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Comparison of multicenter study designs for investigation of carotid endarterectomy efficacy

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Research in Progress

Comparison of Multicenter Study Designs for Investigation of Carotid Endarterectomy Efficacy

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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 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

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TABLE 1. Inclusion Criteria for Six Prospective, Multicenter Clinical Trials of Endarterectomy

Criterion	Asymptomatic trials			Symptomatic trials		
	ACAS	VA #167	CASANOVA	ECST	NASCET	VA #309
Age (yr)	40–79	*Unrestricted*	*Unrestricted*	*Unrestricted*	<80	*Unrestricted*
Hemispheric symptoms				Carotid TIA, amaurosis fugax, retinal infarction, minor ischemic stroke with symptoms lasting <1 week or nondisabling major stroke with return to normal activities ≤6 months after onset.	Nondisabling stroke, retinal infarction, amaurosis fugax, TIA in the territory of an internal carotid artery, ≤120 days before randomization. Qualifying event is most recent event ≤120 days before randomization.	TIA, transient monocular blindness, or completed small stroke (≥1) ≤120 days before randomization.
Ipsilateral	None	None	None			
Contralateral	Permitted	Permitted	None			
Diagnostic criteria	1) Angiography alone >60% lumen diameter reduction, 2) Doppler ultrasonography alone >95% PPV cut point for 60% stenosis, and 3) arteriography required for surgical group only.	1) >50% stenosis by lumen diameter reduction and 2) arteriography required for medical and surgical groups.	Unilateral or bilateral 50–90% lumen diameter reduction by Doppler ultrasonography and angiography.	Stenosis of various degrees by bilateral carotid arteriography.	30%–99% narrowing of ipsilateral carotid by linear measurement from angiography ≤120 days before randomization.	>50% stenosis by angiography.

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 anesthesia 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 2. Exclusion Criteria for Six Prospective, Multicenter Clinical Trials of Endarterectomy

	Asymptomatic trials			Symptomatic trials		
Criterion	ACAS	VA #167	CASANOVA	ECST	NASCET	VA #309
Neurological	Current focal seizures or partial or secondary generalized seizures, migraine, neurological illness, cerebral aneurysm, previous ipsilateral or vertebrobasilar stroke or TIA, Folstein Mini-Mental Status Examination score <20.	Previous cerebral infarction, current neurological syndrome, or intellectual impairments evaluated by principal investigator. (See stratification in Table 4 for definition of groups.)	Signs or symptoms of cerebrovascular disease.	Unstable neurological signs (can be entered >4 weeks after signs stabilize).	No symptoms in appropriate carotid territory, ICA occlusive disease beyond C2, carotid occlusion appropriate to symptoms, non-arteriosclerotic process that may cause ischemic events, progressing stroke.	Cerebral ischemia, focal seizure, vertebrobasilar ischemia, mass lesion, major stroke, possible cardiac source of emboli, subarachnoid or intracerebral hemorrhage, CT scan showing edema, hemorrhage or nonvascular lesions possibly related to symptoms. Preexisting incapacitating neurological disease.
Angiographic	Tandem lesion, cerebral aneurysm, AVM, any other finding that increases morbidity or mortality or contraindicates endarterectomy.	Tandem lesion, cerebral aneurysm, AVM, any other finding that increases morbidity or mortality or contraindicates endarterectomy.	Unilateral or bilateral stenosis of <50% or >90%, occlusion of ICA, tandem lesion of >50%, >50% stenosis CCA, SS syndrome, vertebral artery stenosis or occlusion.	Unrestricted	Lack of clear visualization, tandem lesion, cerebral aneurysm, AVM.	<50% stenosis, tandem lesion with stenosis more severe than cervical lesion.
Surgical history	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.	Previous endarterectomy with restenosis, previous EC-IC bypass.	Asymptomatic carotid surgery within last 3 months.	Previous ipsilateral endarterectomy.	Previous carotid surgery ipsilateral to randomized artery, any surgery ≤30 days before randomization.	Previous endarterectomy on side ipsilateral to symptoms, EC-IC bypass.
Heart	CHF, unstable angina, uncontrolled AF, severe valvular heart disease.	CHF, unstable angina, uncontrolled AF, severe valvular heart disease.	MI ≤6 months before randomization.	Coronary artery disease treated first.	Cardiothoracic ratio >50%, valvular lesion, arrhythmia likely to cause cardioembolic cerebrovascular symptoms, unstable angina while under treatment, MI ≤6 months before randomization.	Chronic AF, MI ≤6 months before randomization, prosthetic heart valve, rheumatic heart disease, mural thrombus, CHF of class III or IV, resting ejection fraction <30%, ventricular ectopy >10/min, unstable angina.

