixon 1982, Schwarz 1990]. Park et. al. reported a higher incidence of previous symptoms (TIAs or stroke) in patients with plaque ulceration as compared to asymptomatic patients undergoing CEA [Park 1998]. In their study, the plaque morphology from 1,252 consecutive operative specimens was examined pathologically. The incidence of plaque ulceration was 77% in patients with prior TIAs and 79% in patients with prior stroke versus 60% in the asymptomatic group ($p = .0001$) [Park 1998].

More convincing data on the dangers of plaque ulceration came as an offshoot of the NASCET trial. Eliasziw et. al. reported a markedly increased risk of stroke in the medically treated cohort who demonstrated plaque ulceration when compared with surgical therapy [Eliasziw 1994]. Patients without ulceration experienced a 21.3% risk of stroke with medical therapy through the duration of the trial. However, with ulceration, the risk rose from 26.3% (for lesions of 75% stenosis) all the way up to 73.2% (for lesions of 95% stenosis) [Eliasziw 1994]. Carotid

Table 6. Hospital Complications According to Preoperative Symptom Status (from Goldstein 1994).

		M.I.		Stroke		Death		Any	
Symptom	**N**	**%**	***P***	**%**	***P***	**%**	***P***	**%**	***P***
Ipsilateral	697	3.2%	.40	5.7%	<.004	1.6%	.50	8.5%	<.01
Other or None	463	2.4%		2.2%		1.1%		4.8%	

endarterectomy reduced the risk of subsequent stroke by 50% in patients with plaque ulceration [Eliasziw 1994].

OPERATIVE RISK

In the past, the leading cause of perioperative mortality after CEA was myocardial infarction. The risk of all cardiac events (including arrhythmias, congestive heart failure, angina, or myocardial infarction) was 8.9% in the study of 291 consecutive CEAs over an 18 month period as reported by Wong [Wong 1997]. With present management, the risk of a fatal cardiac event has been reduced to about 2%. Many patients with carotid stenosis have no active anginal symptoms but are still prone to perioperative cardiac events. Risk factors for postoperative morbidity (stroke or death) include female gender, age > 75 years, or a history of congestive heart failure [Wong 1997, Goldstein 1998]. Eagle et. al. published a set of guidelines for initiating a preoperative cardiac evaluation [Eagle 1989]. Their criteria included any two or more of the following clinical markers:

- Age greater than 70 years
- History or EKG evidence of prior myocardial infarction
- History of prior congestive heart failure (CHF)
- History of angina pectoris
- Diabetes mellitus

A meta-analysis of perioperative risk was performed by Rothwell et. al., including review of perioperative mortality data in 36 published studies dating from 1980 to present and from unpublished data in the European Carotid Surgery Trial (ECST) [Rothwell 1997]. These investigators found that female gender, age greater than 75 years, a systolic blood pressure of 180 mmHg or more, a history of peripheral vascular disease, occlusion of the contralateral internal carotid, and stenosis of the ipsilateral external carotid or siphon stenosis were correlated with perioperative stroke or death. Patients with ocular ischemic symptoms (amaurosis or retinal artery infarct) were at a reduced risk compared with those presenting with hemispheric events.

Symptomatic carotid lesions are associated with an 8.5% incidence of perioperative complications whereas only 4.5% of asymptomatic patients suffered postoperative complications (see Table 6 ◎) [Goldstein 1994]. The majority of these complications were neurologic indicating that patients with symptoms are indeed at neurologic risk during surgery, most likely because of severe anatomy, thrombus, preocclusion, instability of the cerebral infarct etc. Furthermore, Goldstein reported that there were no hospital or surgeon related differences in mortality rates among the 12 hospitals performing CEA for ipsilateral symptoms [Goldstein 1994]. When the group without symptoms was studied on the same retrospective protocol, the combination of stroke and death (as defined by ACAS) was 3.3% (see middle two columns of Table 6 ◎; ACAS did not include non-fatal myocardial infarction as a morbidity endpoint). The 12 centers surveyed by Goldstein thus were within the same performance criteria established by ACAS [Moore 1996]. The only preoperative medical variable associated with complication was the association of age > 75 years with postoperative risk of myocardial infarction (6.6% myocardial infarction above 75 years and 2.3% below 75 years; p = 0.24). In this initial study, the risk of death or perioperative stroke was not age related. Anatomic variables (on preoperative angiography) which correlated with perioperative stroke include [Goldstein 1994]:

- intraluminal thrombus
- stenosis near the carotid siphon (high lesion)
- intracranial (high siphon) lesion
- subtotal or total occlusion

The degree of stenosis in the contralateral carotid had no impact on the risk for perioperative stroke [Goldstein 1994]. Ulceration of the ipsilateral carotid did not increase the risk of perioperative neurologic event [Goldstein 1994]. Patients with evolving stroke had a 20% incidence of perioperative neurologic deficits compared with 5.6% of those without evolving stroke [Goldstein 1994]. Female gender, age > 75 years, and history of congestive heart failure were significant operative risk factors in a later study by the same authors [Goldstein 1998].

The cause of perioperative stroke was thoroughly examined by Riles et. al. in a review of 3,062 carotid endarterectomies performed at New York University Medical Center from 1965 through 1991 with a total of 66 perioperative neurologic events (2.1%). The incidence of perioperative stroke declined from 2.7% to 2.2% to 1.5% over each of the 3 decades analyzed. On review of the charts and operative records, the mechanism of stroke was determined in 63 of 66 cases. The authors identified 20 different mechanisms causing injury, with most being surgeon or technique related (see Table 7 ◎).

