Comparison of Multicenter Study Designs for Investigation of Carotid Endarterectomy Efficacy

Virginia J. Howard, MSPH; James Grizzle, PhD; H.C. Diener, MD; Robert W. Hobson II, MD; Marc R. Mayberg, MD; and James F. Toole, MD

Background: Our report summarizes and compares the characteristics of six prospective, multicenter, randomized clinical trials of carotid endarterectomy underway in North America and Europe.

Summary of Review: Three trials are designed to evaluate the safety and efficacy of endarterectomy in patients with asymptomatic carotid artery stenosis. The other three trials enroll patients who have had transient ischemic attacks or a minor cerebral infarction in the distribution of the randomized artery. Considered together, these six clinical trials span the range of candidates for carotid endarterectomy. The inclusion and exclusion criteria, methodology, and statistical considerations of each study are detailed in tables.

Conclusions: The results from these trials will be helpful in resolving some of the questions surrounding endarterectomy, provided the similarities and differences in the study designs are considered when interpreting the results. (Stroke 1992;23:583–593)

KEY WORDS • carotid artery diseases • endarterectomy • clinical trials

Six prospective, multicenter, randomized trials designed to determine the safety and effectiveness of carotid endarterectomy are now being conducted in North America and Europe. The asymptomatic trials include Asymptomatic Carotid Atherosclerosis Study (ACAS),1-3 Asymptomatic Carotid Stenosis Veterans Administration Study (VA #167),4-6 and Carotid Artery Stenosis With Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA)7-9; the symptomatic trials, European Carotid Surgery Trial (ECST)10,11 North American Symptomatic Carotid Endarterectomy Trial (NASCET)12-16 and Symptomatic Carotid Stenosis Veterans Administration Trial (VA #309).17,18 A seventh trial, the Mayo Asymptomatic Carotid Endarterectomy Study (MACE), is not included in this summary because the majority of patients were recruited from only one center and the trial has been terminated.19,20

Although the trials resemble one another, they vary in essential features, which may make comparisons of results difficult. Consequently, it is important to contrast the features now so that preparations for future comparisons can be considered. Two of the asymptomatic trials (CASANOVA and VA #167) and two of the symptomatic trials (ECST and NASCET) have already published partial results.6,8,9,11,15,16

The symptomatic studies enroll patients who have had transient ischemic attacks (TIAs) or a minor cerebral infarction in the distribution of the randomized carotid artery. Of the three asymptomatic trials, ACAS and VA #167 access patients with stenosis of a carotid artery supplying an asymptomatic hemisphere; these patients are not necessarily asymptomatic in other vascular distributions. CASANOVA requires that subjects have never had cerebrovascular symptoms in any distribution. The primary outcome events for the asymptomatic trials are similar to the entry criteria for the symptomatic studies. Therefore, taken together, these six trials span the range of candidates for carotid endarterectomy. The inclusion and exclusion criteria, methodology, and statistical considerations of each study are contained in Tables 1–4.

Inclusion/Exclusion Criteria

The best measure for predicting whether the results of a trial will be applicable to patient care is the eligibility criteria because sampling is seldom done on truly representative patient populations. Furthermore, knowing how the study patients were assembled is important for constructing comparable subgroups across studies.

An inclusion criterion for all six studies is evidence of stenosis. Whether this stenosis is recorded as reduction of lumen diameter or cross-sectional area is important. The best measure for predicting whether the results of a trial will be applicable to patient care is the eligibility criteria because sampling is seldom done on truly representative patient populations. Furthermore, knowing how the study patients were assembled is important for constructing comparable subgroups across studies.

Inclusion criteria for all six studies is evidence of stenosis. Whether this stenosis is recorded as reduction of lumen diameter or cross-sectional area is important.