TABLE 2. Continued

Criterion	Asymptomatic trials			Symptomatic trials		
	ACAS	VA #167	CASANOVA	ECST	NASCET	VA #309
Cancer	Limiting life expectancy to <5 years.	Limiting life expectancy to <5 years.	Limiting life expectancy.	Unrestricted	Limiting life expectancy to <5 years.	Limiting life expectancy to <3 years.
Uncontrolled diabetes	Serum glucose >400 g/dl, ketones >2+.	Likely to limit life expectancy to <5 years.	Unrestricted	Unrestricted	FBS >300 mg% or 16 mmol/l.	FBS >300 mg or ketoacidosis.
Renal failure	BUN >50 mg/dl; creatinine >3 mg/dl.	Likely to limit life expectancy to <5 years.	Partial kidney failure.	Unrestricted	BUN >twice normal.	Serum creatinine >2.5, concurrent dialysis.
Respiratory failure	Limiting life expectancy to <5 years.	Condition and laboratory values deemed unacceptable surgical risk by the principal investigator.	Unrestricted	Unrestricted	Organ failure.	Severe chronic obstructive pulmonary disease.
Hypertension	Systolic BP >180 or diastolic BP >115 mm Hg over three measurements.	Likely to limit life expectancy to <5 years.	Unrestricted	Unrestricted	Diastolic BP >110 mm Hg when on therapy.	Resting systolic BP >180 or diastolic BP >110 mm Hg.
Hepatic disease	SGOT >80 IU/l, total bilirubin >1.8 mg/dl, alkaline phosphatase >148 units/l.	Likely to limit life expectancy to <5 years.	Unrestricted	Unrestricted	Organ failure.	Unrestricted
Other medical	Contraindications to aspirin or surgery.	Aspirin intolerance, chronic aspirin therapy, chronic anticoagulant therapy, and other surgical contraindications.	Severe general disease, aspirin intolerance.	Unrestricted	Uncorrectable medical contraindications to surgery.	Contraindications to aspirin, concurrent use of oral anticoagulants or >2 g/day aspirin, significant psychiatric illness, intellectual incapacity.

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; 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

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

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.

30 days. In NASCET, the primary outcome event is any fatal or nonfatal stroke ipsilateral to the symptomatic carotid lesion, including stroke or death occurring during the 30-day perioperative period for surgical patients and during a comparable period after randomization for the medical patients. In contrast, the VA symptomatic trial (#309) defines its primary outcome events as cerebral infarctions or crescendo TIAs ipsilateral to the carotid lesion plus death within 30 days of surgery for the surgical group, and it does not include contralateral events. However, in the VA symptomatic (#309) and asymptomatic (#167) trials, all contralateral events are recorded separately, followed, and included in secondary analyses. These differences emphasize the importance of reporting the frequency of each type of event even though the types may be combined in the primary analysis of outcome events.

Some of the trials have standardized the diagnosis of TIA, both for eligibility and outcome ascertainment. Even so, there are differences among their definitions. For example, NASCET considers a nondisabling ischemic event as a stroke if appropriate signs or symptoms persist beyond 1 day, whereas ECST requires symptoms to last for more than 7 days. Ideally, subjectivity in diagnosis or definition could be reduced by algorithms common to all studies. Because of the lack of a uniform objective system, the final reports of these trials must contain, or be able to reference, their methods of diagnosis.

