Objective: The purpose of this study was to compare carotid endarterectomy (CEA) plus medical therapy (MT) with MT alone for symptomatic and asymptomatic patients suffering from carotid artery stenosis in terms of long-term stroke/death rate.

Design: A meta-analysis of parallel randomized, controlled trials (RCTs) (blind or open) published in English.

Participants: Patients suffering from carotid artery stenosis symptomatic or not.

Interventions: Patients were subjected to CEA plus MT or MT alone.

Measurements and Main Results: For asymptomatic patients, 6 RCTs comprising 5,733 patients (CEA = 2,853 and MT = 2,880) were included. CEA did not affect the stroke/death risk for asymptomatic patients (risk ratio [RR] = 0.93; 95% confidence interval [CI], 0.84 to 1.02; F = 0%; p = 0.14).

For symptomatic patients, 2 RCTs were included. They had 5,627 patients (CEA = 3,069 and MT = 2,558) of whom 2,295 patients (CEA = 1,213; MT = 1,082) had severe stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] technique ≥50% and European Carotid Surgery Trial technique ≥70%). CEA decreased the stroke/death risk only for patients with severe stenosis (RR = 0.69; 95% CI, 0.59-0.81; p < 0.001 [random effects model]; F = 0% on the odds ratio and 17% on the RR [benefit or harm side]; number needed to treat = 11 [95% CI, 8-17]).

Conclusions: CEA is helpful for recently symptomatic patients with carotid artery stenosis ≥50% (NASCET technique) but adds no benefit in terms of stroke/death for asymptomatic patients.

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KEY WORDS: carotid endarterectomy, stroke, death

INTRODUCED IN 1954 by Eastcott et al,1 carotid endarterectomy (CEA) has been proposed as the gold standard for the treatment of carotid artery stenosis in symptomatic patients (eg, transient ischemic attack [TIA], nondisabling stroke, or retinal infarction within the last 6 months) and asymptomatic patients (eg, reasonable option) provided that the patient has a 5-year life expectancy and that the combined stroke/death rate at 30 days is lower than 6% for symptomatic patients and lower than 3% for asymptomatic patients.2 Asymptomatic is defined as the absence of symptoms of an ipsilateral stroke or a TIA within the last 6 months and may include patients with a previous contralateral or vertebrobasilar stroke or a TIA. Medical therapy (MT) should consist of at least antiplatelet drugs for patients with a noncardioembolic ischemic stroke or a TIA associated with carotid atherosclerosis; treatment of arterial systolic hypertension; statin agents targeting low-density lipoprotein (LDL) of 100 mg/dL, for those with coronary heart disease or symptomatic atherosclerotic disease and LDL of 70 mg/dL for very high-risk persons with multiple risk factors; intensive insulin treatment for type-1 diabetic patients; and cessation of smoking.3,4

However, recommendations in favor of CEA plus MT versus MT alone are based on randomized, controlled trials (RCTs) only published up to 2004.2 Therefore, it seems appropriate to challenge these recommendations. The purpose of the present meta-analysis was to compare CEA plus MT with MT alone for symptomatic and asymptomatic patients suffering from carotid artery stenosis in terms of long-term stroke/death (ie, the patient died of any cause or is alive but suffered from any type of stroke).

