Current Status of Carotid Endarterectomy

STEVEN A. KAGAN, M.D.
CHIEF RESIDENT IN GENERAL SURGERY
MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

JONATHAN P. GERTLER, M.D., F.A.C.S.
ASSOCIATE PROFESSOR OF SURGERY
HARVARD MEDICAL SCHOOL
DIVISION OF VASCULAR SURGERY
MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Extracranial cerebrovascular disease (ECVD) is a major contributor to cerebrovascular accidents in the modern era. Cerebrovascular accidents (CVAs) are the third leading cause of death in the United States with 500,000 new or recurrent CVAs each year. Approximately 15,000 people die annually as a direct result of a stroke resulting in a cost of approximately $18 billion when hospital charges and loss of productivity figures are tabulated. The social and economic impact of this disease mandates a unified approach to its management.

The purpose of this review will be to discuss carotid endarterectomy (CEA) in the management of ECVD by defining its role in the management of asymptomatic, symptomatic, and neurologically unstable patients. Clinical strategies, discussion of controversies, and identification of future trends in the medical and surgical management of ECVD will be included. Carotid bifurcation atherosclerosis is the focus of the surgical management of ECVD.

CLASSIFICATION OF NEUROLOGIC EVENTS

Carotid disease can manifest in myriad ways. A transient ischemic attack (TIA) is an episode of temporary focal brain ischemia secondary to vascular disease that clears in less than 24 hours. It is caused by luminal narrowing, superimposed thrombosis and/or microembolization. The diagnosis is clinical and is described by symptoms of visual, motor, or sensory ischemia including speech disturbances. Traditionally, medical therapy has included controlling hypertension, hypercholesterolemia, hypertriglyceridemia, and diabetes, as well as discouraging alcohol consumption, smoking, and the use of oral contraceptives. Medical therapy has relied upon antiplatelet regimens, and a recent collaborative study found that antiplatelet regimens reduce the risk of vascular death by one-sixth and CVA by one-third.[1] A patient who suffers a TIA has a 5% risk of CVA per year or a risk of 24% to 29% over five years.[2,3]

Though many health care professionals think of TIAs as an early warning of impending stroke, it is important to note that up to two-thirds of CVAs may be unheralded. A recent Veterans Administration study noted that one-half of all neurologic events were CVAs without warning.[4] Another study found that 4% of 168 patients with an asymptomatic stenosis developed a CVA before any surgical therapy could be initiated.[5]

Although probably an antiquated term, a transient stroke or reversible ischemic neurologic deficit (RIND) defines a neurologic deficit that persists longer than 24 hours but which resolves completely in less than three weeks. A stroke or established CVA denotes those neurologic deficits that persist beyond three weeks.

MEDICAL THERAPY FOR TIA AND STROKE

A brief review of the current status of medical therapy for ischemic stroke is necessary so that surgical therapy can be discussed in the proper context. More extensive reviews of antithrombotic therapy are recently available.[6,7] Antiplatelet agents are usually the first line of treatment for transient ischemic neurologic deficits. Controversies exist regarding dosage, duration of therapy, and risk-benefit analysis; these discussions are beyond the scope of this review. It is generally accepted that dipyridamole is of no clinical benefit and that ticlodipine is effective, but its side effects (diarrhea and neutropenia) limit its applicability.

Intravenous heparin sodium is indicated in specific clinical scenarios, specifically, crescendo TIAs and stroke-in-evolution. In addition, patients with a high risk of recurrent cardiogenic emboli who suffer TIAs or small ischemic CVAs are also appropriate candidates for heparin therapy. Heparin therapy is not without risk, however, and delayed hemorrhagic transformation of a bland infarct (up to 20% depending on size and extent of CVA) must be weighed against the risk of recurrent CVA (estimated to be 12% within two weeks).[8]

Current recommendations for heparin therapy are made with the assumption that the 75% of CVAs which undergo spontaneous hemorrhagic conversion (visible on CT scan) do so within 48 hours. Usually, a head computed tomography (CT) scan is obtained 48 hours after a neurologic event. A normotensive patient with a small to moderate CVA would receive heparin therapy and an appropriate work-up for ischemic CVA. Anticoagulation is postponed in those patients with large embolic CVAs (greater than 30% of one cortical lobe), especially if hypertensive, for one to two weeks.[8] Thrombolytic therapy in acute ischemic stroke is still in the investigational stage.