The minimum degree of stenosis for eligibility in VA #167 and CASANOVA is 50% reduction of lumen diameter; a hemodynamically significant lesion (usually 60% reduction of lumen diameter) is the minimum for ACAS. Patients with highly stenotic disease (≥90%) are...
<table>
<thead>
<tr>
<th>Criterion</th>
<th>ACAS</th>
<th>VA #167</th>
<th>CASANOVA</th>
<th>ECST</th>
<th>NASCET</th>
<th>VA #309</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40–79</td>
<td>Unrestricted</td>
<td>Unrestricted</td>
<td>Unrestricted</td>
<td>&lt;80</td>
<td>Unrestricted</td>
</tr>
<tr>
<td>Hemispheric symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>Permitted</td>
<td>Permitted</td>
<td>Permitted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td>1) Angiography alone &gt;60% lumen diameter reduction, 2) Doppler ultrasonography alone &gt;95% PPV cut point for 60% stenosis, and 3) arteriography required for medical and surgical groups.</td>
<td>1) &gt;50% stenosis by lumen diameter reduction and 2) arteriography required for medical and surgical groups.</td>
<td>Unilateral or bilateral 50–90% lumen diameter reduction by Doppler ultrasonography and angiography.</td>
<td>Stenosis of various degrees by bilateral carotid arteriography.</td>
<td>30%–99% narrowing of ipsilateral carotid by linear measurement from angiography ≤120 days before randomization.</td>
<td>&gt;50% stenosis by angiography.</td>
</tr>
</tbody>
</table>

ACAS, Asymptomatic Carotid Atherosclerosis Study; VA #167, Asymptomatic Carotid Stenosis Veterans Administration Study; CASANOVA, Carotid Artery Stenosis With Asymptomatic Narrowing: Operation Versus Aspirin; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; VA #309, Symptomatic Carotid Stenosis Veterans Administration Trial; TIA, transient ischemic attack; PPV, positive predictive value.
ineligible for CASANOVA. The three symptomatic trials have a wider window for entry: 0% stenosis for ECST, 30% stenosis for NASCET, and 50% stenosis for VA #309. Arteriography is not required by ACAS for verification of degree of stenosis before randomization but is required by VA #167 and CASANOVA. In ACAS, randomization can be based on validated test results from oculopneumoplethysmography-Gee and Doppler ultrasound or arteriography; all patients in the surgery group must have arteriography before endarterectomy. To date, only a small percentage of patients randomized to the surgery group on the basis of oculopneumoplethysmography and Doppler ultrasonography who subsequently had arteriography have been discovered to have less than the required stenosis or another lesion contraindicating endarterectomy.

In view of variability in the measurement of stenosis by angiography, Doppler, or duplex ultrasonography, the 10% difference in entry criteria for the asymptomatic trials is of little consequence. However, the symptomatic trials have very different entry criteria for stenosis; thus, study comparisons or group analyses should be limited to subgroups with the same degrees of stenosis. Further, NASCET and ECST measure the stenosis in the origin of the internal carotid artery in slightly different ways, implying that in each stenosis subgroup the ECST patients have, on average, slightly less stenosis than do the NASCET patients. Studies are currently under way to correlate the two methods of measurement.

Other inclusion criteria appear to be comparable among the trials. One exception is that the qualifying event for eligibility in the symptomatic trials can precede randomization by 120 days for VA #309 and NASCET and by 180 days for ECST. Because it has been shown that the period of greatest risk for subsequent infarction after TIA is the first 30 days, delay in randomization beyond this time could miss patients who had died in the meantime.

All six studies exclude patients with a life expectancy of less than the duration of the studies, those with conditions that would interfere with the evaluation of the results, and those with conditions that contraindicate surgery. Also, all studies except NASCET and ECST exclude patients who have aspirin intolerance.

Methodology
Medical Therapy

The requirement for uniformity of medical management for all treatment groups is assured in double-blinded studies. In these six nonblinded trials of carotid endarterectomy, precautions must be taken to ensure that differences in medical management (such as the follow-up schedule) do not affect the ascertainment of outcome events and that medical management of intercurrent illness is comparable for all treatments.

All the trials are designed to compare medical management plus risk factor reduction with medical management, risk factor reduction, and carotid endarterectomy. NASCET and CASANOVA use 1,300 and 990 mg of aspirin per day, respectively, based on results of previous trials for TIA. However, there are no guidelines for the prophylactic dose of aspirin for patients with asymptomatic carotid stenosis. VA #167 initially used 1,300 mg of aspirin per day but 325 mg was permitted during the last 18 months of the study if patients were intolerant of the higher dose. ACAS and VA #309 use 325 mg per day. ECST permits the use and dosage of aspirin desired by the physician.