METHODS

A search for all RCTs published in English comparing CEA plus MT with MT alone in patients with carotid artery stenosis was performed in the American National Library of Medicine’s PubMed in August 2011 with the following terms: (1) “carotid artery stenosis AND carotid endarterectomy” limited to “English” AND “human” [4,875 hits], (2) randomize* OR Randomized trial* OR Double blind* OR Placebo* OR Clinical trial* OR Randomized OR Controlled trial[Publication Type] OR Controlled clinical trial[Publication Type] OR Meta-analysis OR Review OR Systematic review [1,960,535 hits], and (3) 1 and 2 = 1,779 hits. The references lists of all articles retrieved and the ones of the recent previous meta-analysis on the topic also were checked.2,3,5,6 When data were published in more than one report, available reports were consulted, but the study (not the report) was considered the unit; therefore, no study was considered more than once. As recommended by the Cochrane Collaboration, the RCTs were judged on the information contained in the reports without any assumption of the following: (1) adequate sequence generation (quasi-randomized studies were rejected); (2) allocation concealment (inability of the person who was recruiting the patient to know in advance to what group the patient would be assigned); (3) blinding of patients, the personnel, and the assessor for the 2 outcomes of interest; (4) incomplete outcome data addressed (clear description of the fate of all patients included in the study); (5) free of selective reporting (outcomes of interest clearly available for all patients included in the study); and (6) free of other bias (any other possible factor that could have influenced the results). Data were extracted in texts, tables, or figures as required. Only real data (no estimated figure) were considered. Unless specified otherwise, stroke included all strokes originating from any cerebral vessels (ischemic or hemorrhagic) from any territory (and not just ischemic strokes originating from the ipsilateral carotid artery). Death included deaths from any cause. Data were analyzed with RevMan 5 (for the risk of bias assessment) (Version 5.0; The Nordic Cochrane Centre, Copenhagen, Denmark).
Median follow-up of 2.7 y. Follow-up missing for 11 patients of MT and 9 for CEA.

Aspirin, 325 mg daily plus risk factor-reduction counseling on hypertension, obesity, hyperlipidemia, diabetes mellitus, tobacco or ethanol abuse, sedentary lifestyle, use of estrogen compounds, and polycythemia for both groups. Compliance evaluated by pill count.

Table 1. Characteristics of Included Studies for Asymptomatic Patients

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients</th>
<th>Degree of Stenosis</th>
<th>Type of Anesthesia/Type of Surgery</th>
<th>Medical Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS7*</td>
<td>Patient with symptoms within the last 45 days or conditions likely to produce significant mortality or morbidity or render follow-up difficult within the 5-y period are excluded. Side of higher degree of stenosis taken for the study (no patient entered twice). Smoker: CEA = 28% v MT = 24% Diabetes: CEA = 25% v MT = 21% HT: CEA = 64% v MT = 64% MI = 21% Cancer: CEA = 12% v MT = 10%</td>
<td>≥60% stenosis (diameter reduction) confirmed arteriographically before surgery but after randomization. Patients randomized on other methods and found not operable after the arteriogram were kept in their group (1.2% stroke rate from arteriography). Contralateral nonoperated symptomatic carotid lesion CEA = 22% v MT = 27%. Contralateral occlusion: CEA = 10% v 9%</td>
<td>Not standardized: operated within 2 wks of randomization; 45 local/regional anesthesia and 673 general anesthesia or both; 356 shunted; 240 patch closures; 12 without intraoperative coagulation modifier; 221 intraoperative EEG monitoring; Surgeons had to perform at least 12 CEAs/y with combined neurologic morbidity and mortality: “&lt;3% for asymptomatic patients and 5% for symptomatic patients</td>
<td>Aspirin, 325 mg daily plus risk factor-reduction counseling on hypertension, obesity, hyperlipidemia, diabetes mellitus, tobacco or ethanol abuse, sedentary lifestyle, use of estrogen compounds, and polycythemia for both groups. Compliance evaluated by pill count.</td>
<td>Median follow-up of 2.7 y. Follow-up missing for 11 patients of MT and 9 for CEA</td>
</tr>
<tr>
<td>ACST1*</td>
<td>No known illness preventing long-term follow-up. Excluded if smooth calcified carotid plaque, major life-threatening disease other than stroke, recent acute myocardial infarction, intracerebral neoplasia or aneurysm, restenosis from previous CEA. Diabetes: CEA = 26% v MT = 23% HT: CEA = 44% v MT = 42% Cholesterol &gt;250 mg/dL: CEA = 27% v 27% ischemic heart disease (nonidiabetic): CEA = 26% v 27%. 57 patients were operated on more than once. Smoking status unknown</td>
<td>Ultrasound evaluation, ≥60% (diameter reduction as defined by NASCET†) uni- or bilateral. 11.3% patients included had prior ipsilateral carotid artery symptoms but dating of more than 6 mo before randomization. Contralateral nonoperated symptomatic carotid lesion CEA = 10% v MT = 9%. Contralateral occlusion: CEA = 9% v 8%.</td>
<td>Not standardized: surgeons with at least 50 prior CEAs with a 30-d stroke/death rate &lt;6%; only half had surgery within a month of randomization. Contralateral CEA during study time: CEA = 4% v MT = 2.8%</td>
<td>MT for smoking, HT, diabetes, obesity, hyperlipidemias, polycythemia and ischemic heart disease in both groups. Routine postoperative antiplatelet therapy (aspirin mainly).</td>
<td>Mean follow-up of 3.4 y taken as 3 y. Follow-up also available at a median of 9 y.</td>
</tr>
<tr>
<td>CASANOVA6</td>
<td>Bilateral stenosis not operated on and 32 patients with bilateral disease operated on in 1 side only. Intention-to-treat analysis. 16 patients of CEA and 52 patients of MT had further CEA during the study. Between 1982 and 1988, 99% followed for the entire study time.</td>
<td>Greater than 50% and &lt;90% (ECST criteria†). Mandatory arteriography before surgery</td>
<td>Greater than 50% and &lt;90% (ECST criteria†). Mandatory arteriography before surgery</td>
<td>Aspirin, 330 mg, and dipyridamole 3 times daily for 3 y in both groups. Compliance controlled by urinary tests. Regimen poorly tolerated by patients, continued with lower aspirin doses or dipyridamole alone. At 3 years, 89% are still on medication, taking at least 1 pill of aspirin (62%) or dipyridamole alone (28%).</td>
<td>Surgeons selected in universities and large teaching hospitals. Techniques unspecified.</td>
</tr>
</tbody>
</table>
Mean follow-up 23.6 mo. Premature termination by order of the data and Safety Monitoring Committee.