Stratification (Blocking) and Randomization

Stratification is used to eliminate extraneous patient characteristics that may affect prognosis. Failure to stratify by important prognostic characteristics may obscure differences between groups by increasing the variability in therapeutic response or by bias if there is an imbalance of prognostic factors. Post hoc stratification or multivariate analysis is often used to accomplish the same end, but some efficiency may be lost compared with prestratification before analysis. Most trials stratify by center to control for differences among clinics and also compare baseline prognostic characteristics to ensure similarity between patients in the treatment groups.

Randomization is performed within strata when there is stratification before analysis. Randomization in multicenter studies may be controlled centrally or locally with appropriate central oversight. Different randomization methods are used in the trials, depending on the circumstances.

Aside from stratification by center, among the six trials there is an obvious difference in stratification by patient characteristics that may affect response. Studies of the natural history of carotid stenosis are insufficient to provide much guidance. Subgroup analysis defined by the proposed strata should yield much new knowledge about the natural history of carotid stenosis.

Sample Size

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.[5] 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.[8,9] 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.[15,16] 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.[11] 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.[17]

TABLE 4. Statistical Considerations in Six Prospective, Multicenter Clinical Trials of Endarterectomy

Consideration	Asymptomatic trials			Symptomatic trials		
	ACAS	VA #167	CASANOVA	ECST	NASCET	VA #309
Randomization	By local computer, program controlled centrally.	Managed centrally from study office.	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.	Controlled centrally by telephone.	Information entered locally but randomization controlled centrally.	Controlled centrally by telephone.
Outcome events Primary	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.	Verified TIA, CI in distribution of randomized artery, death within 30 days after surgery.	Stroke or death.	Fatal or disabling ipsilateral stroke, surgery-associated death or stroke (within 30 days).	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.	Ipsilateral stroke, crescendo TIAs, death within 30 days after surgery.
Secondary	Verified TIA or stroke not in the distribution of the randomized artery >30 days after surgery or >42 days after randomization in medical group, MI, or death due to any cause.	Verified TIA or stroke not in the distribution of the randomized artery, MI, or death due to any cause.		Major stroke or death due to any cause, minor stroke, TIA, amaurosis fugax, retinal artery occlusion, or MI.	All strokes, all deaths, severity of stroke.	Death due to any cause, in either vascular distribution, stroke severity.

TABLE 4. Continued

Consideration	Asymptomatic trials			Symptomatic trials		
	ACAS	VA #167	CASANOVA	ECST	NASCET	VA #309
Stratification	By center, sex, unilateral vs. bilateral asymptomatic stenosis, previous surgery on contralateral side.	Stratum I, by center; Stratum II, unilateral symptomatic lesion and contralateral asymptomatic carotid stenosis; Stratum III, incidental cervical bruits with or without global symptoms and positive noninvasive screening tests, and arteriography confirmation of stenosis.	By center, sex, hypertension, smoking behavior, and unilateral vs. bilateral stenosis.	By center and surgeon.	By center, moderate vs. severe stenosis (also included ulceration vs. no ulceration originally).	By center; contralateral <70% stenosis vs. ≥70% stenosis; presenting symptoms: TIA vs. retinal ischemia vs. completed small stroke.
Sample size	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.	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.	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.	As many as possible, 2,000 minimum; predicted accession rate 650/yr (2-sided).	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.	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%.
Data analysis	Survival curves, 5-year survival rate and interim analysis by O'Brien Fleming method.	Comparison of 5-year event rate, life table analysis; no interim analysis described.	Fisher-Irvin test for 4×4 tables, survival analysis, regression models for binary data.	Standard life table analysis.	Survival curves and interim analysis by Kaplan-Meier, Mantel-Haenszel χ^2.	Survival curves, interim analysis requires $Z=3$ for statistical significance.

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 resolving 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.[21,22] 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

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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, GmbH, 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

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