SURGERY FOR ECVD

The diagnosis of ECVD includes the use of Duplex scanning, magnetic resonance imaging/angiography (MRI/A), and conventional arteriography. Although arteriography has been the mainstay of preoperative diagnosis, the increasing ability to achieve a high degree of accuracy with duplex scans and/or MRA has largely supplanted angiography in most scenarios.[9,10] MRA is still evolving with regard to differentiating the 60-99% lesion as this entire range may show up as a signal void. However, given the recent results of the prospective studies and the combined power of Duplex and MRA, angiography is reserved usually for complex reconstructions (e.g., arch disease) and re-do situations. For the purpose of this review, the appropriate diagnostic test results are provided in the context of the discussions that follow.

For ease of discussion, we have concentrated on five groups of patients: (1) asymptomatic carotid stenosis; (2) symptomatic, stable carotid stenosis; (3) symptomatic, unstable carotid stenosis; (4) internal carotid occlusion with symptoms; (5) fixed CVA with carotid stenosis.

ASYMPTOMATIC CAROTID STENOSIS

Asymptomatic carotid stenosis is broadly divided into two categories: preocclusive lesions with hemodynamic compromise and ulcerogenic or irregular lesions with embolic potential (all lesions listed as cross-sectional area stenosis unless otherwise noted). In unselected populations, 54% of patients older than 65 years had some degree of carotid atherosclerosis greater than 10%; 4.6% had lesions greater than 50%; and fewer than 1% had lesions greater than 80%.[8] In patients with carotid bruits, the prevalence of more severe carotid disease increases appropriately. Chambers et al. studied 500 patients and found that 52% of patients had greater than 30% stenosis; 23% had greater than 50% stenosis; and 5% had lesions greater than 75%.[11]

An asymptomatic carotid bruit was thought to be a benign finding until improved noninvasive testing stratified the patients by degree of stenosis, and several studies invalidated this conclusion.[12,13] Roederer et al. found that disease progression of an asymptomatic carotid lesion was associated with a significant risk of TIA and stroke.[14] In addition, progression to greater than 80% stenosis was associated with a 35% chance of occlusion or neurologic symptoms within six months.[14] Chambers and Norris found that stenosis greater than 75% or disease progression within six months (by duplex scanning) was an important predictor of neurologic events. They also found that aspirin therapy did not alter these outcomes.[15] The combined TIA and stroke rate for stenoses greater than 75% was 10.5% per year (greater than 75% were ipsilateral to the stenotic artery); the stroke rate alone was 1.3% per year for lesions less than 75% and 3.3% per year for those greater than 75% occlusive.[16] Plaque morphology may also be a predictive factor for neurologic events.

Obviously, carotid endarterectomy had to prove itself to be better than medical therapy in order to gain acceptance as a stroke prevention strategy. The Stroke Council of the American Heart Association (AHA) has recommended that the combined operative morbidity and mortality due to stroke for asymptomatic carotid disease be less than 3%.[17] A review by Colburn and Moore of studies since 1971 documented a perioperative stroke rate of less than 2% and a mortality of less than 1% in 2000 patients operated on for asymptomatic stenosis.[18] Similarly, Freischlag et al. documented excellent results with a 10-year analysis showing a 0.6% per year rate of TIA and a 0.7% per year stroke rate after CEA. In addition, patients with concomitant coronary disease were found to live long enough to benefit from CEA.[19]

There have been five prospective randomized trials comparing medical therapy to CEA for asymptomatic carotid stenosis. The first study (Claggett et al., 1984) is of historical interest only as no conclusions could be

reached secondary to small sample size and short follow-up.[20]

The Mayo Clinic trial in 1992 also lacked predictive value for two reasons. The study was terminated because of excessive myocardial infarction in the surgical group (for reasons which remain unclear), and too few cerebral events occurred in the study population.[21]

The CASANOVA (Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin) study was the first multicenter randomized European trial. The authors concluded that CEA could not be recommended to asymptomatic patients with stenosis less than 90% by linear diameter criteria;[22] however, the study had several serious design flaws that invalidated its conclusions. First, the study excluded patients with greater than 90% stenosis (all of these patients underwent carotid endarterectomy). Second, over one-half of the patients in the medical group underwent CEA for either symptoms or disease progression; this was not considered a study endpoint or a failure of medical therapy. Lastly, if a patient had bilateral carotid lesions greater than 50% stenotic, the more severe lesion received CEA and the other was treated medically.