Quality Assurance

ACAS, NASCET, VA #167, and VA #309 required retrospective review of surgeons' performance before they were allowed to participate in the trial. ACAS required that a surgeon perform a minimum of 12 endarterectomies annually and that the perioperative and postoperative morbidity and mortality rate be <3%. NASCET required its surgeons to have a 30-day perioperative stroke and death rate of <6% for a minimum of 50 consecutive patients accumulated over 2 years. VA #167 conducted a 2-year retrospective analysis of all consecutive endarterectomy cases at each participating institution before its acceptance into the trial; each institution reported a morbidity and mortality rate of <3%, which became the minimally acceptable level for participation. VA #309 reviewed both the surgeon's and the institution's surgical morbidity and mortality rates for 3 years, 1986–1988; all surgeons and institutions had morbidity and mortality rates of <6%. None of the trials have anesthetics and surgical technique standardized.

Eligible Nonrandomized Patients

ACAS, NASCET, and VA #309 identify all patients who are eligible but not randomized. ACAS and VA #309 collect minimal data on these nonrandomized patients who give consent to be followed. All patients undergoing endarterectomy outside the trial are identified and recorded. VA #309 monitors admission diagnoses of TIA, stroke, and transient monocular blindness.

Statistical Considerations
Outcome Events

Ascertainment of outcome events (treatment failures) can be vexing when based on subjective criteria, as is the case for TIA or for stroke recurrence or worsening. Multiple reviewers expressing expert opinions and uniform definitions are often required to standardize the diagnoses and repeatability of the ascertainment. All efforts must be made to ensure that there is minimal ascertainment bias among the treatment groups.

ACAS and VA #167 define their primary outcome events as any TIA or cerebral infarction in the distribution of the randomized artery. In VA #167, death in the 30-day perioperative period is also included in the primary outcome analysis. In the 30-day perioperative period (or 42-day postrandomization period for the medical group) for ACAS, any TIA, stroke (ipsilateral, contralateral, or in the vertebrobasilar territory), or death is counted as a primary outcome event. The primary outcome events for the other asymptomatic trial, CASANOVA, are stroke and death resulting from surgery or stroke.

The main outcome events for ECST include fatal or disabling ipsilateral stroke or surgery-associated death or stroke, i.e., death from any cause within 30 days of surgery or stroke of any pathology or site within those
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Asymptomatic trials</th>
<th>Symptomatic trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current focal seizures or partial or secondary generalized seizures, migraine, neurological illness, cerebral aneurysm, previous ipsilateral or vertebralbasilar stroke or TIA, Folstein Mini-Mental Status Examination score &lt;20.</td>
<td>Asymptomatic trials: Previous cerebral infarction, current neurological syndrome, or intellectual impairments evaluated by principal investigator. (See stratification in Table 4 for definition of groups.)</td>
<td>Symptomatic trials: Unstable neurological signs (can be entered &gt;4 weeks after signs stabilize).</td>
</tr>
<tr>
<td><strong>Angiographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandem lesion, cerebral aneurysm, AVM, any other finding that increases morbidity or mortality or contraindicates endarterectomy.</td>
<td>Asymptomatic trials: Unilateral or bilateral stenosis of &lt;50% or &gt;90%, occlusion of ICA, tandem lesion of &gt;50%, &gt;50% stenosis CCA, SS syndrome, vertebral artery stenosis or occlusion.</td>
<td>Symptomatic trials: Lack of clear visualization, tandem lesion, cerebral aneurysm, AVM.</td>
</tr>
<tr>
<td><strong>Surgical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous ipsilateral subclavian or EC-IC bypass, carotid surgery ipsilateral to randomized artery, neck surgery or radiation treatment that contraindicates endarterectomy, major surgery during month before randomization.</td>
<td>Asymptomatic trials: Previous endarterectomy with restenosis, previous EC-IC bypass.</td>
<td>Symptomatic trials: Previous ipsilateral endarterectomy.</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF, unstable angina, uncontrolled AF, severe valvular heart disease.</td>
<td>Asymptomatic trials: CHF, unstable angina, uncontrolled AF, severe valvular heart disease.</td>
<td>Symptomatic trials: Chronic AF, MI ≤6 months before randomization.</td>
</tr>
<tr>
<td>Criterion</td>
<td>ACAS</td>
<td>NASCET</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>Cancer</td>
<td>Limiting life expectancy to &lt;5 years</td>
<td>Unrestricted</td>
</tr>
<tr>
<td>Uncontrolled diabetes</td>
<td>Serum glucose &gt;400 mg/dl, ketones &gt;2+</td>
<td>Unrestricted</td>
</tr>
<tr>
<td>Renal failure</td>
<td>BUN &gt; 50 mg/dl, creatinine &gt; 3 mg/dl</td>
<td>Partial kidney failure</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Systolic BP &gt; 180 mm Hg, diastolic BP &gt; 115 mm Hg on three measurements</td>
<td>Unrestricted</td>
</tr>
<tr>
<td>Hypertension</td>
<td>SGOT &gt;80 IU/l, total bilirubin &gt; 1.8 mg/dl, alkaline phosphatase &gt; 148 units/l</td>
<td>Unrestricted</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>Aspirin intolerance, chronic aspirin therapy, chronic anticoagulant therapy, and other surgical contraindications</td>
<td>Unrestricted</td>
</tr>
<tr>
<td>Other medical</td>
<td>Aspirin intolerance, chronic aspirin therapy, chronic anticoagulant therapy, and other surgical contraindications</td>
<td>Unrestricted</td>
</tr>
</tbody>
</table>

