Indications for treatment in Carotid artery disease (CAD)

Dr. Nikolaos Melas, PhD

Vascular and Endovascular Surgeon

Military Doctor
Associate in 1st department of Surgery,
Aristotle University of Thessaloniki, Greece
Associate in Interbalcan Medical Center

Introduction

Stroke is one of the major causes of death and disability in most developed countries.(1,2) It continues to be the third leading cause of death in the United States each year.(2) It also represents a major cause of morbidity and contributes heavily to health care costs throughout the world.(3-6) Reviews of the financial impact of stroke for calendar year 1999 in the United States were estimated to be $45.3 billion of direct and indirect cost. (7) In Australia, there are approximately 40,000 new stroke victims per year, costing the community approximately $1.3 billion in accrued lifetime costs.(8) The current annual incidence of stroke is about 195 per 100,000 people, and the incidence increases with increasing age. Thus, in men aged 55 to 64, the incidence is 300 per 100,000 and increases dramatically in the age group 75 to 84, with an incidence of 1,440 per 100,000.(9) Previously reported incidence rates for transient cerebral ischemic attacks (TIAs) and stroke from the Rochester Epidemiology Project, were even higher .(10-13) *(table 1,2)*

Of the patients who survive the initial stroke, about two thirds will be disabled to some degree. Half of the survivors will live for about five years, and a third of the survivors require prolonged inpatient rehabilitation. (14) The recognition of the correlation between carotid bifurcation disease and ischemic hemispheric stroke from a thromboembolic event was long in coming. Nowadays, extracranial cerebrovascular disease is estimated to be the cause of 70% of ischaemic stroke. (15-17)

Today in the treatment strategy of carotid artery disease some important issues are still under discussion :1) medical therapy versus carotid endarterectomy in terms of which patient and which lesion for which treatment and 2) recently the advent of Carotid artery angioplasty and stenting (CAS) enriched the treatment abilities, causing even more doubt and debate concerning the best treatment for carotid artery disease. In this report we shall discuss and analyze all available data,

including prospective randomized trials and results by expert panels and shall summarize the current indications for carotid endarterectomy and CAS for the treatment of extracranial cerebrovascular disease.

Guidelines for carotid endarterectomy

Since the first reported operation on the carotid bifurcation in 1954, however, there has been a rapid rise in the use of carotid endarterectomy as a strategy for stroke prevention. The annual number of operations rose from 17,000 in 1971 to about 100,000 in 1984.(18) The enthusiasm for the surgical procedure continued to grow until 1984 when a pivotal issue of the journal Stroke appeared (volume 15, number 6) questioning the efficacy and use of carotid endarterectomy.(19-22) This collection was prefaced by an editorial entitled "Carotid Endarterectomy- An Expression of Concern," written by three eminent neurologists.(23) This challenge attracted much attention by scientists, causing sufficient doubt to be cast on the efficacy of this surgical procedure and resulting in a major cutback in its use over the next few years. In addition, and as a consequence of this heated debate, a series of prospective randomized trials begun or further supported and various interest groups got together to develop appropriateness initiatives or practice guidelines for the use of carotid endarterectomy. In 1991 NASCET Collaborators (24) and ECST Collaborative group (25) published their results, proving the superiority of carotid endarterectomy over best medical treatment for prevention of stroke in symptomatic patients with significant carotid artery stenosis. Soon afterwards, ACAS Executive Committee (26) in 1995 released data proving carotid endarterectomy to be the preffered choise of treatment against best medical therapy for specific asymptomatic patients. Wesley S. Moore, first reviewed in 1993 current data and published “Carotid Endarterectomy for Prevention of Stroke” giving appropriate guidelines for this critical issue. (27) In 1995 the American Heart Association released an article entitled “Guidelines for Carotid Endarterectomy” (28) and in 1997 the Canadian Neurosurgical Society published Guidelines for the use of carotid endarterectomy.(29) The impact of these prospective randomized trials caused immediate increase in the number of carotid endarterectomies performed annually in the USA, from 70.000 in 1989 to 150.000 in 1998. Similar increase was noticed in other vascular communities as well.

Today, carotid endarterectomy is considered the treatment of choise for selected symptomatic and asymptomatic patients with severe carotid artery stenoses. But do we really have all the essential data from evidence based medicine to justify such a procedure, performed so often; The answer is rather simple. If the results of carotid endarterectomy are superior than those from best medical treatment alone, regarding stroke prevention, then the operation is mandatory. Obviously these results should be supported by prospective randomized trials or meta-analysis, otherwise it should be mentioned so as the interpreter to make its own conclusion.

In the following text we shall revise current indications for carotid endarterectomy and clarify the level of evidence supporting each indication, mainly based on the American Heart Association and Canadian Neurosurgical Society publications. (28-29)

Symptomatic Patients

Natural History

Profound study of the natural history of each and every disease, is mandatory in order to clarify if the profit of a proposed treatment out weights the risks. Symptoms related to carotid artery lesions include transient or persistent monocular visual loss, hemispheric transient ischemic attacks (TIAs), and ischemic stroke. Retrospectively, it is difficult to assign mechanism-specific stroke risk based on currently available data since an increasing number of recognizable factors that may affect subsequent stroke risk were not considered in the original studies. These include type of event, frequency of events, percent stenosis of the carotid artery in question, and characteristics of the plaque producing the lesion. Despite these recognized limitations, several observations are possible.(28)

Patients with TIAs related to severe carotid stenotic lesions are at risk of stroke at the rate of 12% to 13% within the first year after onset of symptoms, with a cumulative stroke risk of approximately 30% to 35% at the end of 5 years. Those patients with hemispheric TIAs, recent TIA, increasing frequency of TIA, or high-grade stenosis have stroke rates that are probably higher than those with a remote or single event or lesser stenosis.(30-31) Similar findings have been noted by D.O. Wiebers, MD, and H.J.M. Barnett, MD (unpublished data from the Rochester Epidemiological Project and NASCET). Patients who have had a stroke continue to be at risk for subsequent strokes at the rate of 5% to 9% per year, with approximately 25% to 45% of patients having another stroke within 5 years of the original event.(32-34)

Plaque characteristics may significantly affect subsequent ischemic events. Echolucent and heterogeneous plaques have a high content of lipid or intraplaque hemorrhage that may produce plaque ulceration, leading to a greater embolic potential.(35-37) In a study of asymptomatic patients with carotid artery disease (CAD) only 20% to 30% of these patients had echolucent plaques, in contrast to symptomatic patients, in whom echolucent plaques were present in 70% of the cohort.(38-41) Cranial computed tomography of patients with carotid artery plaques demonstrates a 36% frequency of cerebral infarction in patients with echolucent plaques but only a 6% frequency in patients with echogenic plaques, suggesting that patients with echolucent or heterogeneous plaques have a neurological event rate two through four times greater than those with echogenic plaques.(38-42)

An examination of the control group of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) study demonstrated that patients with high-grade carotid stenosis in the absence of angiographic evidence of ulceration had a 2-year stroke rate of 17% in contrast to a 2-year stroke rate of 30% when ulceration was present with similar degrees of stenosis.(24) Finally, the percent stenosis present in the proximal internal carotid artery is the most important plaque characteristic for subsequent neurological events, including stroke. This is true in both asymptomatic and symptomatic patients. The NASCET study control group demonstrated that for

every 10% increase in stenosis beyond 70%, there was an increased rate of subsequent stroke risk.(24)

Patient Evaluation

Atherosclerosis is a difuse, multisectional and generalized disease. Patients who manifest symptoms from one vascular bed, have already atherosclerotic lesions in other vessels as well, in a subclinical-silent stage. Atherosclerotic carotid artery occlusive disease is part of this systemic disease. Evaluation of patients with ischemic strokes, TIAs, and suspected CAD should include a thorough history for the presence of coronary and peripheral vascular occlusive disease and stroke risk factors such as hypertension, tobacco and other substance abuse, use of oral contraceptives, hyperlipidemia, and diabetes mellitus. Neurological examination, blood pressure measurement in both arms and, when appropriate, a test for postural hypotension, measurement of pulse rate and rhythm, cardiac auscultation, and peripheral vascular examination are essential. Arterial pulses and bruits should be described.

Laboratory evaluation must include tests that define the presence, location, and severity of CAD. Ultrasound using pulsed Doppler has been accepted by some investigators in qualified laboratories as a satisfactory means of determining the severity of carotid artery stenosis. Duplex examinations (combined B-mode ultrasound and pulsed Doppler), when performed in settings in which the results have been consistently well validated by comparison with standard angiography, is an accepted and accurate technique for determining the severity of carotid artery stenosis. However, there is a risk of calling a high-grade stenosis total occlusion. This risk has been reported to be as high as 14% (false-positive rate)(43) or as low as 1%,(44) with a spectrum in between.(45-47) Therefore, it is premature to make a definitive statement, since these techniques are still in evolution. On the other hand, u/s examination has the ability to characterize the echogenecity and the morphology of the plaque which is of grate importance to determine which lesion is embologenic (echolucent or heterogeneous lesions have greater embolic potential).(35-37) Magnetic resonance angiography can also be helpful in providing images of the carotid artery, but at the present level of development it can overestimate or underestimate the severity of stenosis. Standard contrast angiography remains the gold standard for providing accurate images of the carotid arteries, the proximal vessels, and the intracranial circulation. In some patients being considered for carotid endarterectomy, duplex examination (in a laboratory whose accuracy has been validated) or duplex examination combined with magnetic resonance angiography may suffice for determining the severity of the extracranial portion of CAD, although arteriography remains the most reliable method of assessing the precise degree of carotid artery stenosis.

Measurement of carotid artery stenosis

It is important to define how the degree of stenosis is measured. At present we recommend that decisions concerning a patient's suitability for CEA be based on catheter cerebral angiography and that the stenosis be measured according to the NASCET method.(24,29) In this method, stenosis is expressed as a percentage from the angiographic view showing the greatest stenosis. The narrowest diameter of the

residual lumen (N) is compared with the luminal diameter of the internal carotid artery well beyond the bulb (D), and the percentage of stenosis is calculated as (1-N/D) X 100 *(Fig. 1)* (level I evidence, grade A recommendation). This is the measurement used in NASCET and the Asymptomatic Carotid Atherosclerosis Study (ACAS). (48) We hope that less invasive investigations such as magnetic resonance angiography (MRA) (49) or 3-dimensional computed tomography (CT-angiography) (50) will be developed and be as accurate as catheter angiography, which they could then replace. Until then, whenever possible, patient management decisions should be based on the accurate and certain measurements obtained from cerebral angiography; in particular, ultrasonographic examinations alone should not form the basis of an important management decision (51), but only as an adjunct for determination of plaque echogenicity. In patients with severe peripheral vascular disease that precludes safe cerebral angiography, and patients who refuse angiography, it may be reasonable to formulate treatment on the basis of the combined results of carotid ultrasonographic investigation and MRA (level III evidence).

Additional studies that provide information about flow and/or pressure in the ophthalmic and intracranial carotid artery branches, such as transcranial Doppler, oculoplethysmography, and single-photon emission-computed tomography are also helpful for evaluating the severity and significance of CAD. Blood tests including hematocrit and platelet count are essential; prothrombin time and activated partial thromboplastin time are desirable. Brain imaging with computed tomography or magnetic resonance imaging is essential for patients with strokes and may be useful in patients with TIAs or asymptomatic patients who are considered for surgery. An electrocardiogram is mandatory. Additional cardiac evaluation and consultation should be considered to seek potential cardiac sources of embolism that might have caused the brain ischemia and to assess the presence and severity of coexistent coronary artery disease. Neurological consultation is important for patients with neurological symptoms or signs. Some patients with concurrent medical illnesses (eg, pulmonary, renal, hematologic, hepatic, and other diseases) will require an evaluation to assess surgical risk.

Results of CEA for Symptomatic CAD

Retrospective Reviews

The cumulative (immediate and long-term) results following carotid endarterectomy with respect to the incidence of subsequent stroke are influenced by the initial 30-day operative stroke morbidity and mortality. These rates are also influenced by the indication for surgery. Patients experiencing TIAs are at somewhat lower operative risk than patients who have had a prior stroke with varying degrees of recovery. A review of four recent series reporting operative experience in the management of symptomatic patients demonstrates a range of combined mortality and stroke morbidity from a low of 2% to a high of 6.1%.(63-66) Aggregating the results of the four series (modified meta-analysis) provided the opportunity to look at the results of

treating 1498 patients with symptoms of TIA or prior stroke with a combined 30-day operative mortality and stroke morbidity of 2.74%.(63-66) Further insight into the risk of surgery is gained from data provided by participants in the ACAS. A review of the experience of surgeons applying to participate in this study provided an experience with 5641 carotid endarterectomies performed for a variety of indications with a combined operative mortality and stroke morbidity rate of 2.23%.(67) Thus, the overall effect of carotid endarterectomy on immediate and subsequent stroke risk will be materially influenced by both patient selection and selection of the operating surgeon.

