



# Carotid endarterectomy— An evidence-based review

## Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

S. Chaturvedi, MD; A. Bruno, MD; T. Feasby, MD; R. Holloway, MD, MPH; O. Benavente, MD; S.N. Cohen, MD; R. Cote, MD; D. Hess, MD; J. Saver, MD; J.D. Spence, MD; B. Stern, MD; and J. Wilterdink, MD

**Abstract—Objective:** To assess the efficacy of carotid endarterectomy for stroke prevention in asymptomatic and symptomatic patients with internal carotid artery stenosis. Additional clinical scenarios, such as use of endarterectomy combined with cardiac surgery, are also reviewed. **Methods:** The authors selected nine important clinical questions. A systematic search was performed for articles from 1990 (the year of the last statement) until 2001. Additional articles from 2002 through 2004 were included using prespecified criteria. Two reviewers also screened for other relevant articles from 2002 to 2004. Case reports, review articles, technical studies, and single surgeon case series were excluded. **Results:** For several questions, high quality randomized clinical trials had been completed. Carotid endarterectomy reduces the stroke risk compared to medical therapy alone for patients with 70 to 99% symptomatic stenosis (16% absolute risk reduction at 5 years). There is a smaller benefit for patients with 50 to 69% symptomatic stenosis (absolute risk reduction 4.6% at 5 years). There is a small benefit for asymptomatic patients with 60 to 99% stenosis if the perioperative complication rate is low. Aspirin in a dose of 81 to 325 mg per day is preferred vs higher doses (650 to 1,300 mg per day) in patients undergoing endarterectomy. **Conclusions:** Evidence supports carotid endarterectomy for severe (70 to 99%) symptomatic stenosis (Level A). Endarterectomy is moderately useful for symptomatic patients with 50 to 69% stenosis (Level B) and not indicated for symptomatic patients with <50% stenosis (Level A). For asymptomatic patients with 60 to 99% stenosis, the benefit/risk ratio is smaller compared to symptomatic patients and individual decisions must be made. Endarterectomy can reduce the future stroke rate if the perioperative stroke/death rate is kept low (<3%) (Level A). Low dose aspirin (81 to 325 mg) is preferred for patients before and after carotid endarterectomy to reduce the rate of stroke, myocardial infarction, and death (Level A).

NEUROLOGY 2005;65:794–801

Extracranial internal carotid artery stenosis accounts for 15 to 20% of ischemic strokes, depending on the population studied. Carotid endarterectomy (CE) is the most frequently performed operation to prevent stroke.

The last statement from the American Academy of

Neurology regarding CE was published in 1990.<sup>1</sup> Since then, several multicenter trials have been completed and this statement reflects an update on major developments since 1990.

**Methods.** Vascular neurologists were appointed by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. A literature search was performed using Ovid Medline for relevant articles published from 1990 to 2001 using the following key words: carotid endarterectomy, carotid stenosis, carotid artery diseases, clinical trials. Further de-

Additional material related to this article can be found on the *Neurology* Web site. Go to [www.neurology.org](http://www.neurology.org) and scroll down the Table of Contents for the September 27 issue to find the title link for this article.

From the Stroke Program and Department of Neurology (Dr. Chaturvedi), Wayne State University; Department of Neurology (Dr. Bruno), Indiana University; University of Alberta (Dr. Feasby); Department of Neurology (Dr. Holloway), University of Rochester, NY; Department of Neurology (Dr. Benavente), University of Texas-San Antonio; Stroke Prevention Program (Dr. Cohen), Sunrise Hospital, Las Vegas, NV; Department of Neurology (Dr. Cote), McGill University; Department of Neurology (Dr. Hess), Medical College of Georgia; UCLA Stroke Center (Dr. Saver); Robarts Research Institute (Dr. Spence); Department of Neurology (Dr. Stern), University of Maryland; and Department of Neurology (Dr. Wilterdink), Brown University.

This guideline was approved by the Therapeutics and Technology Assessment Subcommittee on November 19, 2004; by the Practice Committee on April 13, 2005; and by the Board of Directors on June 26, 2005.

Disclosure: The authors report no conflicts of interest.

Received February 18, 2005. Accepted in final form June 15, 2005.