VACS
EEG monitoring Aspirin, 80 mg/d, in the MT group only, no aspirin in CEA group unless prescribed for known cardiac disease; compliance assessed by urine tests for both groups. Mandatory arteriography before surgery.

Table 1. Characteristics of Included Studies for Asymptomatic Patients (Cont’d)

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients</th>
<th>Degree of Stenosis</th>
<th>Type of Anesthesia/Type of Surgery</th>
<th>MT</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA = 36 uni- or bilateral surgery. MT = 35 Intention-to-treat April 1988 to December 1990 No lost to follow-up. 9 CEA patients not operated for various reasons (including occurrence of stroke in 1) and 2 MT operated</td>
<td>Excluded if: &gt;79 y of age, women of child bearing age or &lt;18 years old; unstable angina or myocardial infarction within 6 mo; cancer or another illness likely to be terminal within 3 y; dementia; nonatherosclerotic carotid disease; polycythemia, renal insufficiency; uncontrolled HT or diabetes; and prior cerebral or retinal ischemic disease or ipsilateral CEA. HT: CEA = 63% v MT = 64% MI: CEA = 14% v 19% Current smoking: CEA = 31% v MT = 25% Hyperlipidemia: CEA = 66% v 44% Diabetes: CEA = 14% v MT = 19% Previous CEA, cerebral infarction, high surgical risks, and life expectancy &lt;5 y excluded Current smoker: CEA = 25% v MT = 21% Diabetes: CEA = 14% v MT = 12% HT: CEA = 30% v MT = 28% MI: CEA = 13% v MT = 11% 8 patients of the surgical group have been included twice in the study.</td>
<td>≥50% linear or ≥75% area on ultrasound or intravenous digital subtraction angiography but no occlusion. Most stenotic segment normalized above or below.</td>
<td>EEG monitoring</td>
<td>Aspirin, 80 mg/d, in the MT group only, no aspirin in CEA group unless prescribed for known cardiac disease; compliance assessed by urine tests for both groups. Other antiplatelet drugs or warfarin allowed and said to be comparable across the 2 treatment groups. Treatment of HT, hyperlipidemia, and diabetes in both groups.</td>
<td>Mean follow-up 23.6 mo. Premature termination by order of the data and Safety Monitoring Committee.</td>
</tr>
<tr>
<td>VACS</td>
<td>CEA = 211 MT = 233 men only mean age 64.5 y (64.1 v 64.7) 1983-1991 intention-to-treat For CEA, 8 patients had staged bilateral procedures, and 8 were not operated on. Patients in the MT group operated on appearance of symptoms.</td>
<td>Patients judged to be an unacceptable risk for arteriography/surgery; scheduled for major operations, contralateral symptomatic disease; previous CEA were excluded.</td>
<td>Abnormal neck bruit plus abnormal OPPG. Arteriography in CEA group only.</td>
<td>Mean 47.9 ± 27.9 mo (planned 5 years), taken as 4 years. 35 lost to follow-up: CEA = 20 MT = 15</td>
<td></td>
</tr>
<tr>
<td>WRAMC</td>
<td>CEA: 15 MT: 14 Patients of MT group operated on appearance of symptoms. In CEA, 2 not operated: 1 developed FV during arteriography and another refused arteriography; 1 had repeated CEA.</td>
<td>Aspirin, 650 mg twice a day in the MT only.</td>
<td>Mean follow-up of 3 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST-1: Asymptomatic Carotid Surgery Trial; CASANOVA, Carotid Artery Stenosis With Asymptomatic Narrowing Operation Vs Aspirin Study; MACE, Mayo Clinic Trial; VACS, Veterans’ Affairs Cooperative Study; WRAMC, Walter Reed Army Medical Center; CEA, carotid endarterectomy; GA, general anesthesia; HT, hypertension; MI, previous myocardial infarction; MT, medical therapy alone; OPPG, ocular pneumoplethysmography; RA, regional or local anesthesia; EEG, electroencephalogram; M, male; F, female.