ACAS, Asymptomatic Carotid Atherosclerosis Study; VA #167, Asymptomatic Carotid Stenosis Veterans Administration Study; CASANOVA, Carotid Artery Stenosis: Operation Versus Aspirin; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; VA #309, Symptomatic Carotid Stenosis Veterans Administration Trial; ICA, internal carotid artery; CT, computed tomographic; TIA, transient ischemic attack; AVM, arteriovenous malformation; CCA, common carotid artery; SS, sick sinus; EC-IC, external carotid-internal carotid; CHF, congestive heart failure; MI, myocardial infarction; AF, atrial fibrillation; FBS, fasting blood sugar; BUN, blood urea nitrogen; BP, blood pressure; SGOT, serum glutamic-oxaloacetic transaminase.
### Table 3. Methodology in Six Prospective, Multicenter Clinical Trials of Endarterectomy

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>ACAS</th>
<th>VA #167</th>
<th>CASANOVA</th>
<th>ECST</th>
<th>NASCET</th>
<th>VA #309</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized patients</strong></td>
<td>Surgical, 30 days after operation; medical, 42 days after randomization; every 3 months clinic visits alternate with telephone contact; 5-year follow-up.</td>
<td>Quarterly during first year, biannually thereafter; 5-year follow-up.</td>
<td>Quarterly; 3-year follow-up.</td>
<td>4 months, annually thereafter.</td>
<td>Surgical, 30 days after operation; medical, 32 days after randomization; clinic visits every 3 months during first year; every 4 months thereafter; 5-year follow-up.</td>
<td>4 weeks after randomization, quarterly during first year, biannually thereafter; 3-year follow-up.</td>
</tr>
<tr>
<td><strong>Eligible nonrandomized patients</strong></td>
<td>Those who give consent, telephone follow-up, same schedule as telephone follow-up of randomized.</td>
<td>Telephone contact every 6 months.</td>
<td>None</td>
<td>None</td>
<td>Baseline characterization.</td>
<td>Followed up according to protocol when possible.</td>
</tr>
<tr>
<td><strong>Medical management</strong></td>
<td>Aspirin 325 mg/day; risk reduction for hypertension, obesity, smoking, hyperlipidemia, diabetes mellitus, minimization of use of estrogen compounds, polycythemia.</td>
<td>During initial years, aspirin 1,300 mg/day; during last 18 months of study, lower dose permitted for patients intolerant of higher dose.</td>
<td>330 mg aspirin, 75 mg dipyridamole t.i.d.</td>
<td>Local discretion; dose of aspirin, hypertension control consistent within center.</td>
<td>Aspirin 1,300 mg/day; risk reduction for hypertension, hyperlipidemia, diabetes mellitus, smoking.</td>
<td>Aspirin 325 mg/day.</td>
</tr>
<tr>
<td><strong>Folstein Mini-Mental Status Examination</strong></td>
<td>At entry and scheduled follow-up visits.</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>CCT</strong></td>
<td>At entry, exit, verified outcome event.</td>
<td>None</td>
<td>At entry, 1 year, outcome event.</td>
<td>At entry, outcome event.</td>
<td>At entry, exit, verified outcome event.</td>
<td>At entry, 1 year, outcome event.</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>Carotid endarterectomy+325 mg/day aspirin vs. 325 mg/day aspirin; all patients receive program for risk factor reduction.</td>
<td>Carotid endarterectomy+650 mg/day aspirin b.i.d. vs. 650 mg aspirin b.i.d. All patients receive program for risk factor reduction.</td>
<td>Carotid endarterectomy+330 mg aspirin and 75 mg dipyridamole t.i.d. vs. 330 mg aspirin and 75 mg dipyridamole three times/day.</td>
<td>Carotid endarterectomy as soon as possible (3/5 of patients) vs. avoid carotid endarterectomy as long as possible (2/5).</td>
<td>Carotid endarterectomy—best medical care vs. best medical care; all patients receive program for risk factor reduction (aspirin 1,300 mg/day recommended).</td>
<td>Carotid endarterectomy+325 mg/day aspirin vs. 325 mg/day aspirin.</td>
</tr>
</tbody>
</table>