Address correspondence and reprint requests to American Academy of Neurology, 1080 Montreal Ave., St. Paul, MN 55116.

**Table 1** *Relevant formulas*

	Formula
No. needed to treat (NNT)	100/absolute risk reduction
No. needed to harm (NNH)	100/absolute risk increase

tails of the search process can be found in appendix E-1 (go to the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)). Standard search procedures were used and subheadings were applied as appropriate. Two committee members also reviewed the Cochrane Library statements on CE for symptomatic and asymptomatic stenosis in August 2004 to confirm that relevant citations from 2002 to 2004 were identified.

The initial search was done in July 2001 and identified 1,462 citations. This list was refined further by reviewing these citation abstracts with exclusion of the following types of articles: case reports, letters to the editor, review articles without primary data, studies addressing CE technical issues, case series from a single surgeon, and non-English articles. Case series from a single institution were not excluded. This reduced the articles to 186 and each of these articles was reviewed independently by two committee members. The committee also stipulated that if a pooled analysis of the major symptomatic CE studies or if the results of the Asymptomatic Carotid Surgery Trial were published prior to the completion of the committee's manuscript, these would subsequently be reviewed. For some of the clinical questions, additional screening criteria were used before the study was selected for full abstraction (see below). The number needed to treat and harm were evaluated in studies as described in table 1. Recommendations were generated based on the application of levels of evidence to the abstracted articles (Appendices 1 and 2).

**Analysis of the evidence.** Nine clinical questions were identified and they are as follows.

**1. Does CE benefit symptomatic patients?** Two Class I studies have been completed: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) (these trials and other articles reported in results can be found in supplementary appendix E-1).<sup>2-4</sup> A third well-designed study, the Veterans Affairs Cooperative Studies Program 309 Trial, was stopped prematurely after the initial NASCET results were announced.<sup>5</sup> 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 2 provides a summary of the main features of the two completed symptomatic studies, NASCET and ECST. Although the overall design of the two studies was comparable, one major difference between the two trials was in the method of angiographic measurement. NASCET calculated the degree of stenosis using the site of maximal narrowing as the numerator, divided by the distal ICA diameter where the vessel walls became parallel and beyond any area of post-stenotic dilatation. ECST calculated the degree of stenosis using the diameter at the site of maximal narrowing divided by the esti-

mated diameter of the normal carotid bulb. This means for a given level of stenosis, the percentage narrowing would be lower using the NASCET method compared to the ECST method. For example, a NASCET 70% stenosis corresponds to an 82% ECST stenosis.

The principal result of NASCET was a significant benefit of CE in patients with 70 to 99% symptomatic stenosis. The 2-year ipsilateral stroke risk was 26% in the medically treated patients and 9% in the BMT + CE group ( $p < 0.001$ ). The absolute risk reduction (ARR) was 17.0% and the number needed to treat (NNT) was six at 2 years. 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,  $p = 0.045$ ). 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 ( $p = 0.16$ ). Results of ECST were slightly different if the comparison was undertaken using the ECST method of stenosis measurement but when the ECST angiograms were re-analyzed using the NASCET method, the two trials produced remarkably consistent results.<sup>6,7</sup>

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 combined analysis of the symptomatic trials, done by Rothwell et al., included 6,092 patients with 35,000 patient-years of follow-up.<sup>8</sup> The combined analysis included individual patient data, reassessed the angiograms, and standardized the outcomes. Due to differences in the three trials in terms of definition of stroke outcome events and disabling stroke, the combined analysis utilized the following NASCET definitions: 1) stroke was defined as any cerebral or retinal event with symptoms lasting longer than 24 hours; 2) disabling stroke was defined as a stroke that resulted in a Rankin score of 3 or more, or an equivalent rating, at a defined follow-up interval. For all these studies, the outcome was ipsilateral stroke or perioperative (30 days) stroke or death. Also, in the three studies represented in the combined analysis, the degree of stenosis was proven by contrast angiography. The major conclusions were as follows.

Benefit for CE was shown for: 50 to 69% stenosis, ARR of 4.6% (over 5 years), NNT = 22.

≥70% stenosis (not near occlusion), ARR of 16% (over 5 years), NNT = 6.3.