*Study halted by the data Safety and Monitoring Board after a 2.7-year median follow-up because of a projected 5.9% absolute risk reduction at 5 years favoring CEA.

†A NASCET 70% stenosis corresponds to an 82% ECST stenosis (formula: ECST = [0.6 × NASCET] + 40).

‡Recruitment prematurely stopped because of a high rate of myocardial infarction (22%) in the surgical group in whom aspirin was withheld.
RESULTS

Asymptomatic Patients

The search produced 6 RCTs, including 5,733 patients (CEA = 2,853 and MT = 2,880) for asymptomatic patients. The characteristics of the trials relevant to asymptomatic patients are given in Table 1. None of the studies had applied a complete medical treatment as to actual standards. The quality of the studies is summarized in Figure 1. The definitions used for the diagnosis of a stroke for each study are given in Table 2. CEA does not affect the stroke/death risk for asymptomatic patients (risk ratio [RR] = 0.93; 95% confidence interval [CI] = 0.84 to 1.02; F = 0%; p = 0.14; Fig 2). There was no relationship between the year when the original report was published and the effect size (log odds ratio; p value of the slope of the meta-regression = 0.81; Fig 3). For these 6 studies, the overall stroke/death rates for follow-ups between 2 and 3.4 years were CEA of 29.7% and MT of 28.3%. For the Asymptomatic Carotid Surgery Trial (ACST)-1 study, a follow-up up to 10 years (median = 9 years; interquartile range, 6-11 years) is available. Data for combined stroke/death rates are not provided. The number of nonperioperative strokes was 39 and 68 for CEA and MT, respectively, for a total number of 56 for CEA and 71 for MT. Half of the strokes were disabling ones (ie, the person will require assistance for daily life activities) for the survivors (RR = 0.79; 95% CI, 0.56-1.11; p = 0.18). The total number of deaths (including the perioperative mortality) was higher for CEA (571 for CEA and 502 for MT; RR = 1.14; 95% CI, 1.03-1.25; p = 0.01).