Late Stroke Risk After CEA in Symptomatic Patients

Patients who have undergone successful carotid endarterectomy for the indication of TIA (without perioperative stroke) continue to be at risk for subsequent ipsilateral hemispheric stroke at the rate of 1% to 2% per year.(68-74) Patients who have had successful carotid endarterectomy for the indication of prior stroke, without neurological complication, are at risk for subsequent ipsilateral stroke at the rate of 2% to 3% per year.(63,75-80)

Position Statements

A number of organizations (81-86) have issued position statements on indications for carotid endarterectomy; for the purposes of this document, statements by the following three organizations were reviewed: the Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS),(84) the Rand Corporation,(85) and an ad hoc committee of the American Medical Association (AMA) (D.B. Matchar, MD, C.T. Huesgen, MD, W.S. Moore, MD, unpublished data). The AMA subcommittee that reviewed the SVS/ISCVS recommendations and compared them with the Rand panel found that the two statements were in substantial agreement.

Does CE benefit symptomatic patients? (Indications for Carotid Endarterectomy Based on Prospective Randomized Trials)

Three major trials (ECST, NASCET, and VA309) evaluated effects of carotid endarterectomy (CEA) for preventing stroke in patients with a recent TIA or ischemic stroke in the distribution of a proximal internal carotid artery stenosis. To date, Two *Class I* studies have been completed: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) 2-4 A third well-designed study, the Veterans Affairs Cooperative Studies Program 309 Trial, was stopped prematurely after the initial NASCET results were announced.5 In the symptomatic studies, patients were classified as symptomatic if

they had a carotid distribution TIA or nondisabling stroke in the preceding 6 months (originally 4 months in NASCET), and these patients were assigned to best medical therapy (BMT) or BMT + CE. Aspirin was the recommended antithrombotic agent. In NASCET, patients were required to have a 5-year life expectancy to ensure adequate follow-up in both groups. *Table 4* (Overview of symptomatic trials) provides a summary of the main features of the two completed symptomatic studies, NASCET and ECST. (222)

In the NASCET Study, 3 years after entering the first patient and after 659 patients with stenoses 70% or greater diameter reduction had been randomly selected, the "stopping rules" were triggered by the Data and Safety Monitoring Board of the National Institute of Neurological Disorders and Stroke. This occurred because there was a clear benefit in favor of carotid endarterectomy. The life table estimate of cumulative stroke risk in the distribution of the study artery at 2 years was 26% in 331 medical patients in contrast with 9% in 328 surgical patients, providing an absolute risk reduction (ARR) of 17±3.5% (mean±SEM) ($P \leq .001$) and the number needed to treat (NNT) was six at 2 years.(24) In patients with 50 to 69% symptomatic stenosis, the 5-year rate of ipsilateral stroke was 15.7% in patients treated with BMT + CE and 22.2% in patients who received BMT alone (ARR 6.5%, NNT 15.4, $p \leq 0.045$). There was a nonsignificant difference in patients with ≤50% symptomatic stenosis, with a 5-year rate of ipsilateral stroke of 14.9% in the CE group and 18.7% in the medical therapy group ($p \leq 0.16$). Similar and confirmatory findings were noted in the European and VA trials. The European trial noted significant benefit in favor of surgery for stenosis >69% but no benefit of surgery in symptomatic patients with <30% stenosis.(86) The VA trial noted the benefit for prevention of stroke and crescendo TIAs with stenoses as low as 50%.(87) We should make clear that ECST calculations use an estimated carotid bulb diameter rather than the internal carotid artery diameter as the denominator, so 70% in ECST is equivalent to 45% stenosis in NASCET. When the ECST angiograms were reanalyzed using the NASCET method, the two trials produced remarkably consistent results. In the NASCET 50 to 69% group, post hoc analyses found that the benefit was heterogeneous. In the 50 to 69% group, there was a greater benefit from CE in men compared to women. For prevention of an ipsilateral stroke of any severity or for prevention of a disabling stroke, the NNT was 12 and 16 for men and 67 and 125 for women. In addition, there was no demonstrable benefit in patients with retinal stroke or retinal TIA.

A recent report from the Carotid Endarterectomy Trialists' Collaboration (88) pooled all available data (n = 6092) with unification of measures of carotid stenosis to provide the most comprehensive evaluation of CEA-related stroke risk reduction in symptomatic carotid stenosis to date. CEA slightly increased the 5-year risk of ipsilateral ischemic stroke in patients with less than 30% stenosis, had no effect in patients with 30% to 49% stenosis, was of marginal benefit in those with 50% to 69% stenosis (absolute risk reduction 4.6%), and was highly beneficial in those with 70% stenosis or greater without near-occlusion or occlusion (absolute risk reduction 16.0%). There was no benefit from surgery in patients with near-occlusion. These results draw attention to the necessity of accurate and reliable measurements of stenosis as the single most important indication for CEA. The beneficial effects of CEA are applicable only if the surgical complication rate is less than 7%.(88) The benefits of CEA will be reduced by 20% for each 2% increase in the complication rate. Importantly, benefits of CEA in the setting of symptomatic stenosis are likely to increase with age. The subset analysis of the NASCET trial demonstrated that the risk for stroke significantly increases with age in a medically treated group, whereas CEA-

related stroke risk reduction (stenosis >70%) is 28.9% for patients older than 75 years versus only 15.1% of risk reduction for patients aged 65 to 74 years.(89) In patients older than 75 years, only three CEAs need to be performed to prevent one stroke within 2 years for stenosis >70% and six CEAs when the stenosis is 50% to 69

Carotid Endarterectomy in Special Circumstances

Acute Carotid Occlusion

Most patients who have a neurological deficit associated with acute carotid occlusion are not candidates for carotid endarterectomy because of the severity of their deficits and/or a delay in diagnosis. A few patients may benefit from emergency surgery by virtue of proximity to a medical center with documented expertise in the management of cerebrovascular disease, having had a mild neurological deficit associated with an acute carotid occlusion, and having undergone a rapid workup (within hours of the event). As there are insufficient data either to support or refute this concept, this is an important topic for future study and trials. In the meantime, decisions must be made on a case-by-case basis, keeping in mind that there may be an opportunity to save carotid artery patency and neurological function with acute surgical intervention in carefully selected patients.

Evolving Stroke

Reports on natural history and attempts at surgical management are now more than 10 years old and predate current imaging technology. This makes conclusions in this area impossible and provides an important area for new investigation.(90-94)

Data regarding CE concurrent with or prior to coronary artery bypass graft (CABG)

Patients with either symptomatic or asymptomatic CAD in the presence of symptomatic coronary artery disease represent a difficult decision matrix. The options include operating on the carotid lesion first, with an increased risk of morbidity and mortality from myocardial infarction; operating on the coronary lesion first, with an increased risk of perioperative stroke; operating on both lesions during the same period of anesthesia; or operating on the coronary arteries alone

A meta-analysis of more than 50 reports reviewed three operative strategies: simultaneous carotid and coronary artery bypass grafting (CABG), carotid surgery followed by CABG, and CABG followed by carotid surgery. The meta-analysis indicates that the perioperative stroke rate was similar if carotid and coronary surgery were combined or if carotid surgery preceded coronary bypass grafting.

There are no randomized clinical trials addressing this question and the best available evidence comes from retrospective case control (Class III) and case series (Class IV) reports . Some studies compared findings between groups with different surgical strategies, but because prospective criteria were not applied, a selection bias is likely that precludes making definitive conclusions. In the studies with 50 or more subjects having simultaneous CE-CABG totaling 1,923 subjects, included patients with a combination of stable and unstable coronary artery disease and symptomatic as well as asymptomatic carotid artery disease. The carotid artery disease was usually greater than 70% stenosis or there was an ulcerated plaque. The overall average perioperative complication rate is 3.0% stroke (range 0 to 9%), 2.2% myocardial infarction (range 0 to 6%), and 4.7% death (range 2.6 to 8.9%). Three studies reported long-term survival and the 5- to 6-year survival among 492 subjects ranged between 73 and 91%. In studies with more than 50 subjects where CE preceded the CABG, 257 patients with stable coronary artery disease were studied and the perioperative stroke rate was 1.9%, for myocardial infarction 4.7%, and for death 1.6%. Thus, the perioperative complication rates appear similar in CE before or simultaneous with CABG based on reports with retrospective data, although the death rates with combined CE-CABG are higher than with CE alone.The frequency of stroke was significantly greater if CABG preceded carotid surgery. However, the frequency of myocardial infarction (*P*=.01) and death (*P*=.02) were greater when carotid surgery preceded coronary bypass grafting (95-158)

The optimal strategy for management of patients with combined coronary and carotid disease will be established only by a well-designed prospective randomized trial.

Acute Carotid Dissection

Acute dissections of the internal carotid artery can occur either spontaneously or after blunt trauma. The pathology is an intimal tear with an intramural hematoma of the internal carotid artery that can remain stable, extend along the artery, or expand to produce a dissecting aneurysm. Thrombi from this site can extend or embolize intracranially. This condition is treated medically. In those rare instances when focal ischemic symptoms recur despite medical treatment, and there is an appropriate vascular lesion, surgery may represent an alternative approach.(159-163)

Asymptomatic Patients

Natural History

Initial studies to clarify the natural history of asymptomatic patients focused on finding a bruit in the cervical region.(164,165) It has now been well documented

that bruits do not define the presence of a critical carotid lesion, nor are critical carotid lesions always associated with a bruit.(166-168) With the advent of carotid duplex scanning and more precise definition of the percent stenosis, natural history studies based on the extent and character of the carotid lesion are now possible. Three specific factors affect outcome: (1) percent stenosis (2) progression between examination intervals (3) presence or absence of ulceration. Evidence of brain infarction or embolization may also be important.(169-171) Patients with stenoses of the internal carotid artery >75%, as measured by Doppler examination, are at risk for stroke in the range of 2% to 5% within the first year of observation. An additional group of patients will develop TIAs as a harbinger of stroke risk and then fall into the symptomatic patient category. For those asymptomatic patients who pass the first year of observation without symptoms, the risk of subsequent stroke falls significantly. Of patients who develop stroke during the observation of an asymptomatic lesion, 83% had no warning symptoms.(172-180)

Ulcerated lesion

The presence of ulceration, as documented by angiography, usually performed during evaluation of a symptomatic contralateral carotid artery, has also been a marker for subsequent stroke risk. The size and extent of ulceration has been correlated with the neurological event rate. Using conventional cut-film angiography, the ulcer size can be defined by multiplying the length and width of the ulcer in millimeters. Thus, ulcers that measure <10 mm^2 are defined as "A" ulcers; ulcers that range from 10 to 40 mm^2 are defined as "B" ulcers; and ulcers that exceed 40 mm^2, as "C" ulcers.(181) The presence of a "C" ulcer, independent of associated carotid stenosis, identified a group of patients who were at risk of stroke at the rate of 7.5% per year. (176,177) The presence of the small "A" ulcers was not associated with an increased stroke risk. (181-182) Controversy exists concerning the natural history of the "B" ulcer, with some reports suggesting that the stroke risk in patients associated with "B" ulcers was 4.5% per year (176,177) and other reports showing no relation between the presence of a "B" ulcer and subsequent stroke risk.(183,184)

Does CE benefit asymptomatic patients? (Results of Carotid Endarterectomy for Asymptomatic Patients)

In order to achieve a reduction in long-term stroke risk in asymptomatic patients in the distribution of the artery, the following criteria must be fulfilled: (1) a lesion must be associated with a demonstrable stroke risk (2) removal of the lesion must eliminate or reduce long term stroke risk (3) the surgeon who operates on the asymptomatic carotid lesion must have a low rate of perioperative neurological morbidity and mortality. Perioperative and long-term results of surgical management are readily available from retrospective reviews. Comparison of these reviews with the natural history reports has resulted in a series of position or consensus statements. Finally, prospective randomized trials provide the most definitive evidence either supporting or refuting the efficacy of prophylactic carotid endarterectomy in asymptomatic patients.