The Veterans Administration study published in 1993 was the first multicenter randomized, prospective controlled trial in the United States. Four hundred forty-four male patients with greater than 50% linear stenosis of the internal carotid artery were randomized to the best medical or surgical therapy.[4] The combined incidence of ipsilateral neurologic events (TIA and stroke) was significantly reduced in the surgical group (20% versus 8%). However, the small sample size diminished the power of the study; in addition, the study patients with endpoints of CVA, TIA, and transient monocular blindness were classified as a single group. These outcomes are not equivalent; however, this is believed to be due to the small number of patients in the study and the higher than expected perioperative morbidity. No significant difference was identified when the groups were analyzed for stroke alone. Also, no significant differences were identified in patients with stenoses between 50% and 75%.

The ACAS study (Asymptomatic Carotid Artery Stenosis Trial) is the largest ongoing, randomized, prospective multicenter trial studying the efficacy of CEA in asymptomatic patients with greater than 60% linear diameter reduction in the internal carotid artery. Participating centers must document a combined morbidity and mortality of less than 3% to participate. The primary endpoints include any stroke or death within 30 days of surgery or any ipsilateral stroke or stroke-related death thereafter. A clinical alert issued on October 3, 1994, from the NIH stated that "carotid endarterectomy is beneficial with a statistically significant absolute reduction of 5.8% in the risk of the primary endpoint of stroke within five years and a relative risk reduction of 55%." This has led to the adoption of the recommendation that greater than 60% asymptomatic lesions undergo repair in patients with otherwise excellent life expectancies.

The recent publication of the ACAS study[23] has clarified the circumstances in which carotid endarterectomy is warranted in asymptomatic disease. It is apparent after review of the data that an aggregate risk reduction of 55% vs. medical therapy alone is present if properly selected patients with a greater than 60% stenosis undergo CEA in combination with maximal medical therapy for stroke prevention and risk factor reduction. The overall perioperative morbidity can be reduced further by the use of noninvasive imaging alone to determine degree of diameter stenosis. Importantly, the diameter reduction of the carotid artery is probably not the only determining factor of stroke propensity, and further work characterizing plaque composition and ultrasonic appearance as well as better definition of intracranial hemodynamics may all hold promise for patient risk stratification.

The ACAS study was conducted in centers where a low surgical morbidity and mortality could be achieved. This remains the single most important factor in recommending CEA in either symptomatic or asymptomatic patients. Ongoing quality assurance review of CEA programs is necessary to ensure that the expected benefit is truly conferred on individual patients.

SYMPTOMATIC CAROTID DISEASE: STABLE

Stable symptomatic carotid disease is defined as hemispheric TIAs or small, nondisabling strokes. The AHA has recommended that for CEA to be effective stroke prevention for patients with TIAs, the combined perioperative neurologic morbidity and mortality must not exceed 5%.[24] There are three important trials which demonstrate the benefit of successful surgical intervention.

The NASCET (North American Symptomatic Carotid Endarterectomy Trial) study demonstrated in a randomized fashion that patients with greater than 70% linear arteriographic stenosis of the ICA ipsilateral to the symptomatic hemisphere showed a statistically significant benefit from surgery (compared to medical therapy) in all of the endpoint categories (i.e., any stroke, any ipsilateral stroke, major ipsilateral stroke, and any major stroke). The 70-99% portion of the trial was stopped at 18 months, and an alert was issued for symptomatic patients with greater than 70% stenosis. The data for lesions less than 70% was inconclusive at that time; interestingly, the presence of plaque ulceration or a contralateral stenosis or occlusion was associated with a worse prognosis in the medical and surgical groups.[25] Intraluminal thrombus was associated with a 25% stroke risk regardless of randomization.[25]