Symptomatic Patients

For symptomatic patients, the search produced 5 trials. One study was excluded from the analysis because it included patients operated on for other vessels than the carotid artery and stenosis from 30% and higher without the possibility to selectively extract the outcomes of interest (stroke/death rate for severe [≥70%] carotid artery stenosis). One trial used a surgical technique that is no longer in use (ie, femorocarotid bypass for all patients) and also was excluded. For 1 study, follow-up is available for only 11.9 months. Two trials that included 5,627 patients (CEA = 3,069 and MT = 2,558) were retained for the analysis (Tables 3 and 4; Fig 4). For a stenosis <50%, adding CEA was either of no benefit or harmful (Fig 5). For stenosis between 50% and 69%, trying to add the data of CEA and MT, respectively, for a total number of 56 for CEA and 1,082). The number needed to treat calculated on the OR and 17% on the RR [benefit or harm side; Fig 5]. This new subgroup contained 2,295 patients (CEA = 1,213 and MT = 1,082). The number needed to treat calculated on the OR is 11 (95% CI, 8-17). The classic fail safe number (ie, the number of missing negative studies required to bring the p value to 0.05) is 19. The stroke/death rates at 2 to 2.7 years of follow-up were 20.9% for CEA plus MT and 30.4% for MT alone.
RESULTS found here differ significantly from the following American Academy of Neurology's recommendation: “It is reasonable to consider CEA 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).” Results from the RCTs available provide a follow-up between 2 and 4 years, with the exception of ACST-1, which gives a follow-up of 9 years. When considering all available data, there is no evidence that CEA provides any benefit to the patient in terms of any stroke/death risk. The benefit of CEA in asymptomatic patients recently has been questioned on the basis that an improvement in MT may overcome the small benefit of CEA added to MT in this population. However, in the present meta-analysis, there was no effect of time on the effect size (Fig 3), implying that the absence of benefit from the surgery in asymptomatic patients cannot be imputed to a better use of medical therapy. Some prior conclusions (eg, those of the Asymptomatic Carotid Atherosclerosis Study [ACAS]) were based, in part, on imputed long-term results extrapolated from medium-term results. These assumptions failed to take into account that this population has an overall short life expectancy. It could be argued that only ischemic strokes occurring in the territory of the operated carotid artery and perioperative death or perioperative death plus nonperioperative deaths secondary to strokes should have been considered. However, it was the opinion of the authors that no matter the reason for the stroke or death, these events should be included. Indeed, if the study population (ie, patients suffering from a carotid artery stenosis symptomatic or not) is at too high of a risk of dying or suffering a stroke of any nature in any other territory any time soon after the surgery, then the intervention would be considered an unnecessary risk for the patient. The number of cardiovascular and cancer deaths in this population during a 5-year interval may by far exceed the number of stroke-related deaths whether they are perioperative or not. As an example, in the ACST-1 study, which had a mean follow-up of 3.4 years only, the number of cardiovascular, cancer, and other deaths was 237 for CEA versus 204 for

Table 2. Definitions Used for Stroke in Studies That Included Asymptomatic Patients

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Stroke</th>
<th>Patients With Other Possible Causes of Emboli Excluded From the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS7</td>
<td>Duration of more than 24 h or with new CT changes, not clear if retinal infarction was included or not.</td>
<td>Unclear</td>
</tr>
<tr>
<td>ACST-1</td>
<td>Duration of more than 24 h or with new CT changes, not clear if retinal infarction was included or not.</td>
<td>Yes</td>
</tr>
<tr>
<td>Casanova9</td>
<td>Duration of more than 24 h, not clear if retinal infarction was included or not.</td>
<td>Unclear</td>
</tr>
<tr>
<td>MACE10</td>
<td>Duration of more than 24 h or with new CT changes, including retinal infarction.</td>
<td>Yes</td>
</tr>
<tr>
<td>VACS11</td>
<td>Duration of more than 24 h, retinal infarction included.</td>
<td>Yes (patients with chronic anticoagulant therapy excluded)</td>
</tr>
<tr>
<td>WMARC12</td>
<td>Duration of more than 24 h, retinal infarction included.</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Abbreviations: ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST-1, Asymptomatic Carotid Surgery Trial; CASANOVA, Carotid Artery Stenosis With Asymptomatic Narrowing Operation Vs Aspirin Study; MACE, Mayo Clinic Trial; VACS, Veterans’ Affairs Cooperative Study; WRAMC, Walter Reed Army Medical Center.