Recent publications have documented the risk of surgery as ranging from 0.0% to 3.8%. (185-188) A survey of surgeons participating in ACAS yielded an experience

of 1511 operations for asymptomatic stenosis with a combined operative mortality and neurological morbidity of 1.7%.(67) A review of an experience in the community of Rochester, NY, during the sample years 1984 through 1985 identified 226 carotid endarterectomies performed for asymptomatic carotid stenosis with a combined operative morbidity and mortality of 3.9%.(189) Finally, the operative risk in the VA prospective randomized trial demonstrated a combined risk of death and stroke of 4.3% in 211 operations.(180) The AHA Stroke Council has stated that for carotid endarterectomy to be efficacious in asymptomatic patients, the target for combined perioperative death and stroke rate should be <3%.(190) A review of six series in the literature documented the outcome of patients followed for prolonged intervals after surgery for asymptomatic carotid stenosis. The ipsilateral annual stroke rate, including perioperative stroke, ranged from 0.7% to 2.0% per year.(190-194)

Position statements concerning the use of prophylactic carotid endarterectomy have been published by the Joint Council of the SVS/ISCVS (84) and the Rand Corporation. (85) An ad hoc committee of the AMA (D.B. Matchar, MD, C.T. Huesgen, MD, W.S. Moore, MD, unpublished data), and an international consensus conference (A. Nicolaides, MD, unpublished data) have also issued statements on prophylactic carotid endarterectomy. The International Consensus Conference on Asymptomatic Patients With Carotid Bifurcation Disease concluded that in an effort to clarify the role of carotid endarterectomy in reducing stroke alone or stroke and death, this consensus group supports randomization of patients with severe asymptomatic stenosis to ongoing prospective clinical trials. However, for patients unable or unwilling to participate in these trials, some members of this panel believe that carotid endarterectomy may be considered in good risk patients free of life threatening coronary disease by surgeons with low surgical complications. (A. Nicolaides, MD, unpublished data.)

Five prospective randomized trials were designed to study the efficacy of prophylactic carotid endarterectomy for the treatment of patients with asymptomatic carotid stenosis.

The first trial to publish its results, the Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin ***(CASANOVA)*** trial, concluded that carotid endarterectomy was not efficacious when compared with their control group. Unfortunately the study was seriously flawed.(195) The CASANOVA study had a suboptimal study design and conduct. A total of 410 patients with 50 to 90% stenosis were enrolled. There was a high rate of crossovers. A total of 17% of the surgical patients never received a CE and 20% of the medical patients were given a unilateral or bilateral CE. In addition, there were many criteria for which medical patients could receive a CE, including progression of stenosis to >90%. This deprived the study of the high risk patients who were of greatest interest and confused the overall interpretation of the data.

The Mayo Asymptomatic Carotid Endarterectomy ***(MACE)***(196) trial included too few observations of cerebral ischemic events to allow the authors to judge between the medical and surgical treatment groups. This trial was stopped early because of the frequency of a secondary end point (myocardial infarction) in the randomized surgical group, an end point that was significantly greater than in the medical part of the trial. Surgical patients in this trial had been discouraged from taking aspirin unless other indications (eg, cardiac) existed for its use.

The ***VA trial*** (180) *(Class I study)* was designed to test the hypothesis that carotid endarterectomy plus aspirin antiplatelet therapy would be more effective than antiplatelet therapy alone in reducing the incidence of neurological events, including

TIA and stroke. The results of this study proved the hypothesis and demonstrated that the combined incidence of ipsilateral neurological events in the surgical group was 8% in contrast to 20.6% in the medical group ($P<.001$). Unfortunately, when the study was designed, the proposed sample size was not large enough to provide statistical power to show a difference for stroke alone. Nonetheless, after a 4-year follow-up interval, the ipsilateral stroke rate in the surgical group was 4.7% (including perioperative strokes), in contrast to 9.4% in the medical group ($P=.056$). However, when perioperative mortality (1.9%) was added to the surgical stroke rate, the difference between the two groups with respect to stroke failed to reach statistical significance. As a consequence, this trial has failed to resolve the controversy.

ACAS, a prospective, randomized, multicenter trial, *(Class I study)* was originally designed to randomly assign 1500 patients from thirty-nine clinical sites across the United States and Canada, to best medical management or surgery plus best medical management. ACAS investigators received permission to expand the sample size to ensure that there are a sufficient number of patients to be able to consider differences in the end point of stroke alone.(197) Between December 1987 and December 1993, a total of 1662 patients with asymptomatic carotid artery stenosis of 60% to 99% stenosis (with the stenosis defined angiographically for the surgical group and primarily with ultrasound for the medical group) were randomized; follow-up data are available on 1659. At baseline, recognized risk factors for stroke were similar between the two treatment groups. After a median follow-up of 2.7 years, with 4657 patient-years of observation, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53% [95% confidence interval, 22% to 72%]). At that point the study was halted by the Data Safety and Monitoring Board after 2.7 years median follow-up because of a projected 5.9% ARR at 5 years favoring CE (NNT=17).(198) For major ipsilateral stroke (defined as a Glasgow scale of 2 or higher) or any perioperative major ipsilateral stroke, the 5-year projected rates were 6.0% for the medically treated patients and 3.4% for the surgical patients ($p = 0.12$). The perioperative stroke rate was 2.3%, providing a number needed to harm (NNH) of 43. In conclusion, according to ACAS results, patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors. (level I evidence, grade A recommendation).

On September 28, 1994, the NINDS issued a clinical advisory indicating a clear benefit in favor of surgery and that the trial has been halted. There was a relative reduction in risk for stroke of 55% in the surgical group compared with the group of patients who did not undergo surgery.

The Asymptomatic Carotid Surgery Trial ***(ACST)*** *(Class I study)* has started randomizing patients in 1993 from approximately 100 centers around Europe. The trial was set up with the aim of being large enough (and, eventually, having long enough follow-up) to assess the net long-term effects of CEA on overall stroke risk and on fatal or disabling stroke among patients with substantial carotid artery narrowing, but with no relevant neurological symptoms in the previous 6 months. Randomisation in ACST ended after 10 years, but long-term follow-up will continue for several more years (199) The present report of the ACST results describes the

hazards and the medium-term benefits of CEA (analysed both separately and together) during just the first 5 years after randomisation. (200)

Patients with substantial (eg, 60–99%) carotid artery narrowing are at increased risk of suffering a disabling or fatal ischaemic stroke in the carotid territory of the brain. But among those without recent neurological symptom (stroke or transient ischaemia), meaning the so called asymptomatic patients, the balance of surgical risks and longterm benefits from carotid endarterectomy (CEA) was unclear, even after the release of ACAS results. During 1993–2003, 3120 asymptomatic patients with substantial carotid narrowing were randomised equally between immediate CEA (half got CEA by 1 month, 88% by 1 year) and indefinite deferral of any CEA (only 4% per year got CEA) and were followed for up to 5 years (mean 3·4 years). Kaplan-Meier analyses of 5-year risks are by allocated treatment.

The risk of stroke or death within 30 days of CEA was 3·1% (95% CI 2·3–4·1). Comparing all patients allocated immediate CEA versus all allocated deferral, but excluding such perioperative events, the 5-year stroke risks were 3·8% versus 11% (gain 7·2% [95% CI 5·0–9·4], p<0·0001). This gain chiefly involved carotid territory ischaemic strokes (2·7% *vs* 9·5%; gain 6·8% [4·8–8·8], p<0·0001), of which half were disabling or fatal (1·6% *vs* 5·3%; gain 3·7% [2·1–5·2], p<0·0001), as were half the perioperative strokes. Combining the perioperative events and the non-perioperative strokes, net 5-year risks were 6·4% versus 11·8% for all strokes (net gain 5·4% [3·0–7·8], p<0·0001), 3·5% versus 6·1% for fatal or disabling strokes (net gain 2·5% [0·8–4·3], p=0·004), and 2·1% versus 4·2% just for fatal strokes (net gain 2·1% [0·6–3·6], p=0·006). Subgroup-specific analyses found no significant heterogeneity in the perioperative hazards or (apart from the importance of cholesterol) in the long-term postoperative benefits. These benefits were separately significant for males and females; for those with about 70%, 80%, and 90% carotid artery narrowing on ultrasound; and for those younger than 65 and 65–74 years of age (though not for older patients, half of whom die within 5 years from unrelated causes). Full compliance with allocation to immediate CEA or deferral would, in expectation, have produced slightly bigger differences in the numbers operated on, and hence in the net 5-year benefits. The 10-year benefits are not yet known. As a conclusion, In asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of whom were on aspirin, antihypertensive, and, in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard). Half this 5-year benefit involved disabling or fatal strokes. But, outside trials, inappropriate selection of patients or poor surgery could obviate such benefits. (level I evidence, grade A recommendation).

The only other large trial, ACAS, involved similar patients in North America and had generally similar findings for stroke prevention to the largely European ACST. Although the overall ACAS Results were less clear, particularly for fatal or disabling stroke, this probably relates to the smaller numbers of patients in ACAS and the somewhat shorter duration of follow-up. (26) *(Table 5)*

Surgical Risk for carotid endarterectomy

Carotid endarterectomy is a prophylactic operation designed to reduce the risk of subsequent stroke and stroke-related death. As such, the effectiveness of prophylaxis is directly related to the perioperative risk of operation. Operative risk is

affected by patient selection, selection of surgeon, and the institution in which the operation is performed.

Operative risk, as a function of patient selection, is determined not only by a patient's general state of health but also by the indication for surgery. A review of the medical literature clearly shows that the lowest complication rates occur with operations on asymptomatic patients. The risk of operation is slightly higher in patients suffering transient cerebral ischemia and appears to be highest in patients who have had a prior stroke, particularly in those who have a greater residual neurological deficit.(67, 201)

It is not possible to assign a generic risk for the operation since major factors associated with operative risk will include the expertise of the surgeon performing the operation and the quality of care available in the hospital in which the operation is performed. Morbidity and mortality data extracted from retrospective reviews tend to be of limited value, inasmuch as they represent the experience of the surgeon or surgeons preparing the report. Population-based community audits provide better insight into the average risk of perioperative complications. These numbers, however, are influenced by the patient selection process and surgical expertise in the community being audited. Results of five community-based audits have demonstrated that the percentage of patients disabled or dead following carotid endarterectomy ranges from a low of 4.8% to a high of 9.0%.(177, 202-205)

The Class I studies discussed above for patients with symptomatic and asymptomatic stenosis serve as a benchmark for desirable surgical results. In the severe group with 70 to 99% stenosis in NASCET, the perioperative stroke and death rate was 5.8%. In ACAS, the stroke and death figure was 2.3%. In the pooled analysis of the symptomatic studies, the stroke and death rate was 7.1% and in the ACST, it was 3.1%. Due to the importance of the surgical complication rate in the risk/benefit equation, it is recommended that hospitals or government regulatory bodies should provide risk adjusted CE morbidity and mortality data to referring physicians.

Recommendations

An ad hoc committee of the AHA Stroke Council reviewed available reports and made recommendations with regard to the upper acceptable level of risk for combined death and/or stroke associated with carotid endarterectomy as a function of indication for surgery. The limits set were 3% for asymptomatic patients, 5% for patients experiencing transient cerebral ischemia, 7% for patients who have suffered a prior stroke, and 10% for patients undergoing surgery for recurrent stenosis.(190) More recently, many series have been reported with complications lower than the upper acceptable limits defined. It is clear that some surgeons perform this operation with low risk while others have an unacceptably high complication rate; thus, it would be desirable to develop methods for auditing the individual surgeon's practice of carotid endarterectomy and to limit surgical privileges to those who can document that their results fall within an acceptable range.

Special issues regarding carotid endarterectomy

Important clinical variables that impact the risk/benefit ratio?

None of the identified trials had clinical variables that impact risk/ benefit as predetermined endpoints. Two variables that stand out in post hoc analyses are sex

and nature of the presenting symptoms. In both the NASCET 50 to 69% group and in ACAS, there was no benefit shown for CE in women. A subgroup analysis from NASCET also demonstrated that patients presenting with retinal ischemia (amaurosis fugax or retinal infarction) have a lower subsequent stroke risk compared to patients with hemispheric events.(208) In a pooled analysis of the three symptomatic studies, the authors identified male sex ($p = 0.003$), age ($p = 0.03$), and study entry within 2 weeks of the last symptomatic event ($p = 0.009$) as modifiers of CE benefit, (209) with the greatest benefit found in men, patients above age 75 years, and those randomized within 2 weeks of their last symptomatic event.

Important radiologic factors that impact the risk/benefit ratio?

Overall, several studies addressed issues such as status of the contralateral carotid artery, angiographic appearance of the ICA, and other factors. The highest level data regarding contralateral occlusion came from the NASCET and ACAS studies. These analyses found that for symptomatic patients, if there is a contralateral occlusion, the surgical complication rate is higher than if the contralateral ICA is patent but there is still a better outcome compared to medical management for patients with 70 to 99% stenosis.(210) Conversely, for patients with asymptomatic stenosis, if there is a contralateral occlusion, the only randomized evidence suggests that patients do slightly better with medical management (2.0% absolute increase in risk with CE at 5 years). (211) For patients with angiographic near-occlusion, the pooled analysis of the symptomatic studies suggests that CE is associated with a trend toward benefit at 2 years but no clear benefit at 5 years (1.7% trend favoring medical treatment at 5 years).(88) It should be recognized that BMT patients in NASCET with severe stenosis, including those with near-occlusion, were offered CE after the 2-year results were made available. Only Class IV evidence or below was available for other factors such as influence of carotid siphon stenosis or posterior circulation stenosis.