Riles et. al. divided the causes of technical errors during CEA into four categories summarized in Table 7 ◎: 1) ischemia during cross clamping (XC), 2) postoperative thrombosis, 3) intracranial hemorrhage, and 4) other mechanisms [Riles 1994]. Ischemia during shunting was

Table 7. Technical Factors Associated with Stroke during Carotid Endarterectomy (Riles 1994)

Ischemia during XC* N=10	Postop Thrombosis N=25	Intracranial Hemorrhage N=12	Other N=8
Difficulty placing shunt (N=5)	Clamp Injuries	Reopening of a severely stenotic vessel	Emboli during vessel dissection (N=1)
Long shunt insertion time (N=3)	Kinked vessel		Emboli during declamping (N=1)
Hypotension during shunting (N=1)	Ledges at endpoints		Thrombectomy of an occluded ICA
Bradycardia with hypotension (N=1)	Stenotic closure		Postop wound bleeding
	Rough surfaces		Extubation with secondary anoxia
	Platelets on patch material		

*XC = cross clamp

most often related to delayed insertion of the shunt or hypotension during the shunt period. Thrombosis after endarterectomy involved one of six mechanisms (verified at reexploration):

- Clamp injuries
- Kinking in a redundant internal carotid
- Ledges or shelves at either proximal or distal endpoint
- Stenosis after suture closure
- Rough endarterectomy surfaces
- Platelet adherence to patch material

Intracranial hemmorhage only occurred after opening a very high grade stenosis and two-thirds of these patients had a history of preoperative stroke [Riles 1994]. It appears that rigorous protection from intraoperative and postoperative hypertension can reduce the likelihood of hyperperfusion and hemispheric bleeding [Pritz 1997]. Other technical factors rarely causing perioperative stroke include emboli during application or release of the cross clamp, attempting to thrombectomize an occluded internal carotid artery, or bleeding complications leading to emergency reexploration and reclamping [Riles 1994].

In the event that acute perioperative thrombosis occurs, immediate reexploration, thrombectomy and patching of the endarterectomy site is indicated. Results are very time dependent. In a retrospective study by Aburahama, et. al. the final neurologic outcome was superior if reoperation and thrombectomy with patch were performed within 2 hours [Aburahma 1996]. Seven of nine patients with early reoperation experienced a complete recovery or significant improvement.

RESTENOSIS

The definition of restenosis (versus residual lesion or other cause) has remained elusive and imprecise. The definitive monograph on restenosis was written by Lattimer and Burnand in which all prior reports of restenosis were reviewed [Lattimer 1997]. These authors summarized the data from 55 prior published reports dating from 1976 to 1996 inclusive of 19,369 arteries with an incidence of restenosis ranging between 1.3% and 32% [Lattimer 1997]. The incidence is highly dependent on the definition and diagnostic methodology used to detect and quantify restenosis. There is no universally accepted method for quantifying a lesion or for defining a recurrent stenosis. The rates of restenosis are slightly higher in earlier publications, probably due to the refined diagnostics (duplex) that are available more recently. In the last decade, most papers are reporting a restenosis rate of around 10% over 3 to 5 years of follow-up [Lattimer 1997].

Diameter of the carotid artery at original CEA is one risk factor for restenosis. The internal carotid averages 4.6 mm in diameter in males and 4.3 in females. Carotids less than 4 mm have an increased risk of restenosis [Ouriel 1987]. This has been one factor leading some surgeons to utilize patch angioplasty during closure of small diameter vessels. Restenosis also appears to be more common in patients who continue to smoke [Ricotta 1997].

Early restenosis (within 2 years) is the result of aggressive fibrointimal hyperplasia. Late restenosis is usually reaccumulation of atheroma with or without accompanying thrombi. Endarterectomy stimulates an aggressive vascular repair process by exposing the muscular media to the lipids, proteins, and cellular elements of flowing blood. Platelet adherence leads to release of platelet-derived growth factors (PDGF) which cause smooth muscle proliferation and chemotaxis of cellular elements of immunity and repair. Release of fibroblastic growth and angiogenesis factors follow with further proliferation of cellular elements and the formation of neointima. Secondary infiltration of lipids can recreate atherosclerotic lesions. The role of hyperlipidemia in the cause of late restenosis has been implicated, but not proven. The advent of new antiplatelet agents and effective lipid lowering therapy offers an opportunity to reduce restenosis by altering the mechanisms of vascular repair and lipid infiltration.

The incidence of ipsilateral symptoms or stroke in patients with recurrent carotid stenosis appears low (2% to 8%) [Lattimer 1997]. Patients without symptoms are not recommended to undergo surgical correction. For symptomatic patients, reoperation can be performed with a mortality rate of 1.0% and a stroke rate of 3.9% [Lattimer 1997].

PATCH ANGIOPLASTY CLOSURE

Restenosis has been associated with a small diameter (less than 4 mm) carotid at the time of original surgery [Ouriel 1987]. Proponents of patch angioplasty closure have demonstrated improved lumen diameter and reduced rates of restenosis [Eikelboom 1988]. However, there are equally good studies that show minimal differences in restenosis rates between primary closure and patch closure [Rosenthal 1990]. It is not possible to ascertain if the surgical technique and the size of the patch, postoperative anticoagulation, or method/definition of establishing restenosis account for these discrepancies. Also, there is no consensus on the best material for patching, but saphenous vein, cervical vein, Dacron® and PTFE have all been used. Venous patches appear to have a low but discrete incidence of aneurysm formation and rupture [John 1993, Yamamoto 1996]. Another concern is the potential for an additional source of proliferating smooth muscle cells which could predispose to fibrointimal hyperplasia.

Prosthetic (fabric) grafts offer the same opportunity for enlargement of the lumen without risk of rupture. The current generation of low-porosity, impregnated Dacron® grafts are favored patch material. Meyer et al. reported excellent results with a collagen-impregnated fabric patch (combined stroke-death rate of only 1.7%, no occlusions, and a restenosis rate of less than 1%) [Meyer 1998]. Graft infection rates were very low (1 in 290 cases) [Meyer 1998]. Expanded PTFE patches have also been used with similar results [Rhodes 1995].

AWAKE (REGIONAL BLOCK) TECHNIQUE FOR CEA

Deep and superficial cervical blocks provide sufficient analgesia to permit CEA in the awake patient. Some sur-

geons prefer awake CEA in order to assess neurologic function during cross clamping. This lessens the need for intraluminal shunts and reduces the uncertainty about cerebral perfusion typical of stump pressure measurement, electroencephalography, and other monitoring techniques. Although awake CEA is not new, there is now a resurgence of interest for several reasons. First, hemodynamic swings, particularly hypertension, are less marked when the patient is awake. Second, the need for postoperative intensive care is lessened with potential reductions in hospital charges and length of stay. Thirdly, there is the potential for reduced perioperative morbidity and mortality, especially in the frail or elderly patient, by avoidance of general anesthesia.