DISCUSSION

Results found here differ significantly from the following American Academy of Neurology’s recommendation: “It is reasonable to consider CEA 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).” Results from the RCTs available provide a follow-up between 2 and 4 years, with the exception of ACST-1, which gives a follow-up of 9 years. When considering all available data, there is no evidence that CEA provides any benefit to the patient in terms of any stroke/death risk. The benefit of CEA in asymptomatic patients recently has been questioned on the basis that an improvement in MT may overcome the small benefit of CEA added to MT in this population. However, in the present meta-analysis, there was no effect of time on the effect size (Fig 3), implying that the absence of benefit from the surgery in asymptomatic patients cannot be imputed to a better use of medical therapy. Some prior conclusions (eg, those of the Asymptomatic Carotid Atherosclerosis Study [ACAS]) were based, in part, on imputed long-term results extrapolated from medium-term results. These assumptions failed to take into account that this population has an overall short life expectancy. It could be argued that only ischemic strokes occurring in the territory of the operated carotid artery and perioperative death or perioperative death plus nonperioperative deaths secondary to strokes should have been considered. However, it was the opinion of the authors that no matter the reason for the stroke or death, these events should be included. Indeed, if the study population (ie, patients suffering from a carotid artery stenosis symptomatic or not) is at too high of a risk of dying or suffering a stroke of any nature in any other territory any time soon after the surgery, then the intervention would be considered an unnecessary risk for the patient. The number of cardiovascular and cancer deaths in this population during a 5-year interval may by far exceed the number of stroke-related deaths whether they are perioperative or not. As an example, in the ACST-1 study, which had a mean follow-up of 3.4 years only, the number of cardiovascular, cancer, and other deaths was 237 for CEA versus 204 for
MT in a cohort of 3,120 patients. These numbers easily erased any benefit (short- or long-term) of CEA, which produced 27 perioperative (30-days all causes) and nonperoperative stroke-related deaths versus 46 for MT. At 10 years, mortality was even higher in the CEA group than in the MT group. Although it was said that smoking counseling would be performed, the smoking status, which is an important risk factor for both death and stroke, of the patients included in the ACST-1 study was not published.

The authors also decided not to consider TIAs. A TIA may serve as a warning sign before proceeding to surgery but will not leave any permanent damage to the patient in itself. Previous authors have argued that TIAs are associated with an increased risk of stroke and that therefore reducing them would be beneficial. However, the present analysis is more definitive because it includes enough patients to be able to eliminate a difference in the more important outcomes, those that will last (ie, the number of patients with strokes/deaths). Therefore, it allows to directly determine an outcome difference in stroke/death rather than relying on a surrogate (TIA). All strokes, minor and major, were entered because even minor strokes may affect the quality of life of the patients as measured by the 36-item Short-Form Health Survey at 1 year.

The 2007 average lifetime cost of a CEA was estimated to be $35,200, and for carotid artery stenting (CAS) it was $52,000 (not including the cost of clopidogrel, ultrasound examinations, follow-up visits at clinics, and other indirect costs). According to the 2006 Nationwide Inpatient Sample, which includes 20% of all US discharges from nonfederal hospitals, approximately 90% of interventions were performed on asymptomatic patients. The average rate of these procedures per 1,000 Medicare patients in 2007 was estimated to be 2.5 for CEA and 0.6 for CAS. Thus, for asymptomatic patients, CEA has an average cost of $79,200 per 1,000 Medicare patients in 2007 was estimated to be 2.5 for CEA and 0.6 for CAS. Thus, for asymptomatic patients, CEA has an average cost of $79,200 per 1,000 Medicare patients (2.5 × $35,200), and CAS represents a cost of $28,188 per 1,000 Medicare patients (0.6 × 90% × $52,000). The total cost of an intervention for asymptomatic carotid artery stenosis represented $107,388 per 1,000 Medicare patients ($107.39 per patient) in 2007. On a national basis, this amounts to $3.7 billion for Canada (Canadian population = 34 million) and $33.4 billion for the United States (US population = 311 million). Those are substantial amounts of money for interventions for which no definite evidence of benefit can be found in the present medical literature.