Emergent CE in patients with progressing stroke of <24 hours (222)

Four relative (Class IV) studies were identified. In three of the studies, neurologic improvement was noted in 81 to 93% of patients who underwent emergent CE. At one institution, however, a postoperative stroke and death rate of 20% was reported for urgent CE. Overall, these studies were fairly small, lacked objective evaluation of the reported neurologic outcomes, and one study was clouded by coexisting treatments including emergent thrombolysis.

Interval between stroke and carotid endarterectomy (222)

It should be recognized that NASCET and ECST excluded patients with no useful function in the ipsilateral carotid territory and randomization was delayed in patients who were drowsy or had significant edema on neuroimaging studies. There have been six retrospective cohort studies comparing the timing of CE in patients after a stroke. Of these six studies, four studies were retrospective reviews from a single institution, one study included two institutions, and another study was a subgroup analysis of the NASCET trial. The total sample sizes ranged from 45 to 201

subjects. The total number of subjects included in the comparative analyses was 641, 307 in the early group and 334 in the late group. Four of the studies defined early surgery as less than 6 weeks from the stroke and two studies defined early surgery as less than 4 weeks from the stroke. None of the studies found any differences in the outcomes in terms of operative morbidity and longerterm follow-up. There were significant limitations in the designs of these studies. Only the NASCET subgroup analysis had randomized patient assignment. Finally, sample sizes were small across all studies. In the pooled analysis of the three symptomatic CE studies, the Carotid Endarterectomy Trialists Collaboration found that patients who were randomized in the trials within 2 weeks of the last symptomatic event had greater benefit from CE.(209) This finding held up in both the severe (70 to 99%) stenosis group and the 50 to 69% stenosis group. It should be reiterated, however, that only patients with TIA or nondisabling stroke were enrolled in these trials.

Summarizing proposed guidelines (Appendix 1,2)

1. CE is established as effective for recently symptomatic (within previous 6 months) patients with 70 to 99% ICA angiographic stenosis (Level A). CE should not be considered for symptomatic patients with less than 50% stenosis (Level A). CE may be considered for patients with 50 to 69% symptomatic stenosis (Level B) but the clinician should consider additional clinical and angiographic variables (Level C). It is recommended that the patient have at least a 5-year life expectancy and that the perioperative stroke/death rate should be <6% for symptomatic patients (Level A). Medical management is preferred to CE for symptomatic patients with <50% stenosis (Level A).

2. It is reasonable to consider CE for patients between the ages of 40 and 75 years and with asymptomatic stenosis of 60 to 99% if the patient has an expected 5-year life expectancy and if the surgical stroke or death frequency can be reliably documented to be <3% (Level A). The 5-year life expectancy is important since perioperative strokes pose an up front risk to the patient and the benefit from CE emerges only after a number of years.

3. No recommendation can be provided regarding the value of emergent CE in patients with a progressing neurologic deficit (Level U).

4. Clinicians should consider patient variables in CE decision making. Women with 50 to 69% symptomatic stenosis did not show clear benefit in previous trials. In addition, patients with hemispheric TIA/stroke had greater benefit from CE than patients with retinal ischemic events (Level C). Clinicians should also consider several radiologic factors in decision making about CE. For example, contralateral occlusion erases the small benefit of CE in asymptomatic patients whereas in symptomatic patients, it is associated with increased operative risk but persistent benefit (Level C). CE for patients with angiographic near-occlusion in symptomatic patients is associated with a trend toward benefit at 2 years but not associated with a clear long-term benefit (Level C). Patients operated on within 2 weeks of their last TIA or mild stroke derive greater benefit from CE (Level C).

5. Symptomatic and asymptomatic patients undergoing CE should be given aspirin (81 or 325 mg/day) prior to surgery and for at least 3 months following surgery to reduce the combined endpoint of stroke, myocardial infarction, and death (Level A). Although data are not available, it is recommended that aspirin (81 or 325

mg/day) be continued indefinitely provided that contraindications are absent. Aspirin at 650 or 1,300 mg/day is less effective in the perioperative period. The data are insufficient to recommend the use of other antiplatelet agents in the perioperative setting.(52-62, 223-225), (*table 3*)

6. At this time the available data are insufficient to declare either CE before or simultaneous with CABG as superior in patients with concomitant carotid and coronary artery occlusive disease (Level U).

7. For patients with severe stenosis and a recent TIA or nondisabling stroke, CE should be performed without delay, preferably within 2 weeks of the patient's last symptomatic event (Level C). There is insufficient evidence to support or refute the performance of CE within 4 to 6 weeks of a recent moderate to severe stroke (Level U).

8. Carotid endarterectomy, whether performed under local or general anaesthesia, should be carried out by an anaesthetist with a vascular interest, training and experience in such cases (Grade C, level IV) (217) Systematic review of the small randomised trials comparing the two techniques provided no definite evidence that either was superior. In the UK most surgeons operate under general anaesthetic and this is usually preferred where there are technical difficulties such as a high bifurcation. Operating under local anaesthetic has the advantage that patients are able to alert the surgeon to new focal symptoms which might be due to focal cerebral ischaemia. This might reduce the need for other types of intra-operative monitoring.

9. Regarding intraoperative shunting, only two randomised trials have been done, both too small to be conclusive. (218,219) As a result it is not possible to make a recommendation on the routine use of shunts. Moreover, some surgeons now routinely insert a patch of vein or synthetic material when closing the artery to enlarge the lumen and, as a result, perhaps to reduce the risk of re-stenosis and, more importantly, of stroke. (220) A meta-analysis of the few randomised trials has shown a possible reduction in re-stenosis and fewer perioperative arterial occlusions in the patched group but, not surprisingly, there were so few strokes that any effect on their risk was quite uncertain. (221) It is not possible to make any firm recommendation regarding this issue.

Guidelines proposed above are consistent with the American Academy of Neurology. (222)

Future research for issues to be solved

Although the quality of data for CE decision making has improved since the last statement from the American Academy of Neurology in 1990, our review highlighted persisting areas of deficiency pertaining to CE. Future research should address these areas, including the setting of urgent CE in patients with progressing stroke, the appropriateness of CE in community settings, the management of coexisting carotid and coronary artery disease, and the timing of CE in patients with recent stroke. In addition, data are needed on newer antiplatelet agents in the perioperative setting.

Indications for Carotid Endarterectomy from a Multidisciplinary Consensus Statement From the Ad Hoc Committee, American Heart Association (AHA)

For historical reasons we should mention the guidelines proposed for CE from the AHA in 1993 (226). A consensus conference sponsored by the AHA (July 16-18, 1993, in Park City, Utah) reviewed the current potential indications for carotid endarterectomy. Twenty-two committee members, representing the disciplines of healthcare policy, neurology, neurosurgery, and vascular surgery reviewed the current medical literature. A list of 96 potential common indications was circulated to each conference participant. This list was based on symptomatic status, percent stenosis, plaque characteristic, status of opposite carotid artery, and various levels of surgical risk. The terms used are defined below. Each participant was asked to rank each surgical indication into one of four options: proven (score=1); acceptable but not proven (score=2); uncertain (score=3); and proven inappropriate (score=4). The scores were averaged for each of the 96 indications. Finally, the indications were aggregated again to make the presentation more manageable. Since many of the indications generated a range of scores, some participants rated a given indication higher (or lower) than other participants. For this reason, an average score was selected rather than attempting to find a unanimously acceptable score.

Definitions of Ranks for Surgical Indication for Carotid Endarterectomy

Four choices were available for each indication as a function of surgical risk. For asymptomatic patients, the options for surgical risk for combined stroke and death as a consequence of operation were <3%, 3% to 5%, and 5% to 10%. For symptomatic patients, the surgical risk options were <6% and 6% to 10%.
Surgical risk is based on a combined estimate of the patient's general medical fitness to undergo surgery and the individual surgeon's risk of morbidity and mortality for patients with a specific surgical indication.
A surgical indication that carries a high benefit-to-risk ratio would be acceptable in patients who were at higher surgical risk, whereas a surgical indication that had a lower benefit-to-risk ratio might be acceptable in only the best-risk patients.

Proven (Score=1)

This designation constitutes the strongest indication for carotid endarterectomy and strongly implies that to withhold surgery in the presence of this indication would be inappropriate under normal circumstances. Indications classified as proven are generally supported by data from contemporary, prospective, randomized clinical trials.

Acceptable but Not Proven (Score=2)

There is general agreement that this represents a good indication for surgery, with the expectation that benefits outweigh the risks. This rank is supported by promising, but

not scientifically certain, data. Indications in this category may be the subject of ongoing prospective randomized trials. In that case, it is expected that patients will be offered the opportunity to participate in the trial. However, when this is not possible, either by geography or patient preference, surgery would be an acceptable alternative at the present level of knowledge.

Uncertain (Score=3)

There are insufficient data to define the risk/benefit ratio. These potential indications should be evaluated in clinical trials.

Proven Inappropriate (Score=4)

The current database is adequate to indicate that the stated risks of carotid endarterectomy outweigh the benefits. In general, the database includes contemporary, prospective, randomized clinical trials.

Definitions of Stroke Categories

Mild Stroke

The residual neurological symptoms and signs of a mild stroke cause no important functional impairment.

Moderate Stroke

The residual neurological symptoms and signs of a moderate stroke result in a loss of function that may be complete in one domain (eg, arm or leg function, speech loss) and incomplete in others, but the total functional loss still allows independent existence.

Severe Stroke

Residual neurological signs of a severe stroke are directly responsible for the patient's loss of independence.

Asymptomatic Patients With CAD

For Patients With a Surgical Risk of <3%

1. Proven indications: none
2. Acceptable but not proven indications: ipsilateral carotid endarterectomy for stenosis ≥75% with or without ulceration, irrespective of contralateral artery status, ranging from no disease to total occlusion
3. Uncertain indications
- Stenosis <50% with a "B" or "C" ulcer irrespective of contralateral internal carotid artery status

- Unilateral carotid endarterectomy with CABG, coronary bypass graft required with bilateral asymptomatic stenosis >70%
- Unilateral carotid stenosis >70%, CABG required, unilateral carotid endarterectomy with CABG

4. Proven inappropriate indications: none defined

For Patients With a Surgical Risk of 3% to 5%

1. Proven indications: none
2. Acceptable but not proven indications: ipsilateral carotid endarterectomy for stenosis ≥75% with or without ulceration but in the presence of contralateral internal carotid artery stenosis ranging from 75% to total occlusion
3. Uncertain indications
- Ipsilateral carotid endarterectomy for stenosis ≥75% with or without ulceration irrespective of contralateral artery status, ranging from no stenosis to occlusion
- Coronary bypass graft required, with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with CABG
- Unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG

4. Proven inappropriate indications: none defined

For Patients With a Surgical Risk of 5% to 10%

1. Proven indications: none
2. Acceptable but not proven indications: none
3. Uncertain indications
- Coronary bypass graft required with bilateral asymptomatic stenosis >70%, unilateral carotid endarterectomy with CABG
- Unilateral carotid stenosis >70%, CABG required, ipsilateral carotid endarterectomy with CABG

4. Proven inappropriate indications
- Ipsilateral carotid endarterectomy for stenosis ≥75% with or without ulceration irrespective of contralateral internal carotid artery status
- Stenosis ≤50% with or without ulceration irrespective of contralateral carotid artery status

Symptomatic Patients With CAD

For Patients With a Surgical Risk of <6%

1. Proven indications
- Single or multiple TIAs within a 6-month interval or crescendo TIAs in the presence of a stenosis ≥70%, with or without ulceration, with or without antiplatelet therapy
- Mild stroke within a 6-month interval, in the presence of a stenosis ≥70%, with or without ulceration, with or without antiplatelet therapy

2. Acceptable but not proven indications
- TIA (single, multiple, or recurrent) within a 6- month interval, in the presence of a stenosis ≥50%, with or without ulceration, with or without antiplatelet therapy
- Crescendo TIAs in the presence of a stenosis >50%, with or without ulceration, with or without antiplatelet therapy

- Progressive stroke in the presence of a stenosis ≥70%, with or without ulceration, with or without antiplatelet therapy
- Mild stroke in the presence of a stenosis ≥50%, with or without ulceration, with or without antiplatelet therapy
- Moderate stroke in the presence of a stenosis ≥50%, with or without ulceration, with or without antiplatelet therapy
- Ipsilateral carotid endarterectomy combined with CABG in a patient experiencing TIAs, in the presence of unilateral or bilateral stenoses ≥70%, coronary bypass grafting needed