ACAS and NASCET as well as independent studies [Hallett 1998] have all demonstrated an increased surgical mortality rate for patients over 70 and nearly all deaths in this age range are due to myocardial infarction [Goldstein 1994]. Awake CEA may be an important alternative which can reduce these risks in the elderly. In a study by Corson et. al., the average duration of need for cardiovascular drugs (vasodilators or vasopressors) was 12.6 hours with general anesthesia and only 3.5 hours with regional block. Gabelman et. al. reported shorter intensive care unit lengths of stay (LOS) (0.7 days mean) with modest cost savings (30%) with awake CEA [Gabelman 1983]. Harbaugh et. al. also found a modest trend towards reduced hospital length of stay with cervical block anesthesia [Harbaugh 1995].

Awake CEA requires excellent and reliable deep cervical block performed by an experienced anesthesiologist. The landmarks for a multilevel cervical block are well known, but not all anesthesiologists are practiced at the technique. Patients with chronic or progressive high grade unilateral stenosis will usually tolerate occlusion surprisingly well due to progressive development of intracranial or extracranial collaterals. However, there are some patients who will not tolerate awake occlusion of the ipsilateral vessel, including those with:

- Severe contralateral stenosis or occlusion
- Severe bilateral stenosis
- Absence of any cross-circulation by angiography or transcranial doppler
- Patients with ulcerative but minimally stenotic lesions
- Arch or vertebral stenosis in addition to cervical carotid disease

Patients who are acutely intolerant of a trial occlusion may loose speech, motor function or consciousness, become combative or experience generalized seizures. Unclamping of the vessel will immediately restore normal function, but leave the surgeon with a dilemma. In most circumstances it is best to stop and proceed with general anesthesia followed by shunting. Attempts to shunt while the patient is still awake can be difficult if combativeness occurs. Restlessness, disorientation, or combative behavior may also be caused by the paradoxical disinhibition typical of hypnotic-sedative drugs, particularly benzodiazepenes, when used in the elderly. Patients with cervical disk disease or arthritic changes may become uncomfortable and restless when the head is extended for operative positioning and exposure. Patients with anxiety, combativeness, or low pain threshold may not be good candidates for awake CEA.

Shah et al. reported a combined stroke-death rate of only 1.5% for awake CEA [Shah 1994]. A continuous series of 654 awake patients were compared with 419 cases under general anesthesia at the same institution over a 14 year period. The mortality in awake patients was 0.76% with a transient neurologic deficit rate of 1.07% and a permanent deficit of 0.76%. Two of the five deaths were cardiac, three were from massive stroke and one was from acute contralateral carotid occlusion [Shah 1994]. Conversion from regional to general anesthesia was needed in only 7 patients (1.1%). Four patients were converted due to inadequate pain control (failed block) and three required intubation for airway control (two patients lost consciousness upon carotid clamping). Intraluminal shunts were used in 46 cases (7%). Most (44 out of 46) were placed due to neurologic compromise upon test occlusion of the carotid, including loss of consiousness at 30 seconds to 11 minutes after clamping (mean 4 ± 3 minutes). A contralateral high grade lesion (> 80%) was noted in 68.2% of those requiring shunt insertion during awake CEA [Shah 1994]. The ability to perform continuous neurologic assessment permits accuracy in selective use of intraluminal shunts.

Rockman et. al. reported a large series of patients (3,382 cases) operated with regional anesthesia over a 32 year span and found very little differences when compared with a group operated at the same institution using general anesthesia. Although the stroke and death rates were slightly higher under general anesthesia (3.2% vs 2.0% and 2.0% vs 1.4%), these were attributable to a slightly higher risk subset receiving general anesthesia [Rockman 1996].

The true role of awake CEA is likely to be the extension of low mortality surgery to the high risk candidate. By avoiding general anesthesia, hemodynamic alterations, hypertension and drug management, the elderly or frail patient can be offered surgery for even asymptomatic lesions without exceeding the mortality/morbidity results of the ACAS trial.

TRANSCRANIAL DOPPLER

Another powerful tool for reducing perioperative morbidity is transcranial doppler (TCD). In about 90% of patients, flow velocities in the middle cerebral artery can be obtained directly through the temporal bone. This allows the observer to evaluate intracranial flow velocity as well as the passage of microparticulates. TCD provides several roles in carotid stenosis. The additional flow velocity information can confirm the severity of the stenosis estimated by screening duplex, adding additional diagnostic power to the non-invasive workup. Also, TCD can determine the adequacy of collateral flow. Preservation of the flow velocity during transient compression of the cervical common carotid is evidence of collateralization.

In a large study reporting on the results of intraoperative TCD during 500 carotid surgeries from a single institution, Spencer reported a reduction in transient and permanent neurologic complications from 7% in the first 100 cases to 2% in the remaining 400 cases [Spencer 1997]. This improvement was attributed to surgical technique modifications made after learning about the causes of flow abnormalities and embolism during surgery. The frequency of microembolic signals detected intraoperatively and in the first few hours postoperatively correlated very closely with the incidence of neurologic events, confirming that emboli were the primary cause of perioperative injury [Levi 1997, Spencer 1997]. In addition, middle cerebral artery hypoperfusion as well as hyperperfusion were detected by continuous intraoperative TCD and correlated with perioperative stroke [Spencer 1997].

Intraoperative TCD provides meaningful analysis of collateralization and in many cases can determine the need for shunting. Preservation of flow velocity during cross clamping is correlated with excellent collaterals and shunting can be avoided. TCD also provides evidence of shunt patency. If the flow velocity decreases prior to shunt insertion and increases after insertion, there is confirmation of shunt function. TCD can also detect intraoperative thrombosis or embolism and provide evidence to allow for correction, including intraoperative urokinase infusion [Gaunt 1994]. Commercial TCD instrumentation is now available. Software algorithms which can differentiate between gas and particulates are under development.

ANTIPLATELET AGENTS

The current standard for non-surgical management of carotid atherosclerosis is aspirin, an inexpensive and safe agent with mild antiplatelet properties. In a recent survey of practice patterns, 96% of neurologists considered aspirin as the first line of therapy for noncardiogenic stroke [Masuhr 1998]. In all of the randomized trials of CEA versus medical therapy summarized in this publication, patients in the medical arms received aspirin as their primary or sole antiplatelet agent.

Aspirin was shown to be effective in reducing future vascular events of all kinds [Antiplatelet Trialists 1994]. However, the aspirin effect is not profound, with at most a 25% reduction in vascular events seen in comparative trials [Easton 1998]. To add to the controversy, a well performed multicenter double-blinded placebo controlled trial (with compliance monitored by pill counts) in patients with asymptomatic bruits and stenosis of at least 50% found no beneficial effect from aspirin [Côté 1995]. After a mean of 2.3 years of follow-up, the late risk of neurologic events was 7.6% with placebo and 6.9% with aspirin (NS). There was a slight advantage in aspirin treated patients within the first year which then disappeared during further follow-up [Côté 1995]. A sustained protective effect may not be seen with aspirin.