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ACAS, Asymptomatic Carotid Atherosclerosis Study; VA #167, Asymptomatic Carotid Stenosis Veterans Administration Study; CASANOVA, Carotid Artery Stenosis With Asymptomatic Narrowing: Operation Versus Aspirin; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; VA #309, Symptomatic Carotid Stenosis Veterans Administration Trial; CCT, cranial computed tomography.
Sample size is determined by the significance level and the statistical power to detect clinically important treatment differences. In choosing the significance level, investigators are stating the risk of concluding that the treatments are different when, in truth, the differences observed are due to chance alone. Two-sided sample size calculations are appropriate when the investigators have no a priori hypothesis regarding the direction of treatment difference. Sample size calculations based on one-sided hypotheses are appropriate when the investigators postulate that one treatment is equal to or better than the other and that differences in the opposite direction, if observed, would be of little interest. Furthermore, one-sided analyses are acceptable when one treatment group must necessarily undergo a higher initial risk, as recognized in the surgery group.

All six trials use the traditional probability level of 0.05 to delineate statistical significance. Only ACAS and ECST use two-sided sample size calculations. In sacrificing this flexibility, the other four trials have gained power to discover differences in one direction only and thus have reduced their necessary sample size.

**Current Status**

Two of the asymptomatic studies have closed their case acquisitions (VA #167, N=444, closed in November 1988; and CASANOVA, N=410, closed in December 1985; ACAS continues after entering 960 (as of August 1991) of its goal of 1,500 patients. Final analyses for VA #167 are currently being completed because the mean clinical follow-up is now >60 months. CASANOVA found no significant difference in the number of neurological deficits and deaths in two groups of patients, but the design of CASANOVA differs from the other studies in that there is not a group with endarterectomy and a group without. Both groups had a large number of endarterectomies performed after randomization (171 of 206 in Group A [surgical] and 42 of 204 in Group B [medical]), which may have reduced the likelihood of achieving a difference in outcome event rates.

Of the symptomatic trials, NASCET found a clinically and statistically significant benefit of endarterectomy in 659 patients with severe (70–99%) stenosis and has closed recruitment of patients in this category of stenosis. Those who underwent surgery had an absolute reduction of 17% in the risk of ipsilateral stroke at 2 years. Interim results for 778 patients with severe (70–99%) stenosis in ECST showed that the risks of surgery were significantly outweighed by the later benefits. For example, although 7.5% had a stroke or died within 30 days of surgery, during the following 3 years the surgical patients had a sixfold reduction in the risk of ipsilateral stroke. Recruitment has not officially been closed for these patients; i.e., the “grey area of uncertainty” continues. The ECST found no benefit of endarterectomy among 374 patients with mild (0–29%) stenosis and has closed randomization to such patients. In both NASCET and ECST, the results for patients with moderate (30–69%) stenosis remain unknown, and case acquisition continues in this subgroup.