Near occlusion, ARR of 5.6% over 2 years ( $p = 0.19$ ) but only -1.7% ( $p = 0.9$ ) over 5 years. Near occlusion is defined as the angiographic appearance

**Table 2** Overview of symptomatic trials

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.

of a collapsed internal carotid artery (ICA) distal to the stenosis, faster filling in the external carotid artery compared to the ICA, and preferential filling of the intracranial circulation via collaterals.

CE was not beneficial for symptomatic patients with 30 to 49% angiographic stenosis and surgery was harmful for symptomatic patients with <30% stenosis (2.2% absolute increase in stroke risk). In the combined analysis, the overall rate of perioperative stroke or death for all surgical patients within 30 days of trial surgery was 7.1%, giving a number needed to harm (NNH) of 14. As mentioned above, the robust benefits of future reduction in stroke risk for patients with severe stenosis and to a lesser extent for patients with 50 to 69% stenosis justified the surgical risks.

*2. Does CE benefit asymptomatic patients?* Three Class I studies are available: the Asymptomatic Carotid Atherosclerosis Study (ACAS), the Veterans Affairs Study, and the Asymptomatic Carotid

Surgery Trial (ACST).<sup>9-11</sup> Two other studies were either completed or planned but these were either stopped prematurely (Mayo Clinic trial) or poorly designed (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Vs Aspirin [CASANOVA] study).

The Mayo Asymptomatic Carotid Endarterectomy (MACE) study was prematurely stopped after only 71 patients due to a high rate of myocardial infarction (22%) in the surgical group.<sup>12</sup> This was likely due to the trial policy of withholding aspirin from the surgical group.

The CASANOVA study had a suboptimal study design and conduct.<sup>13</sup> 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 Veterans Affairs study enrolled 444 men with angiographically proven 50 to 99% asymptomatic stenosis.<sup>10</sup> There was a nonsignificant trend favoring CE for prevention of ipsilateral stroke (9.4% vs 4.7% at 4 years). However, this was a secondary endpoint. The primary endpoint included TIA, which most clinicians consider as an inappropriate endpoint since, by definition, TIA does not leave the patient with any lasting clinical deficit. The 30-day perioperative stroke and death rate was 4.7%, equating to a NNH of 21.

ACAS enrolled 1,662 patients with 60 to 99% stenosis with the stenosis defined angiographically for the surgical group and primarily with ultrasound for the medical group.<sup>9</sup> Patients were randomized to BMT or BMT + CE. 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). The 5-year projected rate of ipsilateral stroke was 11.0% for the medically treated patients and 5.1% for the surgically treated patients (53% relative risk reduction,  $p = 0.004$ ). 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 NNH of 43. The very low perioperative stroke/death rate of 2.3% has not been achieved in most recent observational studies or in the Aspirin and Carotid Endarterectomy (ACE) trial ( $n = 1,512$ , stroke and death = 4.6%).<sup>14</sup>

The ACST was a randomized study of immediate CE vs indefinite deferral of CE with a 5-year follow-up at 126 centers in 30 countries. Determination of stenosis was made by carotid ultrasound and expressed as percent diameter reduction. Eligibility included carotid artery diameter reduction of at least 60% on ultrasound and no symptoms within the past 6 months. Enrollment began in 1993 and continued until 2003 and there is planned 10-year follow-up. A total of 3,120 patients were randomized, 1,560 into each group. Combining the perioperative events (stroke and death within 30 days) and the non-perioperative strokes, the net 5-year risks were 6.4% (immediate CE) vs 11.8% (deferred CE) for all strokes [net gain 5.4% (95% CI, 3.0 to 7.8)  $p < 0.0001$ ] and 3.5% vs 6.1% for fatal or disabling strokes (Rankin > 2) [net gain 2.5% (0.8 to 4.3),  $p = 0.004$ ]. The gain mostly involved non-perioperative carotid territory ischemic strokes [2.7% vs 9.5%; gain of 6.8% (4.8 to 8.8),  $p < 0.0001$ ]. The benefit was seen in both contralateral and ipsilateral carotid-territory strokes. Subgroup analyses showed that the benefits were significant for those younger than 65 years, those between 65 and 74 years, but uncertain for those older than 75 years. The study included 2,044 men and 1,076 women. Men and women both

benefited but there were only a total of 40 (12 vs 28 strokes in the surgical and medical groups) non-perioperative strokes in women so the results were not as definite ( $p = 0.02$ ). The 5-year benefit of CE appeared to be as great for those with <80% diameter reduction (mean 69% stenosis) as for those with 80 to 99% (mean 87%) reduction. There was no significant difference in results in those patients who were never symptomatic (7.1% absolute 5-year gain) compared to those with symptoms greater than 6 months previously (4.6% absolute 5-year gain).