Some doubts persist about the efficacy in women who tend to have a lessened response to the antiplatelet effects of aspirin [UK-TIA 1991, Canadian Coop 1978]. A large meta-analysis of the effectiveness of aspirin in different patient groups did not find a difference between the two genders [Antiplatelet Trialists 1994]. Despite the presence of this collaborative data supporting the use of aspirin in women, a quarter of neurologists are now using newer antiplatelet agents in women with carotid disease [Masuhr 1998].

Ticlopidine (Ticlid®) has been available in the United States since December of 1991 and clopidogrel (Plavix®) is a very recent addition. Both agents are thienopyridine derivatives which act primarily by preventing adenosine diphosphate from binding to receptors on the surface of platelets and thus blocking platelet aggregation [Heptinstall 1995, Sharis 1998]. Ticlopidine is more effective than aspirin in reducing strokes and TIAs [Rothrock 1994, Sharis 1998]. The relative reduction in vascular events compared with aspirin is about 12% [Easton 1998]. In the survey of neurologists by Masuhr, 86% of North American and 59% of Western European neurologists will use ticlopidine (Ticlid®) as a second line of therapy for patients with recurrent TIAs on aspirin [Masuhr 1998]. The possibility exists that these newer agents will reduce both the risk of stroke in non-surgically treated patients but also the risk of post-surgical events. However, this will be very difficult to prove since it would require an entire new series of studies equal in magnitude to the NASCET and ACAS. Thus, we will likely only see anecdotal reports or small series of patients on these newer antiplatelet regimens. Vascular surgeons and medical physicians will need to be cautious in interpreting results from non-randomized or poorly constructed investigations, but the presence of these new drugs does offer some intriguing possibilities in the ultimate prevention of stroke.

There are some potentially serious side effects with ticlopidine such as neutropenia, aplastic anemia, colitis, and thrombotic thrombocytopenia purpurpa (TTP) that mandate close physician monitoring. Fortunately, these are rare events and may actually be due to the use of ticlopidine in combination with aspirin, calcium channel blockers or other drugs [Kao 1997]. Clopidogrel (Plavix®) appears to have the same effect on vascular events, but with the ultimate safety spectrum of aspirin [Easton 1998]. The potential for combination therapy with aspirin and thienopyridines opens up new possibilities in reducing postoperative platelet mediated events (TIAs, fibrointimal hyperplasia, and restenosis), further extending the benefit of endarterectomy for years after surgery. The main problem with these newer antiplatelet agents is cost, especially over a long duration of treatment.

Low molecular weight dextran is another option to prevent immediate postoperative platelet adherence to the raw endarterectomy surface. This polysaccharide is only available as an intravenous infusion but is highly effective in reducing microemboli typical of the new endarterectomy surface. Lennard et. al. reported that 48 out of 100 immediate postoperative endarterectomies were associated with microemboli as detected by continuous transcranial doppler during the first 6 hours after surgery [Lennard 1997]. Patients with a high emboli count (more than 25

per 10 minutes) were started on a Dextran 40 infusion and all had an immediate and significant reduction in emboli counts [Lennard 1997]. In view of the data by Riles et. al. that 37.8% of perioperative strokes are thromboembolic in nature [Riles 1994], perioperative infusions of Dextran may provide an additional level of protection not previously studied. At least in the hands of Lennard et. al., this strategy resulted in a zero (0%) morbidity and mortality [Lennard 1997].

PROTAMINE

The role of protamine at the completion of endarterectomy was addressed by Mauney and associates at the University of Virginia, a busy combined cardiac and vascular surgery service and training center. They compared the neurologic outcomes of CEA in 155 patients who did not receive protamine against 193 in which standard protamine doses were given. The postoperative stroke rate in the protamine group was 2.6% (in the same range as the ACAS criteria) while the neurologic event rate in patients where protamine was avoided was zero (0%). The incidence of hematoma requiring exploration was 1.0% in the protamine group and 1.9% in the non-protamine group. The group without protamine had a higher percentage of intraluminal shunting (84% vs 67%, $p < 0.001$) and a lower incidence of patch closure (15% vs 35%, $p < 0.001$) than the protamine group, but statistical analysis did not show either of these to be independent risk factors. Levinson, et. al. reported similar results, with no perioperative strokes (0%) in 42 patients in whom protamine was withheld as compared to 2.7% in 365 patients in whom protamine was given [Levinson 1999]. Their reported incidence of neck hematomas was 9.5% without protamine and 1.9% with protamine. Avoidance or reduction of protamine dosages may further improve the perioperative neurologic safety and further widen the gap of significance favoring surgery over medical therapy.

Before adopting a routine policy eliminating protamine, it is important to understand the consequences of a neck hematoma following CEA. Although the incidence is low with or without protamine, the occurrence is a major problem. Neck hematomas can be associated with severe airway compromise and may create a difficult re-intubation scenario [Holdsworth 1994, Munro 1996]. Tracheal deviation in combination with impaired venous and lymphatic drainage of the larynx can cause severe vocal chord swelling and stridor [Munro 1996]. Careful attention to the wound in the immediate few hours after surgery is an essential element of care which is even more important if protamine is avoided [Holdsworth 1994].

OPERATING WITHOUT ANGIOGRAPHY

The standard for non-invasive evaluation of carotid stenosis is the duplex scan, a combination of B-mode imaging for plaque morphology and doppler flow analysis of velocities and spectral broadening [Dawson 1993]. There are relative standards for evaluating the flow patterns and velocities associated with hemodynamically significant carotid stenosis [Taylor 1987]. A well performed duplex exam does correlate closely with the findings at angiography [Dawson 1993, Khaw 1997]. For a 50% or greater stenosis detected by duplex, the angiographic correlation showed duplex was 98% sensitive and specific with a 99% positive predictive value [Dawson 1993, Mattos 1994]. All false negative and false positive results were due to poor scanning technique rather than limitations of the equipment or technology [Mattos 1994]. For lesions of 50% or below, the duplex criteria are less precise. In prospective trials, angiography only added surgically relevant information in 7% to 13% of patients [Dawson 1993, Mattos 1994]. In addition, ulceration is not clearly detected with duplex. None-the-less, for a patient undergoing a good quality duplex that identifies a high grade stenosis, the presence or absence of an ulcer is of lesser importance in the decision to operate since the patient already fits the ACAS criteria based on severity of stenosis. Since there is a 1% to 1.6% incidence of neurologic events with angiography, avoidance in patients who already meet the stenosis or symptom criteria for surgical benefit permits a further reduction in overall morbidity.