For symptomatic patients, data extraction was limited to a period of 5 years or less because there would not be any benefit expected from a CEA on a symptomatic patient beyond 2 to 3 years. This study confirms that recently symptomatic patients may benefit from CEA in terms of stroke/death (number needed to treat = 11; 95% CI, 8-11). Certain conditions are required. Patients included in those studies were recently symptomatic (<6 months). After a certain amount of time, the risk of a
further stroke after a TIA or a minor stroke decrease with time, possibly because of some healing of a fragile plaque. If a major stroke is to be avoided, the patient should go to surgery as soon as possible as described in those 2 major trials unless, of course, the patient has progressive neurologic damage. Finally, to compensate for the initial increased risk associated with the surgery, the patient has to have a reasonable life expectancy. Here, the benefit was clear with a 2-year follow-up. Also, the risks associated with the surgery itself have to be low. The 30-day stroke/death rates of the 2 trials were 3.7% and 5.6%. This is consistent with a rate below 4% as in 3 other recent major trials. Finally, this study confirmed that a cutoff in the degree of stenosis is required to make CEA worthwhile; patients with a low degree of stenosis would have no benefit and even, potentially, could be harmed by the procedure.

Some authors have suggested that CEA would be of limited benefit for symptomatic patients with near occlusion, whereas others consider that an emergency intervention is required for preocclusive carotid stenosis or carotid occlusion in patients with an acute stroke, a stroke in evolution, or a crescendo TIA (multiple repetitive events within a 24-hour period that do not respond to antiplatelet therapy). Among all the possibilities, this urgent intervention may include CEA for acute stroke depending on the context. Surgery (endarterectomy of the common and external carotid artery with transection and flush ligation of the internal carotid artery) with the addition of oral anticoagulation also is advocated in patients with occlusion and recurrent neurologic or ocular symptoms. Immediate operative re-exploration also is indicated for early postoperative thrombosis at the endarterectomy site. Patients with carotid artery occlusion are also at a higher risk of a perioperative cerebrovascular accident if they undergo cardiac surgery. The present meta-analysis did not allow any specific conclusion on these subgroups to be made. For patients with a contralateral occlusion, CEA may be associated with a better outcome if the surgery is performed under regional anesthesia as opposed to general anesthesia. The benefit of CEA for women also has been questioned by some authors. Women and individuals with small carotid arteries are at a higher risk of early neurologic events and late restenosis. Because there is some evidence to suggest that carotid patch angioplasty may reduce the risk of perioperative arterial occlusion and restenosis and would appear to reduce the risk of ipsilateral stroke with a nonsignificant trend toward a reduction in any perioperative stroke rate and all-cause case fatality, patch angioplasty may be the answer to this objection. Both the NASCET and the ECST trials were performed before the widespread use of statins. However, it is highly improbable that statins could abolish the effect of CEA in symptomatic patients. In the present meta-analysis, CEA reduced the stroke/death rate by approximately 10% (ie, from 30.4% to 20.9% after 2-2.7 years). Statins have no demonstrable effect in terms of risk reduction within the 1st year of their introduction and will reduce the stroke rate (fatal and nonfatal) by 1.4% (from 5.7% to 4.3%) and any death by 1.8% (from 14.7% to 12.9%) after 5 years.

The conclusions that CEA would benefit only symptomatic patients and not asymptomatic ones agree with those of Nagaki et al who, using a Markov model, found that the number of quality-adjusted life years that asymptomatic patients would obtain from CEA would be very low. CAS has been proposed as an equivalent to CEA. However, results from RCTs failed to establish CAS as an equivalent. Compared with CAS, CEA reduced the RR of stroke at 30 days (RR = 0.50; 95% CI, 0.38-0.67; p = 0.000002; event rate = 2.8% and 5.6%) without any statistically significant effect on the death rate.
Table 3. Characteristics of Included Studies for Symptomatic Patients