3. Uncertain indications

- TIA (single, multiple, or recurrent) with stenosis <50% with or without ulceration, with or without antiplatelet therapy
- Crescendo TIAs, with or without ulceration, and a stenosis <50%
- TIAs in a patient who requires coronary bypass grafting and has a stenosis <70%
- Mild stroke with carotid stenosis <50%, with or without ulceration, with or without antiplatelet therapy
- Moderate stroke with carotid stenosis <69%, with or without ulceration, with or without antiplatelet therapy
- Evolving stroke with carotid stenosis <69%, with or without ulceration, with or without antiplatelet therapy
- Global ischemic symptoms with ipsilateral carotid stenosis >75% but contralateral stenosis <75%, with or without ulceration, with or without antiplatelet therapy
- Acute dissection of internal carotid artery with persistent symptoms while on heparin
- Acute carotid occlusion, diagnosed within 6 hours, producing transient ischemic events
- Acute carotid occlusion, diagnosed within 6 hours, producing a mild stroke

4. Proven inappropriate indications

- Moderate stroke with stenosis <50%, not on aspirin
- Evolving stroke with stenosis <50%, not on aspirin
- Acute internal carotid artery dissection, asymptomatic, on heparin

For Patients With a Surgical Risk of 6% to 10%

1. Proven indications: none

2. Acceptable but not proven indications

- Single or multiple TIAs within a 6-month interval, in the presence of a carotid stenosis ≥70%, with or without ulceration, with or without antiplatelet therapy
- Recurrent TIAs, while on antiplatelet drugs, for a carotid stenosis ≥50% in the presence of ulceration, or ≥70% with or without ulceration
- Crescendo TIAs with a stenosis ≥50%, with or without ulceration, with or without antiplatelet therapy
- Mild stroke in the presence of a stenosis >70%, with or without ulceration, with or without antiplatelet therapy
- Moderate stroke with a stenosis >70%, with or without ulceration, with or without antiplatelet therapy
- Evolving stroke in the presence of a >70% stenosis with large ulceration

3. Uncertain indications

- Single TIA with stenosis <70%, with or without ulceration, with or without antiplatelet therapy

- Multiple TIAs within 6 months with stenosis <70%, not on antiplatelet drugs, with or without ulceration
- Recurrent TIAs while on antiplatelet drugs with stenosis <70%, with or without ulceration
- Crescendo TIAs for stenosis <70%, with or without ulceration, with or without antiplatelet therapy.
- Acute carotid occlusion with transient cerebral ischemia
- Acute occlusion with mild stroke
- Acute carotid artery dissection with continued symptoms while on heparin
- Patient with transient cerebral ischemia secondary to a stenosis ≥70%, in need of CABG, with or without contralateral stenosis, use of combined operation
- Mild stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy
- Moderate stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy
- Evolving stroke with stenosis <70%, with or without ulceration, with or without antiplatelet therapy
- Global ischemic symptoms with an ipsilateral stenosis >75%, with or without symptoms, irrespective of contralateral artery status, with lesions up to and including contralateral occlusion

4. Proven inappropriate indications

- Single TIA, <50% stenosis, with or without ulceration, not on aspirin
- Multiple TIAs within 6 months, stenosis <50%, not on aspirin
- Mild stroke, stenosis <50%, not on aspirin
- Moderate stroke, stenosis <50%, with or without ulceration, not on aspirin
- Evolving stroke, stenosis <50%, with or without ulceration, not on aspirin
- Global ischemic symptoms with stenosis <50%, with or without ulceration
- Acute dissection of internal carotid artery, no symptoms while on heparin
- Asymptomatic unilateral carotid stenosis ≥70% in patient undergoing CABG

Guidelines for Carotid Angioplasty and Stenting

INTRODUCTION

Carotid endarterectomy (CEA) is one of the most commonly performed peripheral vascular procedures and is currently considered the most effective treatment for stroke prevention, compared to medical treatment alone, in patients with high-grade symptomatic or asymptomatic carotid artery disease (CAD) according to the well designed prospective trials NASCET, ECST, ACAS and ACST.

During the last decade PTA has also been used to treat occlusive atherosclerotic disease in the ICA. (227) This treatment was introduced in Scandinavia in 1993 (228,229) but is still not considered a routine procedure probably because reliable long-term results and well defined guidelines are missing. The

immediate benefits of carotid PTA or CAS vs CEA include short treatment duration, no need of general anaesthesia and avoidance of surgical stress as well as possible complications following surgical treatment, e.g. peripheral nerve lesions and haemorrage. It was initially introduced for high risk patients (as those excluded from NASCET) regarding the general condition of the patient or regional – anatomical reasons (hostile neck, restenosis, etc). Despite the lack of clear evidence, it is assumed that the perioperative mortality and morbidity following CAS is comparable with CEA. (230)

Therefore, procedures such as angioplasty and/or stent placement to reverse critical cerebrovascular stenoses may be of great importance. CAS is being performed with rapidly increasing frequency in the United States. We anticipate that more data regarding late outcomes and complications will be collected and published in the near future (the National Institutes of Health–supported Carotid Revascularization: Endarterectomy vs. Stent Trial [CREST] as well as other controlled series have begun) (231).

CAS is not an easy procedure. Far more experience and training and fewer complications compared to diagnostic cerebral angiography are expected of those who perform CAS, similar to what is expected of those who perform coronary interventions. Minimum acceptable requirements for performance of the much less difficult and lower risk procedure of diagnostic cerebrovascular angiography have been documented (232). It is our purpose to point out the minimum prerequisite for the performance of the far more difficult and higher risk procedure of carotid artery angioplasty and stent placement (CAS). Performance of CAS requires prior experience with diagnostic cerebrovascular angiography, as well as experience with angioplasty and stent placement in other vessels. Such requirements for additional training and experience in performing CAS have been recognized by the Accreditation Council for Graduate Medical Education (ACGME) as part of the specialty training requirements for endovascular surgical neuroradiology (228,229,233,287,295,326-329).

CAS is an innovation under evaluation. Until the true risks and appropriate indications for this procedure are clearly known, we recommend that for patients who have average surgical risk, such as those who would have qualified for enrollment in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS), CAS should only be performed as part of a randomized clinical trial or an approved investigational program. The inclusion and exclusion criteria for the NASCET and ACAS studies are summarized in *Table 6*. So far, CAS has shown promise for the treatment of patients known to be at high risk of carotid endarterectomy (Yadav J, presented at the American Heart Association Scientific Sessions, Chicago, November 2002). CAS should only be performed on appropriate patients by an individual or team with training and expertise in vascular surgery, cerebrovascular angiography, pathophysiology, hemodynamics, and neurovascular interventions and/or angioplasty/stent placement (234).

Brachiocephalic revascularization is undergoing rapid change in technology even as it is being increasingly adopted in clinical practice for the treatment of cerebrovascular pathologies. We should encourage the development of procedures that may improve outcomes for patients with carotid artery stenoses. Furthermore, due to the implications concerning stroke prevention, we wish to encourage the careful and scientific study of the safety and efficacy of brachiocephalic revascularization as well as appropriate utilization of these demanding techniques.

CURRENT SITUATION FOR CEA AND CAS

Carotid Endarterectomy

At least four well designed, large, prospective, randomized studies, NASCET, ECST, ACAS and ACST, have established that certain selected patients benefit from surgical treatment of significant atherosclerotic stenosis in the cervical carotid artery, compared to medical treatment alone, whereas at least two other randomized studies (VA and MACE) of endarterectomy for asymptomatic carotid stenosis indicated no significant benefit from surgery (180,196). NASCET, ECST and ACAS showed that lowered stroke morbidity can be achieved in selected symptomatic and asymptomatic patients undergoing carotid endarterectomy (CEA) compared with aspirin therapy if surgical endarterectomy can be performed with an acceptably low complication rate. However, they did not evaluate the risk of endarterectomy versus "best" medical therapy that is now currently available. No trial has evaluated the natural history or risk of stroke from cervical carotid atherosclerotic stenosis treated with warfarin, combination warfarin and aspirin, aspirin and dipyridamole, ticlopidine, clopidogrel, or combinations of antiplatelet agents. More importantly, newer drugs such as statins and angiotensin-converting enzyme inhibitors have been proved to stabilize plaque and thus decrease myocardial infarction risk as well as lower stroke risk (235,236). Only in ACST statins were included, apart from antiplatelet and antihypertensive agents.

The NASCET and ACAS studies must also be judged using the qualifications of the inclusion and exclusion criteria designed to select their study populations. These studies did not establish safety and efficacy for CEA versus aspirin therapy for the majority of patients with carotid artery stenosis screened at that time. For example, NASCET randomized only those patients with symptomatic events occurring within 120 days of surgery. Patients were excluded from this study if they had a coexistent tandem lesion that was more severe than the proximal internal carotid artery lesion, if they had particular renal, liver, or lung diseases, if they had coexistent cardiac disease that resulted in a valvular or rhythm disorder, or if they had undergone a previous ipsilateral CEA. Initially, patients were also not included in the study if they were 80 years of age or older. These factors resulted in NASCET actually enrolling fewer than one-half of the potential patients, and a large portion of current candidates for CEA would be excluded from this trial. NASCET did demonstrate that surgery was beneficial for these carefully selected symptomatic patients with more than 70% carotid artery stenosis (with specific measurement criteria used) and some with more than 50% (237). In addition, ACAS exclusion criteria for asymptomatic patients were similar to those of NASCET, which resulted in actual randomization of fewer than 10% of all screened asymptomatic patients. However, in the United States, a large percentage of CEAs is performed on exactly these patients. CEA has a durable result, with reported restenosis rates ranging from approximately 5% to 20%, and with late stroke rates reported as less than 5% in 5 years (238,239). However, current data indicate that CEA as it is currently practiced bears little resemblance to the populations studied, methods used, or results obtained in NASCET and the ACAS studies (240-243). More recent evaluation of typical clinical practice indicates a

significantly higher perioperative death rate for Medicare patients undergoing CEA at the same institutions participating in the NASCET and/or ACAS studies than for the original study patients (0.6% for NASCET patients, 0.1% for ACAS patients, but 1.4% for all Medicare patients) (242). The perioperative mortality rate for Medicare patients undergoing CEA at nonstudy sites was 1.7% for high-volume institutions, 1.9% for average-volume institutions, and 2.5% for low-volume institutions (as opposed to 0.6% for NASCET and 0.1% for ACAS) (242). Thus, the mortality rate was far higher at all institutions, including high-volume institutions and original trial sites, when unselected Medicare patients were considered. This may be partially explained by the fact that the patients participating in the NASCET and ACAS trials were younger and healthier than the typical Medicare patients now undergoing CEA at these same or other institutions. Older patients and those with significant comorbidity have repeatedly been shown to be at increased risk of perioperative stroke and death from CEA (242-258). Although recent surgical articles dispute the concept that there is a population of patients who have a significantly higher risk of complications after CEA (259-260), the recently completed Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) Trial (Yadav J, presented at the American Heart Association Scientific Sessions, Chicago, November 2002) indicates that these "high surgical risk" patients are indeed at higher risk of complications from CEA. On the other hand Karl A. Illig et al, in his recent article “Is the rationale for carotid angioplasty and stenting in patients excluded from NASCET/ACAS or eligible for ARCHeR justified?” Compared the outcome after carotid endarterectomy (CEA) in patients who would have been excluded from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) or the Asymptomatic Carotid Atherosclerosis Study (ACAS) or would have been eligible for Acculink for Revascularization of Carotids in High Risk Patients (ARCHeR), a current high-risk stent registry, with outcome in a similar cohort at low risk. No statistically or clinically significant differences were found in combined 30-day stroke or death rates after CEA in any group defined by previous surgical trials or current ongoing high-risk stent registry. While high-risk groups may exist, the premise that operative risk is higher in patients excluded from NASCET and ACAS or eligible for ARCHeR is not supported. (261)

The role of endarterectomy in asymptomatic carotid stenosis was controversial, until the release of ACST results. One randomized, controlled trial (ACAS) has shown surgery to be beneficial, whereas at least two (MACE, VA) have not. ACAS, however, did not find benefit for CEA versus medical therapy for major stroke, only minor stroke. Asymptomatic cervical carotid artery stenosis has been repeatedly shown to be of relatively low stroke risk until the remaining lumen approaches 1 mm in diameter (usually corresponding to stenosis of approximately 80%–90% by NASCET criteria) (26,262,263). Even then, the risk is less than even a moderate stenosis in a symptomatic patient (26,24,264). For asymptomatic patients with stenoses of less than 80%, the risk of ipsilateral stroke is approximately 1% per year or 5% in 5 years only treated with aspirin (263,265). Approximately 45% of strokes in patients with asymptomatic stenoses are not caused by the stenosis but rather arise from intracranial or cardiovascular sources, thus further reducing the actual risk of the lesion itself (266). Additionally, contrary to the clinical findings in ACAS, a recent review of the computed tomographic (CT) scans of ACAS patients revealed that carotid endarterectomy does not reduce the frequency of CT identifiable ipsilateral cerebral infarction in patients with high-grade asymptomatic carotid artery stenosis (267). Based on the ACAS trial, the American Heart Association (AHA) considered

CEA to be beneficial for treatment of asymptomatic, angiographically proven carotid stenosis of more than 60% if the combined perioperative stroke/mortality rate is less than 3% (268), which might only be achievable in otherwise healthy individuals. In contrast to the AHA guidelines for endarterectomy, the Canadian Stroke Consortium reached consensus that there was insufficient evidence to endorse CEA for any level of asymptomatic stenosis (269). Reasons cited were lack of proof of reduction of the risk of major disabling stroke, the question of reproducibility of surgical results in the general population, and the unproven long-term benefit of surgical reconstruction. Even a slight reduction in the intrinsic risk of asymptomatic carotid stenosis achieved by treatment with contemporary pharmaceuticals in addition to (or other than) aspirin, such as statins or angiotensin-converting enzyme inhibitors, might render CEA nonbeneficial in the majority of asymptomatic patients (235,236). Therefore, at best, CEA for asymptomatic patients is only indicated according to the AHA guidelines, and carotid stent placement for asymptomatic patients is rarely indicated outside of clinical trials (many of which are underway) until benefit is demonstrated.