The ECST (European Carotid Surgery Trial) study had a slightly different study design but derived conclusions similar to NASCET. The inclusion criteria for symptoms (six months versus three months) and stenosis measurement (carotid bulb diameter versus distal ICA as reference point) did not significantly affect the results. Despite a higher perioperative stroke and death rate of 7.5%, the surgical group (with greater than 70% linear arteriographic stenosis) benefited in all endpoint categories compared to the medical group.[26] Again, like the NASCET study, the data on lesser degrees of carotid stenosis did not reach statistical significance at the same time as the greater than 70% group, and further clarification of this population is an ongoing study.

A Veterans Administration study in 1991 was terminated when a review of the preliminary data corroborated the NASCET and ECST results for high-grade lesions.[27] Additionally, the VA study noted that crescendo TIA patients had significantly improved outcomes with surgery than with medical therapy

(see below). Moore's review in 1992 cited several reports documenting an annual stroke rate of 1% to 2% per year in patients undergoing successful CEA for TIAs.[28]

SYMPTOMATIC CAROTID STENOSIS: UNSTABLE

The proposed CHAT (current status, history, artery, and target) classification by the Subcommittee on Reporting Standards for Cerebrovascular Disease has not been widely applied in clinical practice.[29] For the purposes of this review, we will rely upon less precise but familiar terminology. We have defined TIA, RIND, and CVA previously, but several other terms require definition. A progressive stroke is defined as a progression of a neurologic deficit for more than 24 hours. A stroke-in-evolution (SIE) is a gradual progression of a neurologic deficit without any fluctuation of deficit. Stuttering hemiplegia is a fluctuation of a neurologic deficit superimposed on a progressing stroke with progressing deficit over at least 24 hours. Lastly, crescendo TIAs (CTIAs) refer to patients with more frequent TIAs or more severe TIAs implying a broadening deficit or increasing frequency of attacks.[30] These syndromes represent unstable clinical situations that often demand a more aggressive surgical approach.

SIE and CTIA usually represent pre-occlusive carotid lesions with an atherosclerotic plaque associated with thrombus formation. Severe ulceration with platelet thrombus formation can produce a similar clinical scenario. Evolving stroke syndromes have traditionally had a grim prognosis with good recovery in only 2% to 12% of patients. A review of older data revealed that 40% to 70% of patients had a major neurologic deficit and 15% to 55% succumbed to their stroke despite maximal medical and surgical therapy.[31] There was no clear benefit of aspirin or heparin therapy but some patients did stabilize their neurologic deficit with medical therapy.[32,33] Early results of CEA in the setting of acute stroke or carotid occlusion were similarly abysmal.[34,35] Hemorrhagic conversion of bland infarcts and acute re-occlusions were some of the causes of the poor surgical outcomes.

Advances in medical, anesthetic, and surgical care are most likely responsible for the improved results in recent years with these neurologically unstable patients. Two recent studies demonstrate improvement in neurologic function in 80%, deterioration in 10% to 15%, and death in 5% to 10% of patients treated with a combination of aggressive medical and surgical treatment.[31,36] In a review of our experience at the Massachusetts General Hospital, 93% of patients improved, 4.3% deteriorated, and an overall 2.9% mortality was achieved.[36] This is in marked contrast to historic views of unstable neurologic deficits treated by surgery. Vascular surgeons will see increasing referrals of acutely symptomatic patients since the NASCET study documented improved results with elective surgery, and it is important to recognize that surgery in select circumstances offers a distinct advantage over expectant and medical therapy alone.

A multidisciplinary approach to these patients seems warranted. We recommend evaluation of the neurologically unstable patient and immediate heparinization (if there are no contraindications); a head CT scan or MRI should be obtained to rule out hemorrhage, subdural hematoma, or other intracranial pathology other than central nervous system ischemia; rapid duplex exam and/or diagnostic arteriography is carried out and immediate CEA performed for an appropriate carotid lesion. In our limited series, some acute carotid occlusions do improve with an aggressive surgical approach. Acute, severe neurologic deficits (including dense hemiplegias) secondary to acute ICA occlusion and intracranial emboli respond poorly to surgical intervention, whereas fluctuating neurologic deficits, even when dense, if due to hemodynamic issues, can be treated well by surgery when compared to expected outcomes. Anticoagulation with heparin is indicated if there is no evidence of hemorrhage on brain imaging studies.