One of the weaknesses of duplex is the tendency to underestimate the actual degree of stenosis when reporting lesions of lesser severity (30% to 49% stenotic) [Srinivasan 1995]. Also, duplex is less accurate in the presence of severe tortuosity, calcification, near occlusion, ulceration, intraluminal thrombi, or a distal lesion above the bulb [McCory 1993].

Current indications for angiography include:

- Symptomatic patients (TIA or stroke) with stenosis less than 50% by duplex
- Detection of ulceration in otherwise non-critical lesion (amaurosis, TIAs, Hollenhorst plaques)
- Technically inadequate duplex (poor quality study)
- Discrepancy between the B-mode and doppler estimations of stenosis
- In the presence of extensive calcification (affecting doppler quality)
- Need to evaluate other extracranial vessels (common carotids, vertebrals)
- Rule out siphon or intracranial stenosis
- Rule out total occlusion in presence of low flow or no flow on duplex (possible string sign)
- Evaluate for high lesion extending to base of skull (surgically inaccessible)
- Evaluate for a high bifurcation (surgically inaccessible lesion)
- Evaluation of recurrent carotid stenosis

In addition, patients with non-focal or non-hemispheric symptoms may need to undergo angiography to clarify the entire cerebral circulation in search of multiple lesions, locations, or unusual anatomic features.

The cost and complication spectrum of angiography does affect the risk-benefit equation when evaluating patients for potential surgical treatment, particularly those patients without symptoms. It is estimated that avoidance of angiography saves as much as $4,500 per case. In addition

there is a roughly 1.0% to 1.6% neurologic complication rate (plus additional groin complications) for diagnostic cerebrovascular angiography. In certain subsets, angiography is even more risky. The procedural risk of stroke with angiography is as high as 7.7% for stroke-in-evolution and 12.5% for severe bilateral stenosis [Khaw 1997].

In asymptomatic patients, the angiographic risks of a neurologic event are nearly equal to the perioperative surgical risks [Young 1997]. If angiography is routinely utilized in these patients, the cumulative neurologic risk is thus doubled and the margins of benefit obtained are diminished accordingly.

DISCUSSION

The association between carotid artery disease, microembolism, transient ischemic attacks, amaurosis, and stroke was delineated in a series of classic papers published in the 1950's by C. Miller Fisher [Estol 1996]. The first surgical endarterectomy was reported by Eastcott and colleagues in 1954 [Eastcott 1954]. Over the past 45 years, the progress of knowledge and experience has improved the surgical results to an admirable level. It is no small feat that the ACAS investigators were able to insist on a combined stroke-death rate of only 3% for asymptomatic patients and found that over 70% of the applying surgeons could fulfill these criteria. These low perioperative risks have stimulated proponents to advocate CEA as a preventative measure to reduce future risk of neurologic events. Only in the last decade has enough data from well designed clinical trials been available to justify this strategy. However critics cite the stringent performance criteria required for ACAS approved surgeons and the need to match these standards before recommending widespread acceptance of ACAS and surgical management of asymptomatic stenosis.

There is more than ample data to show that various programs and surgeons are able to meet the ACAS performance criteria. The carotid registry in the state of Maine (364 procedures by 28 surgeons in 10 different hospitals) yielded nearly identical morbidity results to ACAS [Mayo 1998]. The incidence of postoperative stroke in this statewide registry was 2.5% with a TIA incidence of 2.2% [Mayo 1998]. The mortality rate was very low at 0.3%. Furthermore, there was no difference in neurologic morbidity identified between high volume and low volume hospitals, or between high volume and low volume surgeons [Mayo 1998]. Similar ACAS comparable data from community practice settings was reported by Maxwell et. al. using cumulative data from the North Carolina Medical Database Commission [Maxwell 1997]. They reported a perioperative stroke rate of 1.7% and a mortality rate of 1.2% in 11,973 carotid endarterectomies performed across the state of North Carolina over a 6 year consecutive period [Maxwell 1997]. The combined stroke-death rate was 2.9%, exactly the same as required for ACAS surgeons. Yates, et. al. reported a 2.3% combined stroke-death rate from the Kentucky Vascular Surgery Society registry involving 22 surgeons from diverse community as well as academic centers who performed 1,490 CEAs over a 2 year period [Yates 1997]. Clearly the modern results of CEA in the hands of many different surgeons and institutions can match the criteria for safety required in order to apply the results of ACAS to a wider population of asymptomatic patients.

A great deal of emphasis has been placed on the presence or absence of symptoms. It is true that the margins of benefit documented in clinical trials are greater for symptomatic patients (see Figures 1 ◎ and 2 ◎). However, there is a gray zone in this differential. Brott and coworkers found that screening CAT scans in so-called asymptomatic

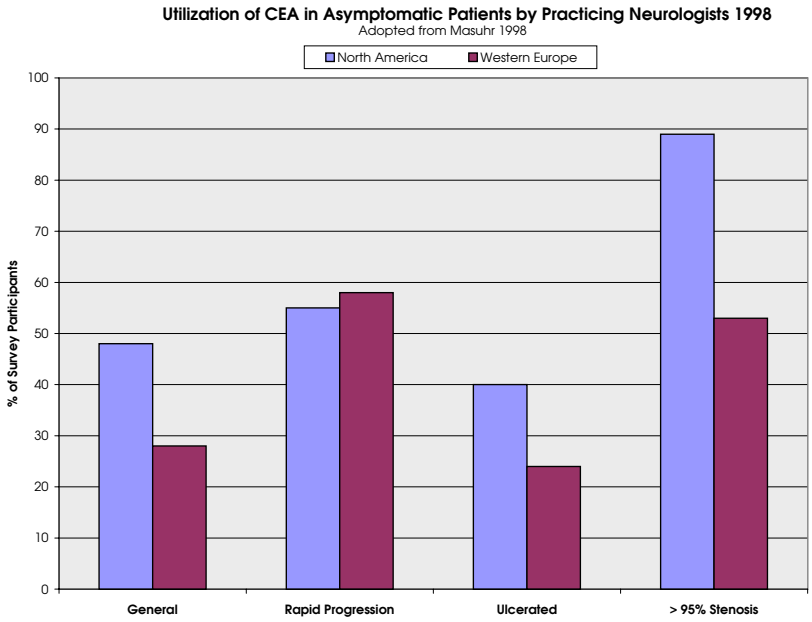

Figure 7. Asymptomatic stenosis: Reasons for surgical referral among leading neurologists following the publication of the ACAS trial results.

patients enrolled in the ACAS trial revealed prior infarcts in 15% of the patients [Brott 1994]. It is hard to argue that patients with completed infarcts are really asymptomatic even if they did not have a documented clinical event. The results of the symptomatic trials such as NASCET (see Figures 1 and 3 ◎) probably apply better to their situation.