On the other hand the recently released ACST, as we have already mentioned above, (200) proved superior results for asymptomatic patients, less than 75 years old, with stenosis greater than 70% who were submitted to CEA versus best medical treatment alone, which was left to the discretion of the clinician (antiplatelet, anticoagulant, antihypertensive, or lipid-lowering drugs). Exclusion criteria included previous ipsilateral CEA, an expectation of poor surgical risk (eg, because of recent acute myocardial infarction), some probable cardiac source of emboli (because the main stroke risk might then be from cardiac, not carotid, emboli), or any major life-threatening condition other than carotid stenosis. Thus, patients likely to require joint CEA and coronary artery bypass grafting were not randomised. Obviously the exclusion criteria of this trial were not very strict and rigid as in NASCET, including the vast majority of typical patients requiring treatment for asymptomatic carotid artery stenosis.

Carotid artery stenting

CAS is a promising innovation under evaluation with comparable short term results to CEA. However, we should remember that the lesion being treated is usually not emergent, and therefore transfer to a facility with the skills, training, and knowledge to perform this procedure with acceptable results is almost always possible. There are several preliminary single-center experiences that have been published as well as an international multicenter compilation (270-288). In the following text we comment on some of the most important trials for evaluation of this technology.

The Carotid and Vertebral Artery Transluminal Angioplasty Study **(CAVATAS)** was a large, prospective, randomized, multicenter trial comparing CEA with carotid artery angioplasty with selective stent placement in 504 patients with symptomatic stenoses (at least 30% luminal diameter reduction) who were suitable for surgery (289). This study did not use distal protection, and stent placement was performed in only 26% of cases. There was no significant difference in the risk of stroke or death related to the procedure between CEA and CAS. The technical success rate for CAS was 89% (successful balloon inflation or stent placement; the percentage of residual stenosis was not reported). The rate of any stroke lasting longer than 7 days or death within 30 days of first treatment was approximately 10% in both the CEA and CAS groups. The rate of disabling stroke or death within 30 days of first

treatment was 6% in both groups. Preliminary analysis of long-term survival showed no difference in the rate of ipsilateral stroke or any disabling stroke in patients up to 3 years after randomization. The rates of stroke or death within 30 days in CAVATAS in both groups are higher than many previous reports but not significantly different from the European Carotid Surgery Trialists (ECST) rate of 7% (51). The 1-year restenosis rate was 20% for CAS and 5% for CEA. Cranial nerve injury (9%) and myocardial ischemia (1%) occurred at the time of treatment in the CEA group only. Long-term follow-up is not yet available.

The **Wallstent Trial** was an industry supported prospective, randomized trial comparing CEA and CAS for symptomatic stenosis of 60% or more (290,291). This was an early study, performed without distal protection and without the currently accepted antiplatelet therapy. In this study, 219 patients with symptomatic carotid stenosis of 60%–90% diameter were randomized to CEA or stent placement. The technical success rate for CAS was 97% (successful deployment with less than 30% residual stenosis). The risk of any perioperative stroke or death was 4.5% for CEA and 12.1% for CAS. At 1 year, the risk of a major stroke was 0.9% for CEA compared with 3.7% for CAS. This trial was stopped prematurely due to poor results from CAS.

A **single-center community hospital study** (292) randomized 104 symptomatic patients to either CEA or CAS without distal protection. Perioperative stroke or death rate was 2% for CEA and 0% for CAS. Other complications for the CEA group totaled 16% and include hematoma (requiring treatment), cranial/cervical nerve injury, and hypotension (requiring treatment). Other complications for the CAS group totaled 45% and included transient cerebral ischemia, leg amputation, retroperitoneal hemorrhage, bradycardia (requiring temporary pacing), and hypotension (requiring treatment).

The **ARCHeR TRIAL** (**A**CCULINK™ for **R**evascularization of **C**arotids in **H**igh **R**isk Patients) is a prospective non randomized Clinical Trial for Carotid Stenting in High Surgical Risk Patients which enrolled 436 patients from 41 Investigational Sites (Multi-center single-arm trial) to evaluate carotid artery stenting in patients at high risk for CEA. High risk Inclusion criteria of this trial are listed in *table 7.* 436 patients (67% male, 33% female) with symptomatic stenoses greater than 50%, or asymptomatic stenoses greater than 80% (according to NASCET angiographic criteria), were treated with ACCULINK stent (158) or with ACCULINK stent plus ACCUNET protection device (278). Mean age was 69,4+/-9,6 years. Follow up was 30 days and every 6 months thereafter. Successful stent deployment was achived in 97.8% and in 92,7% for ACCUNET device. Debris was found 57% of the filters. The 30-days complication rate (death,stroke, MI) was 7.8%. Major ischemic event or death was 3,8% (non filter group) and 2,5% (filter group). The total rate of 30-days adverse events plus ipsilateral stroke within the 1st year was 8,3% (non filter group) and 10,2% (filter group), while for CEA similar risk groups (from NASCET) was 14,5%. We should mention that this trial enrolled 141 patients with recurrent carotid stenosis treated successfully with a total rate of any stroke or death 0,7 %. In conclusions the ARCHeR trial, demonstrated that CAS with filter protection can be safely performed in high-risk patients and that CAS is a viable and possibly better alternative to CEA in select high-risk patients. The ARCHeR Trial was presented at the SIR Annual Scientific Meeting, Salt Lake City, UT, March 2003 by Eles G.

The **SAPPHIRE** trial randomized prospectively 307 patients from 29 US centers to CEA (151) or CAS (156) with a distal protection device. Both surgeons

and interventionalists participating in the trial were high-volume operators with low complication rates. The stent used in the trial was the Precise™ Nitinol Self-Expanding Stent (Johnson & Johnson) with AngioGuard distal protection device (Cordis carotid stent system). Perioperative (30 days) results were presented (Yadav J, presented at the American Heart Association Scientific Sessions, Chicago, November 2002). High risk patients were not rejected. The inclusion and exclusion criteria are listed in *Table 8*. The results are listed in *Table 9,10*. Perioperative stroke and death rates were 7.3% for CEA and 4.4% for CAS. Total major adverse event rate (death, any stroke, or myocardial infarction) for CEA was 12.6% and for CAS was 5.8%. Rates of myocardial infarction were 7.3% for CEA and 2.6% for CAS. Of note, the stroke or stroke/death rate for asymptomatic patients was 6.1% for CEA and 5.8% for CAS, both of which are worse than medical therapy alone in ACAS, and higher than the recommended AHA guidelines for treatment, albeit in a different patient population. CAS may have a role in the management of some patients with significant stenoses of the extracranial cervical carotid artery. In addition, percutaneous endovascular therapy offers a less invasive method of repair with apparent reduction of nonneurologic morbidity. In the NASCET study, for example, reported complication rates were 7.6% for cranial nerve palsies, 5.5% for wound hematoma, 3.4% for wound infection, 0.9% for myocardial infarction, and 3.0% for other cardiac complications (24). These complications are virtually all related to the operative procedure, are not trivial, and are rarely associated with CAS.

No large (more than 100 patients) currently reported carotid stent study has achieved periprocedural (as long as 30 days after the procedure) morbidity and mortality rates as low as the natural history of medically treated uncomplicated asymptomatic carotid stenosis (289,293-297). In reported case series and registries of CAS, for example, Roubin et al (293) reported an overall stroke rate of 5.9% and a mortality rate of 0.7%; Diethrich et al (295) reported a stroke rate of 10.9% and a mortality rate of 1.7%; Wholey et al (296,297) reported a stroke rate of 4.4% and a mortality rate of 1.4% in their initial report and 4.2% and 0.9%, respectively, in their follow-up report. These results compare favourably with the risk-to-benefit ratio of CEA for symptomatic cervical carotid stenosis but fall short of the intrinsically low risk of stroke for medically treated asymptomatic disease. However, Jordan et al (298), analyzing the same patients and data as did Roubin et al (293), reported a stroke rate of 12.7% and a mortality rate of 1.1% for CAS. In addition, the durability of stents, stent restenosis rates, and long-term rates of subsequent stroke have not been determined. For these reasons, angioplasty and stent placement for asymptomatic carotid artery stenosis should only be considered in special circumstances.

Current clinical trials evaluating carotid stenting have focused on high-risk patients and may not reflect the broad population of patients with carotid stenosis who undergo treatment to prevent stroke. The Carotid Revascularization Using Endarterectomy or Stenting Systems (**CaRESS**) phase I study (299) is a multicenter, prospective, nonrandomized trial designed to address the question of whether carotid stenting (CAS) with cerebral protection is comparable to carotid endarterectomy (CEA) in patients with symptomatic and asymptomatic carotid stenosis. Patients with symptomatic (with >50% stenosis) or asymptomatic (with >75% stenosis) carotid stenosis were entered into the study in a 2:1 ratio of carotid stent and GuardWire Plus distal protection device. This unique trial model was developed through collaboration with the International Society of Endovascular Specialists, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, the National Institutes of Health, and industry representatives. The primary end points included

death and stroke at 30 days and a composite 1-year end point of death, stroke, or myocardial infarction (MI) from 0 to 30 days and death or stroke from 31 days to 1 year. The secondary end points included residual stenosis, restenosis, repeat angiography, and carotid revascularization at 30 days and 1 year and quality-of-life changes at 1 year. A total of 397 patients (254 CEA and 143 CAS) were enrolled in the study: 32% were symptomatic and 68% were asymptomatic. There were no significant differences in patient characteristics, symptoms, or surgical risk profiles between groups at baseline. Kaplan-Meier analysis revealed no significant differences in combined death/stroke rates at 30 days (3.6% CEA vs 2.1% CAS) or at 1 year (13.6% CEA vs 10.0% CAS). Similarly, there was no significant difference in the combined end point of death, stroke, or MI at 30 days (4.4% CEA vs 2.1% CAS) or at 1 year (14.3% CEA vs 10.9% CAS). There were no significant differences between CEA and CAS in the secondary end points of residual stenosis (0% CEA vs 0.9% CAS), restenosis (3.6% CEA vs 6.3% CAS), repeat angiography (2.1% CEA vs 3.6% CAS), carotid revascularization (1.0% CEA vs 1.8% CAS), or change in quality of life (_1.56 points CEA vs _4.22 points CAS). The CaRESS phase I study suggests that the 30-day and 1 year risk of death, stroke, or MI with CAS is equivalent to that with CEA in symptomatic and asymptomatic patients with carotid stenosis.

The National Institutes of Health has funded **CREST** to answer particular questions pertaining to the safety and efficacy of angioplasty and stent placement at the cervical carotid bifurcation and to clarify the specific indications for this procedure. This trial will compare CEA and CAS in patients with a symptomatic severe stenosis (70% or more by ultrasonography or 50% by NASCET angiographic criteria). It is important to note that because CREST has inclusion/exclusion criteria similar to those of NASCET, CREST is not designed to assess the safety and efficacy of stent placement in patients known to be at higher risk of CEA.