A significant difference between ACAS and ACST was the primary endpoint. ACAS and the previous symptomatic trials utilized ipsilateral stroke as the primary endpoint whereas ACST included all strokes, including contralateral events and vertebro-basilar strokes. If the ACST analysis was limited to ipsilateral stroke only, the absolute benefit would be reduced.

3. *Is emergent CE beneficial in patients with progressing stroke of <24 hours?* Four Class IV studies were identified that met the criteria. 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.

4. *What are the most 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.<sup>15</sup> 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,<sup>16</sup> with the greatest benefit found in men, patients above age 75 years, and those randomized within 2 weeks of their last symptomatic event.

5. *What are the most 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.<sup>17</sup>

**Table 3** Carotid endarterectomy (CE)–coronary artery bypass graft (CABG) studies

Report no., y	Class	Group	Perioperative Stroke, %	Perioperative MI, %	Perioperative death, %	Long-term survival, %
824, 1979*	III	Simultaneous CE-CABG (n = 51)	0	3.9	5.9	NR
		Staged CABG then CE (n = 84)	0	2.4	1.2	NR
931, 1992*	III	Simultaneous CE-CABG (n = 52)	1.9	0	3.8	91 at 6 y
		Staged CE then CABG (n = 45)	0	8.8	4.4	87 at 6 y
896, 1996	IV	Simultaneous CE-CABG (n = 100)	0	1	4	NR
17, 1996	IV	Simultaneous CE-CABG (n = 100)	9	6	8	73 at 5 y
813, 1997*	III	Simultaneous CE-CABG (n = 255 with unstable angina)	3.9	4.7	3.5	NR
		Staged CE then CABG (n = 257 without unstable angina)	1.9	4.7	1.6	NR
875, 1997	IV	Simultaneous CE-CABG (n = 304)	4.3	0	5.3	NR
832, 2000	IV	Simultaneous CE-CABG (n = 408)	1.4 within 3 mo	NA	3.4	NR
836, 2000	IV	Simultaneous CE-CABG (n = 340)	3.2	0.6	2.6	79 at 5 y
840, 2000	IV	Simultaneous CE-CABG (n = 313)	2.2	3.2	8.9	NR

Qualified studies on CE before or simultaneous with CABG.

\* Statistical comparison between the two surgical groups of interest not reported.

MI = myocardial infarction; NR = not reported.

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).<sup>18</sup>

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).<sup>8</sup> 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.

**6. What is the ideal dose of aspirin preoperatively in patients undergoing CE?** The ACE trial enrolled 2,849 subjects into a double-blind randomized clinical trial comparing 81 mg, 325 mg, 650 mg, and 1,300 mg of aspirin, starting before carotid endarterectomy, and continued for 3 months (Class I).<sup>14</sup> The combined rate of stroke, myocardial infarction, and death was the primary outcome. This endpoint was lower in the low-dose groups (81 mg and 325 mg) than in the high-dose groups (650 mg and 1,300 mg) at 30 days (5.4 vs 7.0%,  $p = 0.07$ ) and at 3 months (6.2 vs 8.4%,  $p = 0.03$ ). Another trial enrolled 232 subjects to 75 mg aspirin or placebo started before CE and continued for 6 months (Class I).<sup>19</sup> Although likely underpowered, this trial demonstrated fewer strokes without recovery in those subjects randomized to aspirin compared with placebo at 1 month (zero strokes vs 7 strokes,  $p = 0.003$ ) and 6 months (2 strokes vs 11 strokes,  $p = 0.01$ ).

**7. What is the evidence/practice gap? Can trial results be achieved in practice?** Only studies with at least 100 patients were included in the final analysis.