When compared with medical therapy, every well designed trial was terminated early by the monitoring committee after demonstrating clear superiority of early endarterectomy (see Figures 1 ◎ and 2 ◎). None-the-less, there has still been a considerable lag in the acceptance of these studies by neurologists and primary care physicians. In the post-ACAS era, Goldstein performed a questionnaire of 2,000 US physicians (with a 67% response rate). Analysis showed that almost a quarter of noninternist primary care physicians seldom or never use carotid endarterectomy even for high grade stenosis associated with new onset symptoms [Goldstein 1996]. This is in contrast with 80% of neurologists and surgeons favoring CEA for the same indications [Goldstein 1996]. Even among neurologists who are up to date on trial results, the treatment for asymptomatic patients has not completely turned to surgery. Masuhr et. al. reported the results of a detailed survey of prominent neurologists in North America and Western Europe following publication of the major randomized trials. Figure 7 ◎ shows that less than half of the neurologists in North America and only about 25% of the neurologists in Western Europe would refer patients with asymptomatic carotid bruits for surgical therapy [Masuhr 1998]. However, if the stenosis was greater than 95%, then the vast majority of North American neurologists would refer the patient, and approximately half of the Western European neurologists would do the same. A surprisingly low number would refer a patient with carotid ulceration, but rapid progression of the stenosis was an acceptable indication for half of the surveyed physicians. Despite the results of ACAS, the practice patterns revealed by Masuhr et. al. indicate a general conservatism in referring patients for surgery unless the stenosis is very high grade.

One factor reducing referral for CEA is the confidence placed in aspirin therapy as the sole means of reducing new events. However, confidence in aspirin is largely due to assumptions based on proven reductions in coronary events and there is a paucity of data to support a significant benefit when used in carotid atherosclerosis. The Antiplatelet Trialists data demonstrated only a 25% relative reduction in new events with aspirin, while the Asymptomatic Carotid Bruit trial showed no effect at all when aspirin was compared to placebo in a very controlled manner [Côté 1995]. Furthermore, there is data that raises suspicion about the efficacy of aspirin over time and its effectiveness in women. The reliance on aspirin may actually be a false crutch for medical physicians who are reluctant to recommend surgery.

At the same time, the power of surgery as a long range preventive therapy may be underestimated by the current information. One of the crucial limitations of the NASCET, ACAS and other comparative trials is the very short period of follow-up (see Table 2 ◎). This is not a coincidence, but rather the result of premature closure when the monitoring committees found marked differences in favor of surgery within less than 3 years. In the NASCET study, there was no deterioration in post-surgical event rates in years 2 through 4 of late follow-up, while the medical group continued to decline [Easton 1994]. This implies that the effect of the operation is durable over periods beyond those studied. Hallett and coworkers in a community based surgical program from Olmsted County, Minnesota reported that the late freedom from neurologic events persists even to 10 years. Their event-free rate

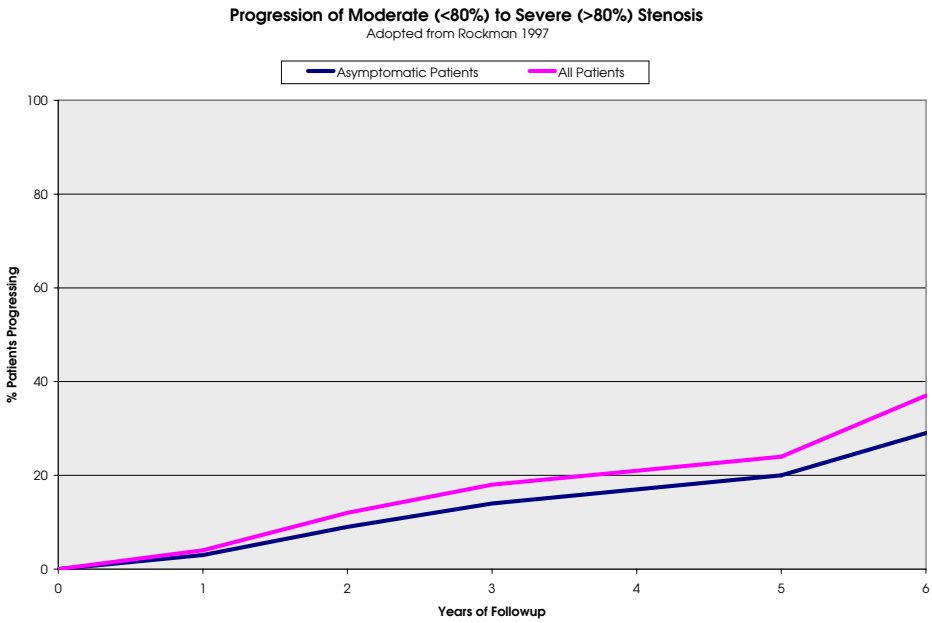

Figure 8. Progression of carotid stenosis over time.

(measured, not calculated) was 91% at 10 years indicating persistence of the prevention offered by CEA [Hallett 1998].

Endarterectomy physically modifies the pathologic process by removing the offending plaque and remodeling the luminal surface. Medical therapy is based only on slowing progression or blunting the blood-surface interactions without modifying the plaque in any real way. We know from the work of Rockman et. al. that lesions in medically treated patients continue to progress (see Figure 8 ◉) and that progression is predictive of future events (see Figure 9 ◉) [Rockman 1997]. As newer strategies become available to further improve the power of surgical intervention (TCD, no protamine, improved antiplatelet lipid lowering and antihypertensive agents), the advantages of surgery will likely increase over time.