Cerebral Protection Devices

CAS is undergoing rapid evolution. An area of intense investigation is the use of various protection devices and techniques to prevent what is perceived to be the most common and severe complication of the procedure: embolization of debris to the brain. This recognition that distal embolization is the major complication associated with CAS has led to the development of numerous devices designed to prevent distal embolization by proximal flow control, distal flow control, or distal particulate filtration (300). Several ongoing trials of CAS have incorporated protection devices in the study design (301-307), but no one device or type of device has been proved to be superior. A metaanalysis of carotid stent placement series suggests that these protective devices do actually reduce the incidence of periprocedure neurologic deficit (308), but the extent of this reduction remains to be determined in a randomized, controlled trial. More specifically, Kastrup A, et al, (308) in order to evaluate the efficacy of cerebral protection devices in preventing thromboembolic complications during CAS, he conducted a systematic review of studies reporting on the incidence of minor stroke, major stroke, or death within 30 days after CAS. He searched for studies published between January 1990 and June 2002 by means of a PubMed search and a cumulative review of reference lists of all relevant publications. In 2357 patients a total of 2537 CAS procedures had been performed without protection devices, and in 839 patients 896 CAS procedures had been performed with protection devices. Both groups were similar with respect to age, sex distribution, cerebrovascular risk factors,

and indications for CAS. In many studies the periprocedural complication rates had not been presented separately for patients with symptomatic and asymptomatic CAD. The combined stroke and death rate within 30 days in both symptomatic and asymptomatic patients was 1.8% in patients treated with cerebral protection devices compared with 5.5% in patients treated without cerebral protection devices ($P<0.001$). This effect was mainly due to a decrease in the occurrence of minor strokes (3.7% without cerebral protection versus 0.5% with cerebral protection; ($P<0.001$) and major strokes (1.1% without cerebral protection versus 0.3% with cerebral protection; ($P<0.05$), whereas death rates were almost identical (0.8%; $P=0.6$). In conclusion, on the basis of this early analysis of single-center studies, the use of cerebral protection devices appears to reduce thromboembolic complications during CAS. These technical aspects should be taken into account before the initiation of further randomized trials comparing CAS with carotid endarterectomy. The expectation is that these devices will potentially help to further decrease the risk of CAS to the point that this procedure would be equal or superior to CEA (309,310). Recent data also suggest their use is not without difficulty or potential complication (311,312). A prolonged "learning curve" may exist before realization of actual benefit, about which there is still controversy (311,312).

INDICATIONS AND CONTRAINDICATIONS

A. Acceptable Indications for CAS

1. Symptomatic, severe stenosis that is surgically difficult to access (eg, high bifurcation requiring mandibular dislocation) (313)
2. Symptomatic, severe stenosis in a patient with significant medical disease that would make the patient high risk for surgery (242-258,314–319) (*Table 8*).
3. Symptomatic severe stenosis and one of the following conditions:
    a. Significant tandem lesion that may require endovascular therapy
    b. Radiation-induced stenosis (320,321)
    c. Restenosis after CEA (322,323)
    d. Refusal to undergo CEA after proper informed consent
    e. Stenosis secondary to arterial dissection
    f. Stenosis secondary to fibromuscular dysplasia
    g. Stenosis secondary to Takayasu arteritis (324)
4. Severe stenosis associated with contralateral carotid artery occlusion requiring treatment before undergoing cardiac surgery
5. Severe underlying carotid artery stenosis revealed after recanalization of carotid occlusion after thrombolysis for acute stroke (presumed to be the etiology of the treated occlusion) or to enable thrombolysis for acute stroke
6. Pseudoaneurysm (325)
7. Asymptomatic preocclusive lesion in a patient otherwise meeting criteria 1–3

B. Relative Contraindications

1. Asymptomatic stenosis of any degree, except in particular circumstances, as described above (A4, A6, A7)
2. Symptomatic stenosis associated with an intracranial vascular malformation
3. Symptomatic stenosis in a patient with a subacute cerebral infarction
4. Symptomatic stenosis in a patient with a significant contraindication to angiography

C. Absolute Contraindications

1. Carotid stenosis with angiographically visible intraluminal thrombus
2. A stenosis that cannot be safely reached or crossed by an endovascular approach

Definitions

Severe stenosis: is 70% or greater diameter stenosis by NASCET measurement criteria.
Preocclusive stenosis: is 90% or greater diameter stenosis by NASCET criteria or NASCET definition of "near occlusion" (24).

TECHNICAL SUCCESS

There is insufficient information to define technical success scientifically. For extremity and renal angioplasty, technical success requires less than 30% diameter residual stenosis by angiography and may require improvement in transstenotic pressure gradient (330,331). In the coronary literature, technical success for balloon angioplasty and stent placement had originally been defined as 20% relative improvement with a decrease in stenosis to less than 50%, but it has recently been revised to a decrease in stenosis to less than 20% (332,333). However, unlike extremity, renal, or coronary stenoses, carotid stenoses are very rarely symptomatic due to hemodynamic compromise. Rather, symptoms arise from embolization from a carotid plaque. It is unknown what degree of correction of carotid stenosis is necessary to reduce the risk of embolization, but removal of the embolic source is fundamental. It is possible that in the attempt to more completely eliminate residual stenosis by full balloon dilation, additional emboli may be produced during the procedure that could cause a higher risk of procedure complications. Alternatively, leaving a higher degree of residual stenosis may lead to a higher rate of late restenosis, which at this time is of uncertain clinical significance. Some carotid stent placement trials have defined technical success as residual stenosis of less than 30% (Yadav J, presented at the American Heart Association Scientific Sessions, Chicago, November 2002). Others have used a definition of residual stenosis of less than 50% (Eles G, The ARCHeR Trial, presented at the SIR Annual Scientific Meeting, Salt Lake City, UT, March 2003). In the absence of definitive scientific evidence, technical success in this document is arbitrarily defined as stent placement resulting in improvement of the stenosis by 20% or more with a final residual stenosis of less than 50% with NASCET

measurement criteria. Some practices may prefer to use a lesser degree of residual stenosis as their desired endpoint for technical success.

COMPLICATION RATES

As with many endovascular and surgical techniques, there is a learning curve associated with CAS. Complications will be more frequent when the procedure is performed by less experienced practitioners. This phenomenon is also recognized with the performance of CEA as well as coronary intervention. To account for the level of physician experience, an ad hoc committee of the AHA Stroke Council (334) proposed that a "beginning surgeon be assigned 100 trouble-free cases as a theoretical statistical basis." For example, 75 cases would be added proportionately by indication categories to a beginning surgeon's 25 cases to form a statistical basis of 100 total cases. The number of trouble-free cases is decreased by the number of real cases performed until the practitioner has actually performed 100 cases. With this system, a new physician would be considered to have a 5% complication rate, rather than 50%, if he or she had complications with five of the first 10 cases. This concept appears to be a valid method to account for physician inexperience. Because we have recommended relatively high thresholds *(Table 11)* for the complications associated with CAS, the number of trouble-free cases assigned to a new physician should be less than the 100 cases used for evaluation of CEA. Otherwise, excessive complications might continue without triggering a review. For the performance of CAS, 30 trouble-free cases will be assigned (in both the asymptomatic and symptomatic patient categories) to new physicians for initial statistical analysis that will be performed as described in the AHA document.

Previous reports of experience with CAS have described complications, particularly neurologic, in an inconsistent and nonstandardized fashion. We recognize the need for more detailed, clinically relevant, and uniform outcome measures. Both the duration and severity of neurologic complications are important. The necessity for significant postoperative interventions, such as emergency thrombolytic therapy, is also thought to be important. However, defining precisely what would constitute a "significant" posttreatment intervention would be difficult, as would reporting and analyzing all such interventions. Use of the NIHSS facilitates rapid and uniform assessment of neurologic complications. In addition, the NIHSS may serve as a reasonable surrogate measure for significant posttreatment interventions. The rationale for using the NIHSS for this purpose is that small increases in the NIHSS are thought to be much less likely to result in significant interventions, including repeated angiography and thrombolytic therapy. Therefore, adoption of the NIHSS as a standard outcome measure will allow uniform assessment of complications and approximate the incidence of significant postoperative interventions. Differentiation between outcomes and complications in patients with asymptomatic versus symptomatic arterial stenoses is critical. The natural history of the two groups of patients differs dramatically, with much lower risk of stroke in asymptomatic patients. As with CEA, the risks associated with CAS appear to be lower in asymptomatic patients and the risk-to-benefit ratio for CAS appears to be significantly different for asymptomatic versus symptomatic patients.

While practicing physicians should strive to achieve perfect outcomes (eg, 100% success, 0% complications), in practice, all physicians will fall short of this

ideal to a variable extent. Thus, indicator thresholds may be used to assess the efficacy of ongoing quality improvement programs. For the purpose of these guidelines, a threshold is a specific level of an indicator that should prompt a review. When measures such as indications or success rates fall below a (minimum) threshold or when complication rates exceed a (maximum) threshold, a review should be performed to determine causes and to implement changes, if necessary. Routine periodic review of all cases having less than perfect outcomes is strongly encouraged. Intracranial embolization and subsequent stroke are the major complications associated with CAS (269-297). A review may be triggered when the threshold values described, are exceeded. The thresholds were derived from critical evaluation of the literature and evaluation of empirical data from the committee members' practices.

Summary

The social and economic burden of stroke is as devastating as morbidity and mortality caused by the disease it self.(205-207) We should encourage every scientific effort aiming towards the establishment of the most appropriate treatment for carotid bifurcation disease. We believe that both carotid endarterectomy and carotid stenting as well as medical therapy have a special role in CAD therapeutic management. While this statement represents a thorough current recommendation form, it should be noted that many issues are still unclear, or are currently the subject of study in prospective randomized trials. It is our hope that this document will undergo periodic revision, as these trials reach completion, and it is likely that the recommendations in this document will be subject to change.

Appendix

Classification of evidence

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:
a) primary outcome(s) clearly defined
b) exclusion/inclusion criteria clearly defined
c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias
d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a RCT a representative population that lacks one criterion a-d.
Class III*:* All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV*:* Evidence from uncontrolled studies, case series, case reports, expert opinion.

Classification of recommendations

A _ Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)
B _ Probably effective, ineffective, or harmful for the given condition in specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)
C _ Possibly effective, ineffective, or harmful for the given condition in specified population. (Level C rating requires at least one Class study or two consistent Class III studies.)
U _ Data inadequate or conflicting given current knowledge, treatment unproven.

Definitions

Neurologic complication: neurologic deterioration evidenced by an increase in the NIHSS score of one or more points
Transient deficit: a neurologic complication having complete resolution within 24 hours
Reversible stroke: a neurologic complication having a duration of more than 24 hours and up to 30 days
Permanent stroke: a neurologic complication having a duration of more than 30 days
Minor deficit: neurologic deterioration evidenced by an increase of the NIHSS score of less than four points without the presence of aphasia or hemianopsia
Major deficit: neurologic deterioration evidenced by an increase of the NIHSS score of four or more points or the presence of aphasia or hemianopsia
Technical success: inflation of angioplasty balloon/placement of stent in the carotid stenosis with improvement of the stenosis by 20% or more with a final residual stenosis of less than 50% using NASCET measurement criteria.

Abbreviations: ACAS = Asymptomatic Carotid Atherosclerosis Study, • ACR = American College of Radiology, • AHA = American Heart Association, • ASITN = American Society of Interventional and Therapeutic Neuroradiology, • ASNR = American Society of Neuroradiology, • CAS = carotid angioplasty and stent placement, • CEA = carotid endarterectomy, • CREST = Carotid Revascularization: Endarterectomy vs. Stent Trial, • NASCET = North American Symptomatic Carotid Endarterectomy Trial, • NIHSS = National Institutes of Health Stroke Scale, • SIR = Society of Interventional Radiology

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Tables and figures

Table 1 : Mean annual incidence rates of first TIA, Rochester, Minnesota, 1955-1979 (n = 392)

Incidence rate per 100,000 population per year

	Women		Men		Total	
Age (yr)	No.	Rate	No.	Rate	No.	Rate
<50	7	1	14	3	21	2
50-59	16	28	35	77	51	50
60-69	47	99	69	213	116	145
70-79	87	252	49	263	136	256
>=80	49	268	19	248	68	263
Total adjusted	206	29*	186	45*	392	37+
>= 50 adjusted	199	111*	172	168*	371	138+

* Directly age-adjusted to 1970 U.S. white population.
+ Dire&ly age- and sex-adjusted to 1970 U.S. white population.

Table 2 : Mean annual incidence rates of first cerebrovascular event, age >=50 years, Rochester, Minnesota. 1960-1972

Incidence rate per 100,000 population per year

	TIA (n = 185)		Stroke (n = 777)		TIA/stroke* (n = 907)	
	F	M	F	M	F	M
Age (yr)	(n =101)	(n=84)	(n=402)	(n 375)	(n =470)	(n =437)
50-59	24	40	99	264	119	294
60-69	97	218	373	740	446	928
70-79	240	268	824	1288	996	1422
>=80	323	343	1581	1796	1742	2087
Age-adjusted	111	162	436	725	513	844
Age- and sex-adjusted +	134		565		661	

* Whichever occurred first.
+ Age- and sex-adjusted to 1970 U.S.