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients</th>
<th>Degree of Stenosis</th>
<th>Type of Anesthesia/Type of Surgery</th>
<th>Medical Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST(^{14})</td>
<td>Randomized only if no definitive indication for surgery or medical therapy was present.</td>
<td>Maximal narrowing/estimated diameter of normal carotid bulb for 3 subgroups:*</td>
<td>Surgery could be delayed 4-6 wk after a recent stroke.</td>
<td>MT for HT and counseling for cigarette smoking, aspirin (CEA = 77% v MT = 79%), other antiplatelet drugs (CEA = 16% v MT = 18%), anticoagulants (CEA = 6% v MT = 8%), lipid-lowering drugs (CEA = 6% v MT = 8%).</td>
<td>Mean 2.7 y for mild and severe and 4.5 y for moderate stenosis.</td>
</tr>
<tr>
<td>CEA 1981-1991 for mild and severe stenosis and to 1994 for moderate stenosis. CEA = 1,811 (62 no surgery within a year) MT = 1,213 (42 operated within a year)</td>
<td>TIA or minor stroke &lt;6 mo (eye or brain). Excluded if poor general health; previous CEA; poor distal vessel; verteobasilar events only.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous stroke: mild = 61%; severe = 50%; diabetic: mild and severe = 9%; previous MI/angina: Mild = 13%, Severe = 27%</td>
<td>Not occlusion. Arteriography or IV digital angiography. Excluded if occluded, previously operated or presence of a more severe lesion distally.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NASCET(^{16})</td>
<td>Brain or eye TIA or nondisabling strokes within the past 120 days. Excluded if &gt;79 y, disease likely to cause death within 5 y, cerebral infarction in the territory of interest susceptible to deprive the patient of any useful function in this territory, prior ipsilateral CEA, uncontrolled diabetes or HT, recent MI of less than 6 mo, progressive neurologic signs, contralateral CEA &lt;4 mo or major surgery &lt;30 days. For severe stenosis, MI = 18%; HT = 61%; diabetes 19%; hyperlipidemia 23%; cigarette smoking 35% (all balanced across groups except number of patients with diastolic &gt;95 mmHg for CEA 13% v 8%).</td>
<td>Maximal narrowing/distal site with parallel vessel walls beyond any poststenotic dilatation.* Stenosis ≥30% proximal to the 2nd cervical vertebral body from atherosclerotic disease, adequate distal vessel, no occlusion on arteriography.</td>
<td>The center has to show a 30-day stroke/death rate ≤6%. Surgical technique, including anesthetic method and the use of intraoperative monitoring, shunting, and patch grafting are left to the discretion of the surgeon but are recorded. Patients with severe stenosis operated with a median of 2 days after randomization.</td>
<td>Aspirin, 1,300 mg/d, (severe = 96%) or any antiplatelet drugs (severe ≥ 99%, others 98%), treatment of HT (severe = 56% others = 68%), diabetes, and hypercholesterolemia (moderate or less = 40%), smoking counseling.</td>
<td>None lost to follow-up for ≥70%, average 1.5 y. Mean follow-up 5 y for &lt;70% for 99.9% of the patients.</td>
</tr>
<tr>
<td>1988-1991 for ≥70% Patients incorrectly enrolled (0.5%) excluded. Crossover patients (CEA = 1; MT = 21) excluded from analysis after the switch. 1998-1996 for moderate stenosis (&lt;70%); CEA = 1,108, MT = 1,118 (including 425 patients: CEA = 212 and MT = 213 with stenosis &lt;30%); crossovers: CEA = 1.9% and MT = 7.9%).</td>
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* A NASCET 70% stenosis corresponds to an 82% ECST stenosis (formula: ECST = [0.6 × NASCET] + 40).

Abbreviations: NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial; GA, general anesthesia; HT, hypertension; MI, myocardial infarction; RA, regional or local anesthesia; IV, intravenous.
In conclusion, the present meta-analysis provides evidence that CEA is helpful for recently symptomatic patients with a 50% (NASCET technique equivalent to 70% ECST technique) degree of carotid artery stenosis or more and with at least 2 years of life expectancy but adds no benefit in terms of stroke/death for asymptomatic patients.

REFERENCES


18. Veterans Affairs Cooperative Studies Program 309 Trialist Group; Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. JAMA 266:3289-3294, 1991


24. The EVA-3S Investigators: Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: Results up to 4 years from a randomised, multicentre trial. Lancet Neurol 7:885-892, 2008