The third symptomatic trial, VA #309, has stopped recruiting over all strata after randomizing 192 patients. At a mean follow-up of 11.9 months, there is a significant 60% reduction in ipsilateral stroke or crescendo TIA for patients with carotid endarterectomy. In a subgroup analysis of 129 patients with severe stenosis, there is a significant 70% reduction.
<table>
<thead>
<tr>
<th>Consideration</th>
<th>ACAS</th>
<th>VA #167</th>
<th>CASANOVA</th>
<th>ECST</th>
<th>NASCET</th>
<th>VA #309</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>By local computer, program controlled centrally.</td>
<td>Managed centrally from study office.</td>
<td>Controlled centrally by telephone. Randomization resulted in two groups: 1) surgical (endarterectomy for unilateral ICA stenosis; for bilateral stenosis, second endarterectomy within 3 months) and 2) medical (medical treatment for unilateral ICA stenosis) for bilateral stenosis, endarterectomy on more severe artery, plus additional antiplatelet drugs.</td>
<td>Controlled centrally by telephone.</td>
<td>Information entered locally but randomization controlled centrally.</td>
<td>Controlled centrally by telephone.</td>
</tr>
<tr>
<td>Outcome events Primary</td>
<td>Verified TIA, CI, or retinal infarction in the distribution of the randomized artery. Any TIA, CI, or death ≤30 days after surgery or ≤42 days after randomization for medical group.</td>
<td>Verified TIA, CI in distribution of randomized artery, death within 30 days after surgery.</td>
<td>Stroke or death.</td>
<td>Fatal or disabling ipsilateral stroke, surgery-associated death or stroke (within 30 days).</td>
<td>Ipsilateral carotid stroke (fatal and nonfatal) or stroke-related death independently verified. Stroke (regardless of side) and death (regardless of cause) ≤30 days after surgery, ≤32 days after randomization for medical group.</td>
<td>Ipsilateral stroke, crescendo TIAs, death within 30 days after surgery.</td>
</tr>
<tr>
<td>Secondary</td>
<td>Verified TIA or stroke not in the distribution of the randomized artery &gt;30 days after surgery or &gt;42 days after randomization in medical group, MI, or death due to any cause.</td>
<td>Verified TIA or stroke not in the distribution of the randomized artery, MI, or death due to any cause.</td>
<td>Major stroke or death due to any cause, minor stroke, TIA, amaurosis fugax, retinal artery occlusion, or MI.</td>
<td>All strokes, all deaths, severity of stroke.</td>
<td>All strokes, all deaths, in either vascular distribution, stroke severity.</td>
<td></td>
</tr>
<tr>
<td>Consideration</td>
<td>ACAS</td>
<td>VA #167</td>
<td>CASANOVA</td>
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<td>VA #309</td>
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<tr>
<td><strong>Stratification</strong></td>
<td>By center, sex, unilateral vs. bilateral asymptomatic stenosis, previous surgery on contralateral side.</td>
<td>Stratum I, by center; Stratum II, unilateral symptomatic lesion and contralateral asymptomatic carotid stenosis; Stratum III, incidental cervical bruises with or without global symptoms and positive noninvasive screening tests, and arteriography confirmation of stenosis.</td>
<td>By center, sex, hypertension, smoking behavior, and unilateral vs. bilateral stenosis.</td>
<td>By center and surgeon.</td>
<td>By center, moderate vs. severe stenosis (also included ulceration vs. no ulceration originally).</td>
<td>By center; contralateral &lt;70% stenosis vs. ≥70% stenosis; presenting symptoms: TIA vs. retinal ischemia vs. completed small stroke.</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>750 each group, alpha=0.05 (2-sided). Assuming 3% perioperative morbidity and mortality rate 3%/yr TIA, 1%/yr CI rate; power 90% for detection of 35% difference in 5 years.</td>
<td>250 each group, alpha=0.05 (1-sided). Assuming 10% loss to follow-up 20% 5-year failure rate for medical group and 5% 5-year failure rate for surgery group; power 90% for detection of a 50% difference in treatment in 5 years.</td>
<td>400 total, alpha=0.05 (1-sided). Assuming 13% 3-year stroke rate; power 90% for detection of 13—4.5% reduction of stroke risk.</td>
<td>As many as possible, 2,000 minimum; predicted accession rate 650/yr (2-sided).</td>
<td>Originally 3,000, but revised to exclude ulceration as stratum; revised requires 1,900 total: 600 severe stenosis, 1,300 moderate stenosis, alpha=0.05 (1-sided). Assuming 6% perioperative risk of stroke and death and 4—7%/yr risk of fatal and nonfatal stroke in medical patients; power 90% for detection of 50% reduction due to surgery in each subgroup.</td>
<td>250 each group, alpha=0.05 (1-sided) Assuming 15% loss to follow-up and 3-year event rate of 20% in medical group and 10% in surgical group; power 90%.</td>
</tr>
</tbody>
</table>

ACAS, Asymptomatic Carotid Atherosclerosis Study; VA #167, Asymptomatic Carotid Stenosis Veterans Administration Study; CASANOVA, Carotid Artery Stenosis With Asymptomatic Narrowing: Operation Versus Aspirin; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; VA #309, Symptomatic Carotid Stenosis Veterans Administration Trial; ICA, internal carotid artery; TIA, transient ischemic attack; CI, cerebral infarction; MI, myocardial infarction.
Data Analysis

The analysis of well-designed and well-implemented studies is straightforward and built around the preselected outcome events of TIA, stroke, and death. All trials propose, among other analyses, to compare treatment efficacy with respect to length of time before treatment failure (first outcome event after randomization) by means of survival analysis. A common analysis among studies facilitates easier comparison of the results.