With respect to surgical techniques, continuous anticoagulation with intravenous heparin sodium and minimal carotid dissection (to decrease embolization risk) are crucial maneuvers. The ICA is not cross-clamped initially but is opened beyond the plaque and allowed to back-bleed. Embolectomy catheters may be used at this point if no back-bleeding occurs. A shunt is used, and a postoperative arteriogram is usually recommended to document intracranial patency.[36]

CHRONIC INTERNAL CAROTID OCCLUSION WITH SYMPTOMS

Subacute occlusion of the ICA may lead to hypoperfusion of the ipsilateral hemisphere when collateral blood flow through the Circle of Willis is insufficient. Similarly, occlusion may lead to clot propagation to the distal ICA with resultant embolization–this may occur days to weeks following the ICA occlusion. Lastly, embolization through a patent external carotid artery (ECA) or hypoperfusion through a stenotic ECA may produce symptoms of cerebral ischemia. The mechanism of ischemia is important as this will dictate the surgical options (for example, a contralateral ICA stenosis with an intact Circle of Willis will lead to the recommendation of contralateral CEA). Stroke due to an ICA occlusion carries a 10% stroke risk per year; there is no clear benefit of surgery if the patient is asymptomatic with an ICA occlusion.

Chronic anticoagulation for six months is believed warranted for a new ICA occlusion. While there is no data to support use of warfarin in patients with atherothrombotic disease of extracranial arteries, warfarin therapy is logical to prevent clot propagation and embolization in asymptomatic internal carotid occlusion. Contralateral CEA is indicated in the correct anatomic setting, and Hertzer et al. provide evidence that successful CEA in this clinical situation reduces the incidence of late strokes.[37] The extracranial-intracranial bypass trial demonstrated prospectively that patients with ICA occlusion treated with aspirin alone had a stroke rate of 15% at one year.[39]

ECA endarterectomy is indicated in symptomatic patients with ICA thrombosis and hypoperfusion of ECA to ICA collaterals with a high-grade ECA stenosis documented by arteriography. ECA endarterectomy may also be indicated in patients with a large stump formed by the occluded ICA, which serves as an embolic source through ECA collaterals, in patients with ECA stenosis.[38] The technique involves removal of the ICA stump with creation of a smooth transition from the common to the external carotid artery with patch angioplasty of the ECA orifice. Completion arteriography may be help-

ful.[37] In a collective review of over 200 reported patients, we found that 83% of patients were rendered asymptomatic and 7% improved following the procedure. The perioperative mortality was 3% and the neurologic complication rate 5%. The best results were obtained in patients with specific hemispheric or retinal symptoms.

Extracranial–intracranial bypass deserves historical mention only. Although the procedure has been shown to be of no benefit in previous reports,[39] it may be used as a last resort for severely symptomatic patients with appropriate anatomy.

FIXED STROKE WITH MINIMAL DEFICIT

This last group of patients likely represents a composite of patient categories. Part of the confusion stems from the fact that brain CT scans of asymptomatic patients reveal a 20% incidence of recent cerebral infarction. Similarly, patients with TIAs have a 33% incidence of prior cerebral infarction on brain CT scans.[15,40] We will discuss patients with prior cerebral infarction who have a mild functional neurologic deficit.

Patients with a prior hemispheric stroke have a subsequent stroke risk of 5% to 20% per year, and an average five year recurrence rate of 50%. Medical therapy yields a 10% to 15% stroke rate per year. After successful CEA, the recurrent stroke rate is 2% per year.[28] The NASCET and VACT studies confirm the benefit of CEA in patients with fixed stroke and an ipsilateral high-grade ICA lesion.[25,27]

The criteria for surgery include a patent ICA ipsilateral to the affected hemisphere; a degree of stenosis and/or ulceration consistent with current standards of severity to justify CEA; and a suitable recovery from prior stroke to benefit from further surgical prophylaxis.