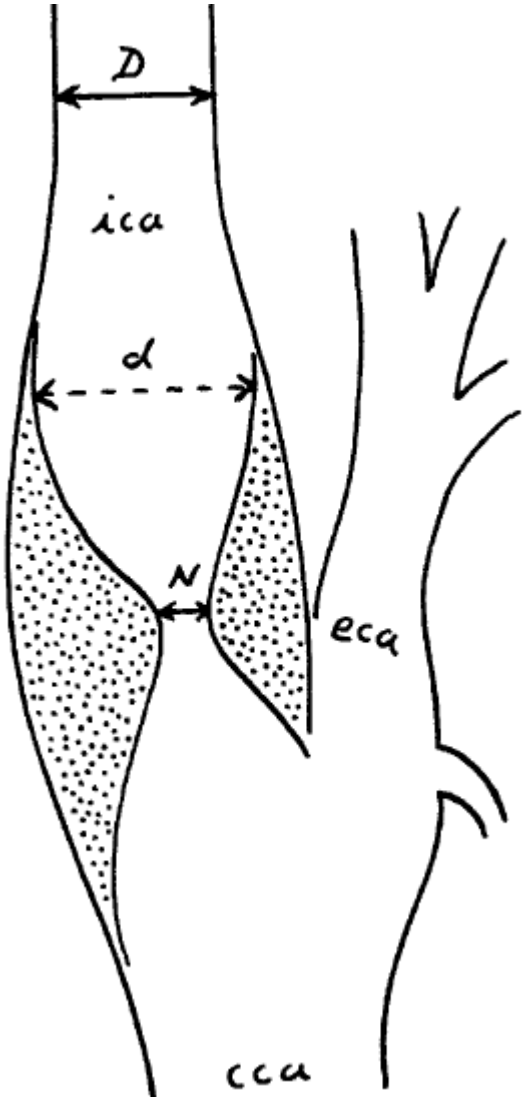

Fig. 1: Recommended method of measuring carotid stenosis. The residual lumen diameter (N) is measured at the point of greatest narrowing on the angiographic projection that shows the stenosis at its maximum. This diameter is compared with the lumen diameter of the distal internal carotid artery at a point where the arterial walls become parallel (D), not at a point of poststenotic dilatation distal to the obstruction (d). The percentage stenosis is calculated as (1- N/D) · 100. cca = common carotid artery, eca = external carotid artery, ica = internal carotid artery. (29)

Table 3: Summary of appropriate ratings for, antiplatelet therapy, anticoagulation therapy, and management of blood pressure for recurrent stroke prevention (225)

Role of medical therapy

	No atrial fibrillation	Atrial fibrillation	
		Low bleeding risk	High bleeding risk
Antiplatelet therapy	Appropriate	Not on warfarin: Appropriate On warfarin: Uncertain	Not on warfarin: Appropriate On warfarin: Inappropriate
Anticoagulation	Inappropriate	Appropriate	Uncertain

Antiplatelet therapy

Cerebrovascular event	Ticlopidine	Clopidogrel	Aspirin	Extended-release dipyridamole + Aspirin	Clopidogrel + Aspirin
Prior event did not occur on aspirin	Inappropriate	Appropriate	Appropriate	Appropriate	Uncertain*
Prior event occurred on aspirin	Inappropriate	Appropriate	Uncertain	Appropriate	Appropriate*

*Match trials results pending.

Table 4: Overview of symptomatic trials (222)

Author/y (report no.)	Class	Randomized	Follow-up, mo	Stenosis, %	Treatment arm	Cohort size	Crossovers, %	Ipsilateral stroke risk + periop stroke and death, %	Periop stroke and death, %	Periop disabling stroke and death, %	Any stroke	Major stroke or death, %
NASCET collaborators/ 1991 (403)	1	Yes	24*	70-99†	CEA + BMT	328	0.3	9	5.8	2.1	12.6	8.0
					BMT	331	6.3	26	3.3	0.9	27.6	18.1
ECST Collab. Group/ 1991 (398)	1	Yes		70-99‡	CEA + BMT	455		9.5¶	7.5¶	3.7		4.8
					BMT	323		13.6¶				8.4
V.A./1991 (391)	1	Yes	11.9	50-99†	CEA + BMT	91	0	4.4	6.5	4.4		
					BMT	98	3.3	7.1	2.2	0		
ECST Collab. Group/ 1996 (244)	1	Yes	96*	50-69‡	CEA + BMT	570				7.9	16.8	
					BMT	372					14.2	
NASCET collaborators/ 1998 (137)	1	Yes	60*	50-69†	CEA + BMT	430	1.9	15.7			23.9	18.3
					BMT	428	7.0	22.2			32.3	25.2
ECST Collab. Group/ 1996 (244)	1	Yes	96*	30-49‡	CEA +BMT	389				8.0	16.2	
					BMT	259					10.4	
ECST Collab. Group/ 1991, 1998 (398, 155)	1	Yes		0-29‡	CEA + BMT	240		11.3¶	3.3¶	1.7	17.1¶	36.7¶
					BMT	179		5.6¶	0	0	12.8¶	30.7¶
CE Trialists/2003			65	<50†	CEA +BMT	1707			6.7			
				50-69†	CEA +BMT	812			8.4			
				>=70†	CEA + BMT	581			6.2			
				Near occlusion	CEA + BMT	148			5.4			

* Estimated using Kaplan–Meyer survival curves.
† Measured using narrowest diameter compared to normal upstream internal carotid diameter.
‡ Measured using narrowest diameter compared to estimated original carotid diameter.
¶ Stroke lasting _7 days.
CEA _ carotid endarterectomy; BMT _ Best medical therapy.

Table 5: Combined analysis of results from ACST and ACAS

	ACST		ACAS		Total	
	Immediate	Deferral	Immediate	Deferral	Immediate	Deferral
Number of patients	1560	1560	825	834	2385	2394
Follow-up (years)	3,4	3,4	2,7	2,7	3,1	3,1
CEA undertaken	1348		724		2072	
Procedural morbidity*						
Death†	15	2	3	1	18	3
Non-fatal stroke	25	9	16	2	41	11
Non-procedural stroke						
Fatal (within 5 years)†	12	44‡	6	9	18	53‡
Non-fatal	30	76‡	35	74‡	65	150‡
5-year risk (%) of stroke or procedural morbidity§	6·4	11·7‡	5·1	11·0	6·0	11·5‡
Other deaths						
Other vascular	144	127	37	50	181	177
Neoplastic	64	47	15	13	79	60
Respiratory	9	11	10	9	19	20
Other/unknown	20	19	12	9	32	28

*Perioperative events in ACST, angiographic or perioperative events in ACAS. (One patient in the deferral arm of ACST had a procedural stroke after having another stroke.) Note that absolute numbers suffering procedural morbidity and non-procedural stroke cannot simply be added to assess net benefit: instead, life-table methods must be used, as in figure 3. †Net 5-year risk of procedural death or stroke death in ACST is 2·1% versus 4·2%, p=0·006. ‡p<0·0001. §Procedural morbidity or ipsilateral stroke in ACAS.

Table 6 : Inclusion/Exclusion Criteria for Carotid Endarterectomy Trials

NASCET
Inclusion
1. Symptoms of focal cerebral ischemia ipsilateral to a stenosis of <70% (moderate group) or ≥70% (severe group) within 180 days, as shown on angiography 2. Symptoms lasting <24 hours or producing nondisabling stroke (Rankin score <3)
Exclusion
1. Age >80 years (initial phase of moderate and severe stenosis; continuing study of moderate stenosis included these patients) 2. Lack of angiographic visualization of symptomatic artery 3. Lack of informed consent 4. Intracranial stenosis more severe than the cervical stenosis 5. Other disease limiting life expectancy to <5 years 6. Cerebral infarction limiting useful function in the affected arterial territory 7. Nonatherosclerotic carotid disease 8. Cardiac lesions likely to cause cardioembolism 9. History of ipsilateral carotid endarterectomy
ACAS
Inclusion
1. Age 40–79 years 2. Compatible history and findings on physical and neurologic examination 3. Acceptable laboratory and electrocardiogram results 4. Arteriography within the previous 60 days indicating stenosis of at least 60% reduction in diameter (if arteriography performed 61–364 days before randomization, repeat Doppler showing artery still patent) or Doppler examination within 60 days showing a frequency or velocity greater than the instrument-specific cut point with 95% positive predictive value or Doppler examination showing a frequency or velocity greater than the instrument-specific 90% positive predictive value cut point confirmed by ocular pneumoplethysmographic examination within the previous 60 days
Exclusion
1. Cerebrovascular event in the distribution of the affected carotid artery or the vertebrobasilar system 2. Symptoms referable to the contralateral cerebral hemisphere within the previous 45 days 3. Contraindication to aspirin therapy 4. Any disorder that could seriously complicate surgery 5. Any condition that could prevent continuing participation or likely to produce death or disability within 5 years 6. Lack of informed consent

Table 7 : ARCHeR TRIAL High Risk Entry Criteria

Characteristic	N = 437
Restenosis after CEA	**32.2%**
EF <30% or NYHA≥ III	**28.6%**
2 or more diseased coronary arteries	**27.5%**
Need open heart surgery ≤ 30 days	**15.6%**
Contralateral ICA occlusion	**14.6%**
Unstable angina	**8.5%**
Surgically inaccessible lesion	**7.6%**
Prior radiation to neck	**6.6%**

Table 8: Inclusion/Exclusion Criteria for the SAPPHIRE Trial of Carotid Stent Placement

Inclusion
Asymptomatic stenosis >80% or symptomatic stenosis >50% by angiography or ultrasonography and at least one of the following conditions that would result in high surgical risk:
1. Age >80 years 2. Congestive heart failure (class III/IV) and/or left ventricular ejection fraction <30% 3. Open heart surgery needed within 6 weeks 4. Recent myocardial infarction (>24 hours and <4 weeks) 5. Unstable angina (CCS class III/IV) 6. Severe chronic obstructive pulmonary disease 7. Contralateral carotid occlusion 8. Contralateral laryngeal nerve palsy 9. Severe tandem lesions 10. Lesions distal or proximal to the usual location 11. Previous endarterectomy with restenosis 12. Previous radiation therapy or radical neck surgery
Exclusion
1. Acute ischemic neurologic event within past 48 hours 2. Total occlusion of the target carotid artery 3. Surgical or interventional procedure planned within the next 30 days 4. Common carotid ostial lesion

Table 9: SAPPHIRE: 30-day complications

Complication	*stenting (%)*	*endarterectomy (%)*	*p*
Transient ischemic attack	*3.8*	*2.0*	*0.50*
Major bleeding	*8.3*	*10.6*	*0.56*
Cranial nerve injury	*0.0*	*5.3*	*<0.01*

Table 10: SAPPHIRE: 30-day MACE (death, any stroke or MI)

Group	**stenting (%)**	**endarterectomy (%)**	**p**
Overall	**5.8**	**12.6**	**0.047**
Symptomatic patients	**4.2**	**15.4**	**0.13**
Asymptomatic patients	**6.7**	**11.2**	**0.33**

Table 11: Thresholds for Indications, Technical Success, and Complications (326)

	Complications Threshold	
Neurologic complication	Asymptomatic Patient (%)	Symptomatic Patient (%)
Minor transient deficit	At present, there are minimal and insufficient data available to suggest threshold values for transient deficits after CAS. We believe that these data should be collected and reported to further our understanding of CAS and, perhaps, to help to decrease the incidence of permanent neurologic complications. When adequate data about transient neurologic complications become available, this document will be revised to include threshold values for such transient complications.	
Major transient deficit		
Minor reversible stroke	3.5	6
Major reversible stroke	2	3
Minor permanent stroke	3	4.5
Major permanent stroke	2	3
Death	All deaths should be reviewed	
Indications	Meets the indications listed in the text 95%	
Technical success	90%	

Inappropriate comparison of the *thresholds* in this table to the reported *incidences of complications* after CEA might lead to an erroneous conclusion that higher rates of neurologic complications are acceptable for CAS compared with lower rates for CEA:

(a) A "threshold" is not intended to represent a desirable incidence of complications. A "threshold" implies a complication rate that is significantly above the expected rate of complications, such that an audit should be conducted to examine the cause of the unexpectedly high incidence of complications.

(b) These thresholds are significantly higher than the complication rates for CEA published in the randomized ACAS and NASCET trials. Those trials included only low-risk patients. The thresholds in this document pertain only to high-risk patients. Except for patients treated as part of an approved investigational trial, patients considered to have normal risk of CEA do not fall within the acceptable indications for carotid artery angioplasty and stent placement as defined in this document.

(c) The thresholds described in this document are comparable with the incidences of complications resulting from CEA performed on similar high-risk patients.

(d) The thresholds described in this document do not apply to low-risk patients treated under an approved investigational trial. Lower thresholds, comparable with the well-established experience with CEA in low-risk patients, would apply for CAS performed under these conditions.

(e) The definitions for the neurologic complications on which these thresholds are based differ from those used in many reported series. No accepted, standardized methodology for reporting all neurologic complications exists. The neurologic complications defined in this document should be applicable to a broad range of cerebrovascular interventions and surgery.

(f) The thresholds described in this document reflect complications occurring within 30 days of CAS, not immediate postoperative results.

(g) Thresholds for the reversible stroke categories are based on the expectation that reversible deficits are likely to be slightly more common than permanent strokes. We recognize that there is not yet adequate scientific literature to confirm this.