Some previous publications have raised concerns that the CE results achieved in the clinical trials may not be reproducible in routine clinical practice. This is referred to as the evidence/practice gap. To address this issue, 33 total articles within this category were identified and 17 were excluded for the reason mentioned above. Several methodologic shortcomings in these articles were identified, including the following: inconsistency in the time horizon (inpatient vs 30 day results), inconsistency in the method of reporting (self-report from one's own records vs "vascular database" vs medical record audit), difficulty in drawing conclusions about symptomatic status of the patients and degree of stenosis. "Appropriateness" studies and studies on volume/outcome relationships were also not well represented. Due to the methodologic shortcomings in this area, we recommend further high quality studies to evaluate these issues in the future (see Future research).

**8. What are the data regarding CE concurrent with or prior to coronary artery bypass graft (CABG)?** The initial search identified 48 studies for review and 9 of these met criteria for inclusion (50 or more subjects). 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 (table 3). 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.

**Table 4** Timing of carotid endarterectomy

Design, class, study no.	Population sample	Total sample	Early group (<6 wk)	Late group (>6 wk)	Comparison of groups at baseline	Blinded outcome assessment	Outcome differences	Adjustments made	
Retrospective, IV (117)	One institution, 1981 to 1998	207	86	121	Comparable except race	No	No differences	No	Hoffmann
Retrospective, IV (425)	Two institutions, 1978 to 1988	129	82	47	Comparable	No	No differences	No	Piotrowski
Retrospective, II (326)	NASCET trial	100	42*	58	Comparable	Yes	No difference	No	Gasecki
Retrospective, IV (343)	One institution, 1980 to 1990	85	28	57	Not mentioned	No	No differences	Yes	Makhoul
Retrospective, IV (112)	One institution, 1991 to 1998	75	49*	26	Greater vascular risk factors in early group	No	No differences	No	Kahn
Retrospective, IV (80)	One institution, 1986 to 1996	45	20	25	More stenosis in early group	No	No differences	No	Parrino

\* <4 wk, >4 wk.

There were nine studies with 50 or more subjects having simultaneous CE-CABG totaling 1,923 subjects. These studies included subjects 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 the only study 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.

**9. How long should one wait after a stroke to perform CE?** 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 (table 4). 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 longer-term follow-up. There were significant limitations in the designs of these studies. Only the NASCET subgroup analysis had randomized patient assignment. Three of the studies (references 117, 112, and 80 from table 3) had differences in baseline characteristics between the group and adjustments were made in terms of the outcome assessment. 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.<sup>16</sup> 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.

**Perioperative morbidity and mortality.** 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%. Based on these results and statements from other professional groups,<sup>20</sup> recommendations are given below for maximal acceptable levels of perioperative morbidity and mortality for CE in symptomatic and asymptomatic patients. 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.** 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, see below). 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.

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 pa-

tient'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).

**Recommendations for future research.** 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.

There are several other important areas for further investigation pertaining to CE. One area of current investigation is how CE compares to less invasive, endovascular treatment with stenting in patients with symptomatic and asymptomatic carotid stenosis.<sup>21</sup> The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study reported improved outcomes in patients at high risk for surgery who were treated with carotid stenting.<sup>22</sup> In low to medium risk patients, the Carotid Revascularization Endarterectomy vs Stent Trial (CREST) is comparing CE vs carotid stenting in patients with symptomatic, 50 to 99% angiographic stenosis.<sup>23</sup> An amendment to include patients with severe asymptomatic stenosis in CREST has recently been approved. Several other trials are in progress as well.

Also, the role of cerebral hemodynamics in risk stratification for patients with carotid stenosis was not emphasized in the recent multicenter trials. It would be of great interest to examine indices of vasoreactivity and cerebral perfusion in future studies of patients with both symptomatic and asymptomatic carotid stenosis.<sup>24</sup>

Medical treatment for atherosclerosis has evolved considerably since the original CE trials. In studies such as NASCET and ECST, statins were not in widespread use and only a minority of patients was aggressively treated with lipid lowering agents. A panel of experts has recommended statins for patients with a LDL of >100 mg/dL and symptomatic carotid stenosis or carotid stenosis of >50%.<sup>25,26</sup> Other agents have also been approved for stroke prevention such as newer antiplatelet agents and angiotensin receptor blockers. There is a paucity of data on stroke rates in patients with carotid stenosis who receive an aggressive treatment regimen with statins, newer antiplatelet agents, and targeted blood pressure lowering. Intensive medical therapy of this type may erase the small benefit of CE in patients with asymptomatic stenosis or 50 to 69% symptomatic stenosis.<sup>27</sup> Studies to address this issue are needed.