In addition to the multicenter trial data outlined previously, there are other key studies which demonstrate advantages for CEA in specific patient populations. Diabetics appear to be one subgroup in which surgical results are superior to medically treated patients (similar to recent findings in diabetics with coronary artery disease). Prior to the release of the ACAS study, Libman reported a retrospective analysis of patients treated with either surgery or medical therapy [Libman 1994]. These investigators at Columbia Presbyterian Medical Center in New York reviewed the charts of 107 asymptomatic carotid stenosis patients treated with CEA compared with 108 treated medically. All records were reviewed by the study neurologist who contacted the patient for late outcomes analysis with only 4% lost to follow-up. When all patients together were subjected to a 5 year life-table analysis, there was no difference detected between surgically and medically treated patients for the risk of late ipsilateral stroke, any stroke, or survival free of stroke. However, these investigators identified the presence of diabetes as a major risk factor for late stroke during medical management of asymptomatic carotid bruits. The 5-yr risk of stroke for the medically treated diabetics was 20% while there were no events in the surgically treated diabetics (0%) [Libman 1994].

Additional support for these conclusions comes from the report by Rockman et. al. who studied the natural history of moderate (not severe) carotid stenosis (50% to 79%) detected by duplex in patients referred for evaluation of an asymptomatic bruit [Rockman 1990]. Four hundred twenty six patients with a mean age of 74.5 years were followed for an average of just over 3 years. These investigators also found an increased risk of late events in diabetics (9.8% versus 3.3%, $p < 0.01$). The protective benefit of CEA in diabetics is greater than in the general population and should be recommended early, even without symptoms.

Further data from the Rockman study indicated that the risk of lesion progression from moderate (<80%) to severe stenosis (> 80%) was 26.5% at 5 years (see Figure 8) [Rockman 1990]. There was a significantly higher risk of stroke during follow-up if the lesion had progressed (10.4% versus 2.1%, $p > .02$, see Figure 9 ◉) [Rockman 1990]. New ipsilateral completed strokes occurred in 16 patients (3.8%), of which only one-third occurred in a duplex stable lesion. New ipsilateral TIAs occurred in an additional 5.9% of patients. Again there was a significantly higher risk of TIAs if the lesion progressed on duplex (27.1% versus 5.1%, p=.001). Of the 48 arteries that developed progression, the incidence of new onset TIAs was 27.1% and new completed stroke rate was 10.4% with the incidence increasing over time. Total occlusion developed in an additional 1.4% of patients within the follow-up period. A major disabling stroke is known to occur in 20% of patients when the vessel occludes [Côté 1983, Nicholls 1986].

Now that benefit has been established, the next battle is cost. Opponents of CEA have raised concerns about run

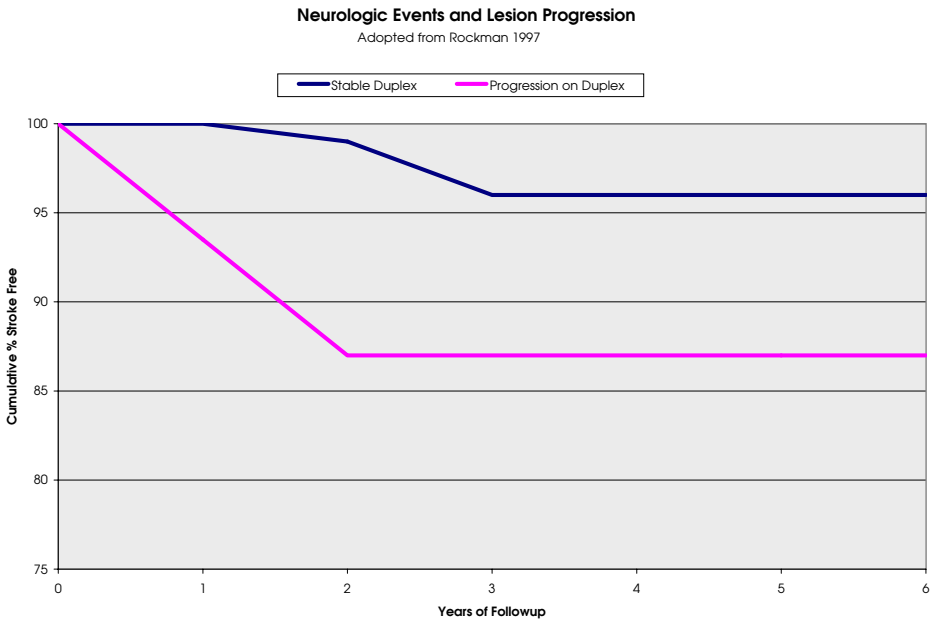

Figure 9. Lesion progression predicts risk of future events.

away expenditures to the national health care system from expanding surgical case volumes. In the VA hospital system alone, there was a 43% increase in carotid endarterectomies performed in 1995 as compared to 1993 [Huber 1997]. Ricotta et. al. estimated a utilization of 414 procedures per 100,000 population over 65 years of age and 31 procedures per 100,000 population under 65 years of age [Ricotta 1998]. There are many studies that argue both for and against cost-effective results, but if applied within the guidelines of the study investigators, surgical therapy does have a positive cost/benefit ratio [Kuntz 1996, Cronenwett 1997]. Significant cost savings are possible when compared to medical therapy with aspirin [Nussbaum 1996]. In a rigorous analysis of cost-benefit performed after the initial ACAS trial results were published, Cronenwett et. al. reported a significant cost advantage when surgery was used for the treatment of asymptomatic bruits when compared with the medical ACAS cohort. Surgical treatment of asymptomatic carotid bruits was associated with an $8,000 advantage per quality-adjusted life year (QALY) when compared to medical therapy. The initial cost of endarterectomy was easily overcome when the high cost of care of the patients suffering stroke in the medical arm of the study was taken into consideration [Cronenewett 1997]. In addition, since 26% of the medically treated group underwent endarterectomy for the development of symptoms during the trial period, these expenses were considered part of medical follow-up and further advantaged the savings of primary surgery [Cronenewett 1997]. Further cost savings may be seen in the future as the average length of stay for carotid surgery continues to fall [Collier 1995, Friedman 1995, Harbaugh 1995]. Strokes are a major indication for admission to chronic care facilities with expensive annual support costs. Stroke prevention can save money for both the insurance company as well as the family who may otherwise face financial ruin trying to pay for chronic care that could have been avoided.