It is mandatory that interim analyses be performed before the specified end of the follow-up period because of ethical concerns about needlessly continuing a study after a significant difference has been convincingly demonstrated or after it is clear that no difference can be demonstrated. The methods and timing of these interim analyses should be specified in advance to protect against increasing the risk of a false-positive finding.

Conclusions

Six multicenter studies designed to ascertain the safety and efficacy of carotid endarterectomy are in progress. Despite differences in their protocols, the results from these trials will be helpful in solving some of the problems surrounding endarterectomy, provided the similarities and differences in the study designs are considered when interpreting the results.

Physicians must recognize that the place of endarterectomy in the management of carotid stenosis is currently an open question for patients with asymptomatic disease and for symptomatic patients with moderate (30–69%) stenosis. Premature conclusions will increase the challenge to meet recruitment goals and will leave both physicians and patients without answers regarding indications and contraindications for this procedure.

Once the trials have been completed, the maximum information will be obtained by keeping in mind differences and similarities in the protocols. This process could be helped considerably by collaboration among the trials to define comparable subgroups in which unified analyses and statistical overviews might be made. Additional work to unify entry and outcome event criteria would be helpful.

Appendix

Asymptomatic Trials

Asymptomatic Carotid Atherosclerosis Study (ACAS)
Principal investigator: James F. Toole, MD
Operations center:
Department of Neurology
Bowman Gray School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1078
Statistical coordinating center:
Collaborative Studies Coordinating Center
Department of Biostatistics
School of Public Health
University of North Carolina
Chapel Hill, NC 27514
Funding agency: National Institute of Neurological Disorders and Stroke
Recruitment status: Open

Cooperative Study #167: Asymptomatic Carotid Stenosis: Etiological Importance in Development of Stroke (VA #167)
Principal investigator: Robert W. Hobson II, MD
Coordinating center:
Cooperative Studies Program Coordinating Center
VA Medical Center
Perry Point, MD 21902
Funding agency: Department of Veterans Affairs
Recruitment status: Closed

Carotid Artery Stenosis With Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA)
Principal investigator: H. Hamann, MD, and H.C. Diener, MD
Central administration:
Department of Vascular Surgery
University of Ulm
D-7900 Ulm, FRG
Funding agency: German Federal Government and Dr. Karl Thomae, GmbB, Biberach-Riss, FRG
Recruitment status: Closed

Symptomatic Trials

The European Carotid Surgery Trial (ECST)
Principal investigator: Charles Warlow, MD
Trial office:
Edinburgh University
Department of Clinical Neurosciences
Western General Hospital
Crewe Road
Edinburgh EH4 2XU, Scotland
Funding agency: British Medical Research Council and University of Oxford ICRF/MRC Clinical Trial Service Unit
Recruitment status: Open for stratum of moderate (30–69%) and severe stenosis (70–99%)
Closed for mild (0–29%) stenosis

North American Symptomatic Carotid Endarterectomy Trial (NASCET)
Principal investigator: H.J.M. Barnett, MD
Central administration:
Robarts Research Institute
PO Box 5015, 100 Perth Drive
London, Ontario N6A 5K8, Canada
Funding agency: National Institute of Neurological Disorders and Stroke and Canadian Medical Research Council
Recruitment status: Open for stratum of moderate (30–69%) stenosis
Closed for severe (70–99%) stenosis

Cooperative Study #309: The Role of Carotid Endarterectomy in Preventing Stroke From Symptomatic Carotid Stenosis (VA #309)
Principal investigators: Marc R. Mayberg, MD; Eric Wilson, MD; and Frank Yatsu, MD
Coordinating center:
Cooperative Studies Program Coordinating Center
VA Medical Center
Perry Point, MD 21902
Funding agency: Department of Veterans Affairs
Recruitment status: Closed
Acknowledgments

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References

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Comparison of multicenter study designs for investigation of carotid endarterectomy efficacy.

V J Howard, J Grizzle, H C Diener, R W Hobson, 2nd, M R Mayberg and J F Toole

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