The timing of CEA after stroke is another area of debate. Traditionally, a six-week waiting period has been advocated to allow full neurologic recovery and resolution of cerebral edema. Modern CT scanners and MRI may alter this previously accepted practice, as we can better judge the response of the central nervous system to ischemic injury. Some studies show no increased morbidity for CEA at less than six weeks after stroke,[41] and others show increased neurologic morbidity and mortality when significant changes on brain CT scan are noted in the setting of recent stroke.[17] Obviously, each patient's care must be individualized when all studies are not in agreement. The ideal patient for CEA is a neurologically stable individual with serial CT scans showing no cerebral hemorrhage and a cerebral arteriogram, MRA, or duplex consistent with a greater than 70% lesion.

CONCLUSIONS

We recognize that all patients do not fit the defined categories outlined above, but we have attempted to construct a framework to deal effectively with carotid disease. CEA has been clearly shown to be an effective means of stroke prevention in symptomatic and asymptomatic patients with appropriate carotid artery lesions. Selective patients with symptomatic ICA occlusion derive benefit from successful contralateral CEA or alternative revascularization procedures, as do patients with prior stroke. We await the further elucidation of lesser degrees of symptomatic carotid stenoses and clarification of the data from the asymptomatic trials.

The Stroke Council of the AHA guidelines for morbidity and mortality in CEA patients appear reasonable.[29] At present, practicing neurologists, neurosurgeons, and vascular surgeons must make decisions based on the best available data. The care of the patient must be individualized, yet guided by the retrospective data and randomized trials presently available. STI

REFERENCES

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.
2. Dennis M, Bamford J, Sandercock P, et al. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. Stroke 1990;21:848-853.
3. Whisnant JP, Matsumoto N, Elueback LB. Transient cerebral ischemic attacks in a community. Rochester, Minnesota, 1955 through 1969. Mayo Clin Proc 1973; 48:194-198.
4. Hobson RW II, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328:221-227.
5. Humphries AW, Young JR, Santilli PM, et al. Unoperated, asymptomatic significant internal carotid artery stenosis. Surgery 1976;80:695.
6. Barnett HJ, Eliasziew M, Meldrum HE. Drugs and surgery in the prevention of ischemic stroke. N Engl J Med 1995;332:238-248.
7. Sherman DG, et al. Antithrombotic therapy for cerebrovascular disorders. Chest 1992;102(4 Suppl):5295-5375.
8. Mitsias P, Welch KMA. Medical therapy for TIAs and ischemic stroke. In: Ernst CB, Stanley JC, eds. Current therapy in vascular surgery. 3rd ed. St. Louis: Mosby Year-Book; 1995. p 1-45.
9. Blakeley DD, Oddone EZ, Hasselblad V, et al. Noninvasive carotid artery testing. A meta-analytic review. Ann Intern Med 1995;122:360-367.
10. Gertler JP, Cambria RP, Kistler JP, et al. Carotid surgery without arteriography: noninvasive selection of patients. Ann Vasc Surg. 1991;5:253-256.
11. Chambers RB, Norris JW. Outcome in patients with asymptomatic neck bruits. N Engl J Med 1986;315:860-865.
12. Heyman A, Wilkinson WE, Heyden S, et al. Risk of stroke in aymptomatic persons with cervical arterial bruits. A population study in Evans County, Georgia. N Engl J Med 1980;302:838-841.
13. Wolf PA, Kannel WB, Sarlie P, et al. Asymptomatic bruit and risk of stroke: the Framingham study. JAMA 1981;245:1442-1445.
14. Roederer GO, Langlois YE, Jager KA, et al. The natural history of carotid artery disease in asyptomatic patients with cervical bruits. Stroke 1984;15:605-613.
15. Chambers RB, Norris JW. Outcome in patients with asymptomatic neck bruits. N Engl J Med 1986;315:860-865.
16. Norris JW, Zhu CZ, Bornstein NM, et al. Vascular risks of asymptomatic carotid stenosis. Stroke 1991;22:1485-1490.
17. Ricotta JJ, Ouriel K, Green RM, et al. Use of computerized cerebral tomography in selection of patients for elective and urgent carotid endarterectomy. Ann Surg 1985;202:783-787.
18. Colburn MD, Moore WS. The risk of carotid endarterectomy in asymptomatic patients. In: Bernstein EF, Callow AD, Nicolaides AN, et al, eds. Cerebral revascularization. London: Med-Orion; 1993. p 523.
19. Freischlag JA, Hanna D, Moore WS. Improved prognosis for asymptomatic carotid stenosis with prophylactic carotid endarterectomy. Stroke 1992;23:479-482.
20. Clagett GP, Youkey JR, Brigham RA, et al. Asymptomatic cervical bruit and abnormal ocular pneumoplethysmography: a prospective study comparing two approaches to management. Surgery 1984;96:823-830.
21. Mayo Asymptomatic Carotid Endarterectomy Study Group. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Clin Proc 1992;67:513-518.
22. The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. Stroke 1991;22:1229-1235.

23. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study: endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-28.
24. Beebe HG, Clagett GP, DeWeese JA, et al. Assessing risk associated with carotid endarterectomy. Stroke 1989;20:314-315.
25. North American Symptomatic Carotid Endarterectomy Trial Collaborators: beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-453.
26. European Carotid Surgery Trialists' Collaborative Group: MRC European carotid surgery trial: interim results for symptomatic patients with severe (70%-99%) or with mild (0%-29%) carotid stenosis. Lancet 1991; 337:1235-1243.
27. Mayberg MR, Wilson SE, Yatsu F, et al. For the Veterans Affairs Cooperative Studies Program 309 Trialist Group: carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. JAMA 1991;266:3289.
28. Moore WS. Carotid endarterectomy for prevention of stroke. West J Med 1993;159:37-43.
29. Baker JD, Rutherford RB, Bernstein EF, et al. Suggested standards for reports dealing with cerebrovascular disease. Subcommittee on Reporting Standards for Cerebrovascular Disease, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/ North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg 1988;8:721-729.
30. Greenhalgh RM. Carotid Stenosis with Unstable Fluctuating Neurologic Deficit. In: Brewster DC, ed. Common problems in vascular surgery. Year Book Medical Publishers; 1989. p 13-21.
31. Meyer FB, Sundt TH Jr, Piepgras DG, et al. Emergency carotid endarterectomy for patients with acute carotid occlusion and profound neurologic deficits. Ann Surg 1986;203:82-89.
32. Biller J, Bruno A, Adams HP Jr, et al. A randomized trial of aspirin or heparin in hospitalized patients with recent transient ischemic attacks. A pilot study. Stroke 1989;20:441-447.
33. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-453.
34. Blaisdell WF, Clauss RH, Galbraith JG, et al. Joint study of extracranial arterial occlusion. IV. A review of surgical considerations. JAMA 1969;209:1889-1895.
35. Wylie EJ, Hein M, Adams JE. Intracranial hemorrhage following surgical revascularization for treatment of acute strokes. J Neurosurg 1964;21:212-215.
36. Gertler JP, Blankensteijn JD, Brewster DC, et al. Carotid endarterectomy for unstable and compelling neurologic conditions: do results justify an aggressive approach? J Vasc Surg 1994;19:32-42.
37. Hertzer NR, Flanagan RA Jr, Beven EG, et al. Surgical versus nonoperative treatment of symptomatic carotid stenosis. Surgery 1986;204:154-162.
38. Gertler JP, Cambria RP. The role of external carotid endarterectomy in the treatment of ipsilateral internal carotid occlusion: collective review. J Vasc Surg 1987;6:158-167.
39. Barnett WJM. Extracranial-Intracranial Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. N Engl J Med 1985;313:1191-1200.
40. Street DL, O'Brien MS, Ricotta JJ, et al. Observations on cerebral computed tomography in patients having carotid endarterectomy. J Vasc Surg 1988;7:798-801.
41. Whittemore AD, Ruby ST, Couch NP, et al. Early carotid endarterectomy in patients with small, fixed neurologic deficits. J Vasc Surg 1990;11:45-52.