The preventive benefit for prophylactic endarterectomy is not easy to demonstrate when the only end point under consideration is a “major disabling” stroke. However, the definition of major disabling stroke is quite different to the patient than it is to the study investigators. For example, a simple opthalmic infarct may seem to be a minor stroke to the study investigators, but if the visual defect signifies that the patient can no longer drive a car, be gainfully employed, read a book, or see his/her granddaughter graduate from high school then the impact may be devastating as perceived by the patient. The current multicenter protocols do not include any quality of life analysis of the end point, i.e. neurologic deficit and the time it takes to rehabilitate, the number of months in therapy, the time lost from work, family, and productive activities. Nor do the studies address the potential of CEA for preventing multi-infarct dementia. So much concern has been placed on the prevention of a major stroke that the emphasis has been lost on prevention of all different types of events. TIAs may seem to be minor to the physician, but they are very frightening to the patient and family who do not know if the deficit will resolve. Multiple TIAs in a crescendo pattern are a heralding sign of carotid occlusion, an event with a known 20% risk of massive stroke. Thus, any study that reports only the presence or absence of TIAs, but does not indicate the pattern and thus the heralding event of a future stroke is missing the whole point of prophylactic therapy.

Vascular surgeons, internists and family physicians all practice prophylactic surgical therapy when seeing a new patient in the office with an abdominal aortic aneurysm even though the studies show that the annualized risk of rupture is low. For example, the risk of rupture for a 5 centimeter abdominal aortic aneurysm (AAA) is roughly 20% over the following 6 years, or 3.3% annualized risk per year [Guirguis 1991]. These numbers are not much different than the 2% to 5% annualized risk of stroke with an asymptomatic carotid stenosis [Hennerici 1987, Autret 1987, O’Holleran 1987, Norris 1991]. However, we all accept that the aneurysm patient is a “time bomb waiting to go off” and no primary care physician refuses to refer a patient for elective aneurysm resection. The concept of trading future cumulative risk over time for a short term immediate (perioperative) risk is practiced every day for aneurysm surgery and yet many of these same referring physicians will not practice this tradeoff for the prevention of stroke. This is likely due to the fact that aneurysms appear to be a “fixable” cause of death and that fatality is nearly guaranteed once it ruptures. Strokes don’t kill every patient and are thus not referred to surgeons as aggressively as aneurysms. However, strokes cause a lifetime of dysfunction and misery. The authors submit that sometimes this is a worse fate for a patient and thus the same tradeoff (short term perioperative risk of less than 3%) to prevent a cumulative risk over many years is analogous to the humanitarian intervention of elective AAA resection and should be offered to all patients with symptomatic or asymptomatic carotid stenosis, ulceration, or focal cerebral infarction. The physical trauma of CEA is certainly far less than AAA resection or other major surgeries. Most CEA patients have little pain and spend only 1 or 2 days in the hospital with a rapid return to full activities [Collier 1995, Friedman 1995, Harbaugh 1995].

It is expensive to manufacture polio vaccine and distribute it to millions. Would anyone argue that the expense of vaccinating millions against polio is worthwhile? At the same time, the incidence of major paralysis from wild polio virus was extremely low (around 2 cases per 100,000 population per year). Millions of dollars are spent every year to continue the vaccination of the US population just to prevent between 20,000 and 60,000 annual cases of disabling neuromuscular polio [Hoeprich 1994, Fauci 1998]. Clostridium tetani causes an extremely rare form of tetanic paralysis and yet millions of dollars are spent on tetanus vaccine to prevent a few thousand cases (4 per million population) per year [Hoeprich 1994]. These may seem like extreme examples and yet the incidence of

these disabling events are minimal compared to the sheer magnitude of ischemic stroke in the population today (over 500,000 new strokes per year). Carotid endarterectomy for asymptomatic bruit may not be totally analogous to polio vaccine, but the mission of the physician to reduce suffering applies in a similar manner. The presence of large multicenter prospective randomized trials which address some of the indications for prophylactic CEA now shift the burden of prevention to the treating physicians. No trial or group of trials will answer all questions. In fact, to reach statistical significance, the trials must focus on discrete endpoints and tight patient selection. The treating physicians in general practice rarely sees such a well defined patient or situation. Thus it rests with the physicians compassion to prevent rather than treat a stroke in order for the patient to be protected in the future.

CONCLUSIONS AND RECOMMENDATIONS

Identification of a carotid bruit or stenotic lesion by duplex is an opportunity to intervene and prevent future neurologic injury. Physicians should perform duplex exams on any patient with a newly diagnosed bruit, recent hemispheric or opthalmic TIA or completed infarct. If the stenosis is less than 50%, angiography may be indicated to detect ulcerative disease which then warrants surgery. For lesions less than 50% without ulceration, antiplatelet therapy and yearly duplex exams will be sufficient. Even with this, there is at least a 25% risk of progression to a high grade stenosis over the next 6 years (see Figure 8 ◎) [Rockman 1997].

For patients who initially present with a lesion of 70% or greater, the treatment is surgery regardless of the presence or absence of symptoms. Once a surgical lesion has been detected, angiography only provides further surgically relevant information in 7% to 13% of cases. If the duplex does not show unusual anatomic features (tortuosity, high lesion, high bifurcation), most patients can be spared the cost and morbidity of angiography without compromising the surgical result. For elderly or medically frail patients, awake CEA under cervical block may provide some advantages. For those patients with severe high grade bilateral disease or uncooperative personalities, general anesthesia with shunting is preferable. Experienced teams have additional strategies that permit selective use of shunts with equally admirable results.

Meticulous debridement of loose plaque material and feathering of the plaque transition at both endpoints will reduce perioperative platelet and thrombotic adherence and corresponding stroke rates. Perioperative treatment with antiplatelet agents (low molecular weight dextran) and elimination (or reduction) of protamine may further lower the incidence of perioperative stroke and transient embolic showers. For patients with small native vessels, an enlargement patch will reduce the incidence of restenosis. Further long term protection and reduction of late events may be possible with lipid lowering therapy and modern antiplatelet agents such as ticlopidine or clopidogrel if the patient can afford the cost of these medications over time. Annual postoperative duplex exams should be performed, mainly to evaluate the contralateral side which often will progress and require surgery a few years later.

With the present state of knowledge there is no reason to deny carotid endarterectomy to a patient with a significant stenosis.

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