**Disclaimer.** This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

## Acknowledgment

The committee thanks Drs. Chung Hsu and David Lefkowitz as liaisons from the TTA Subcommittee, Alison Nakashima, Paul Hetland, Nancy King, and Wendy Edlund from the American Academy of Neurology for their assistance in coordinating the review, and Vicki Glasgow for assistance with the literature search.

## Appendix 1

### Classification of evidence

**Class I:** Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

- primary outcome(s) clearly defined
- exclusion/inclusion criteria clearly defined
- adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias
- 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 in 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, or expert opinion.

## Appendix 2

### 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 the 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 the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
- U = Data inadequate or conflicting given current knowledge, treatment is unproven.

## Appendix 3

**Therapeutics and Technology Assessment Subcommittee Members:** Douglas S. Goodin, MD (Chair); Yuen T. So, MD, PhD (Vice-Chair); Carmel Armon, MD, MHS; Richard M. Dubinsky, MD, MPH; Mark Hallett, MD; David Hammond, MD; Cynthia Harden, MD; Chung Hsu, MD, PhD (ex-officio); Andres M. Kanner, MD (ex-officio); David S. Lefkowitz, MD; Janis Miyasaki, MD; Michael A. Sloan, MD, MS; James C. Stevens, MD.

## References

- Interim assessment: carotid endarterectomy. Report of the American Academy of Neurology, Therapeutics and Technology Assessment Subcommittee. *Neurology* 1990;40:682-683.
- Barnett HJM, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415-1425.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-453.
- European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-1387.
- Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA* 1991;266:3289-3294.
- Barnett HJ, Warlow CP. Carotid endarterectomy and the measurement of stenosis. *Stroke* 1993;24:1281-1284.
- Rothwell PM, Gutnikov SA, Warlow CP. Reanalysis of the final results of the European Carotid Surgery Trial. *Stroke* 2003;34:514-523.
- Rothwell PM, Eliasziw M, Fox AJ, et al. for the Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107-116.
- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid stenosis. *JAMA* 1995;273:1421-1428.
- Hobson RW, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993;328:221-227.
- MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491-1502.
- Mayo Asymptomatic Carotid Endarterectomy Study Group. Effectiveness of carotid endarterectomy for asymptomatic carotid stenosis: design of a clinical trial. *Mayo Clin Proc* 1992;64:897-904.
- Carotid surgery versus medical therapy in asymptomatic carotid stenosis. The CASANOVA Study Group. *Stroke* 1991;22:1229-1235.
- Taylor DW, Barnett HJM, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999;353:2179-2184.
- Benavente O, Eliasziw M, Streifler JY, et al. Prognosis after transient monocular blindness associated with carotid-artery stenosis. *N Engl J Med* 2001;345:1084-1090.
- Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM, for the Carotid Endarterectomy Trialists' Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915-924.
- Gasecki AP, Eliasziw M, Ferguson GG, et al. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. *J Neurosurg* 1995;83:778-782.
- Baker WH, Howard VJ, Howard G, Toole JF, Investigators ftA. Effect of contralateral occlusion on long-term efficacy of endarterectomy in the Asymptomatic Carotid Atherosclerosis Study (ACAS). *Stroke* 2000;31:2330-2334.
- Lindblad B, Persson N, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. *Stroke* 1993;24:1125-1128.
- Billir J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1998;29:554-562.
- CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729-1737.
- Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493-1501.
- Hobson RW. CREST (Carotid Revascularization Endarterectomy versus Stent Trial): background, design, and current status. *Semin Vasc Surg* 2000;13:139-143.
- Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA* 2000;283:2122-2127.
- Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497.
- Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004;110:227-239.
- Chaturvedi S. Should the multicenter carotid endarterectomy trials be repeated? *Arch Neurol* 2003;60:774-775.