Study design for randomized prospective trial of carotid endarterectomy for asymptomatic atherosclerosis. The Asymptomatic Carotid Atherosclerosis Study Group

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Original Contributions

Study Design for Randomized Prospective Trial of Carotid Endarterectomy for Asymptomatic Atherosclerosis

The Asymptomatic Carotid Atherosclerosis Study Group

This report summarizes the study design and organization of a multicenter, randomized trial of carotid endarterectomy for the treatment of asymptomatic carotid stenosis. The Asymptomatic Carotid Atherosclerosis Study will determine whether the addition of carotid endarterectomy to aspirin plus risk factor modifications affects the incidence of ipsilateral transient ischemic attack, amaurosis fugax, and retinal and cerebral infarction in patients with asymptomatic hemodynamically significant carotid stenosis in at least one artery. Power calculations are based on assumptions of $\alpha=0.05$ (two-sided test) with annual event rate 3% transient ischemic attack and 1% cerebral infarction per year. The study has 90% power for detection of a 25% difference in events in a 5-year study. Two continuous validation programs are in use: a Doppler/angiogram correlation study for each Doppler instrument used in screening potential candidates and a transient ischemic attack/stroke questionnaire/validation study for verification of end points. Quality assurance is a major component in study design. (*Stroke* 1989;20:844–849)

Only rarely are carotid endarterectomies performed on symptomatic patients such as those with stroke in evolution; therefore, strictly speaking, almost all endarterectomies are performed on asymptomatic individuals. Some, however, have had previous transient ischemic attacks (TIAs) or cerebral infarctions (CIs) in the distribution of one carotid artery. Other individuals are symptomatic in the hemisphere opposite an asymptomatic carotid stenosis or in the vertebrobasilar arterial distribution.

There have been no statistically valid studies assessing the natural history of asymptomatic carotid stenosis. Most of our knowledge of the natural history of asymptomatic stenosis is derived from longitudinal studies of unoperated stenotic arteries contralateral to carotid vessels that have been subjected to carotid endarterectomy for symptomatic disease. Thirty to forty percent of patients having endarterectomy for symptomatic carotid artery atherosclerosis have greater than 50% stenosis of the asymptomatic contralateral carotid vessel.[1–5] In the distribution of the previously asymptomatic carotid artery, TIA occurred in 13–18% of patients available for a 1–20-year follow-up.[1–8] Annual rates of combined TIA and CI are 1.5–7.4% in the territory of the asymptomatic carotid artery.[4,5,8] Mortality rates are consistently in the 4–6% per year range.[2,5]

The incidence of cerebral infarction related to intracranial and extracranial arterial disease has declined.[9] As a consequence, there is controversy as to whether endarterectomy should be limited to patients in a specific age group or to those with failure of medical management.[10] There have been many publications regarding the excessive morbidity and mortality from endarterectomy performed in some institutions or by some surgeons.[11–13] Others have pointed to the enormous excess of endarterectomies in the United States compared with the rest of the world, which is taken to be ipso facto evidence that there are too many performed in the former.[14,15] These assertions have been rebutted with the thesis that when performed by experienced surgeons with low morbidity/mortality, the appropriate time for carotid endarterectomy (if it is to be performed at all) is before symptoms have developed,[16–21] because morbidity/mortality from endarterectomies in this subgroup is far less than that of persons who have had TIAs. The main reasons for this reduced complication rate include a younger age group, fewer associated risk factors, and the likelihood that the asymptomatic vessel responds better to surgical treatment than does the symptomatic artery, which usually harbors long-standing ulcerated plaques.

Furthermore, there is growing evidence that "asymptomatic" patients may in fact have had unrec-

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ognized symptoms that might have occurred during sleep or periods of impaired alertness, when transitory neurologic deficits could be ignored or forgotten. In support of this contention are the recent findings that as many as 4% of patients with carotid stenosis who are clinically asymptomatic are found by computed tomography (CT) scan or magnetic resonance imaging (MRI) to have had cerebral infarctions in the appropriate arterial distribution.[22–25] This surprising finding is leading to the suspicion that the genesis of some multi-infarct dementia is showers of emboli or chronic cerebral hypoperfusion caused by stenosis of extracranial arteries.[26–28]

Even though there has been no study to demonstrate the effectiveness of aspirin for prevention of stroke in asymptomatic patients, it is often used in association with risk factor reduction as the management of choice.[29–31] Still others assert that platelet antiaggregant therapy, because of its effectiveness for abolishing TIA due to thromboembolism, while not retarding progress of atherosclerosis, actually increases the risk of cerebral infarction because it removes the heralding TIA.

To resolve the question of long-term risk-to-benefit of carotid endarterectomy for asymptomatic stenosis, the Asymptomatic Carotid Atherosclerosis Study (ACAS) was designed to determine whether the addition of carotid endarterectomy to aspirin plus risk factor modifications will affect the incidence of ipsilateral TIA, amaurosis fugax, and retinal and cerebral infarction in patients with asymptomatic hemodynamically significant carotid stenosis in at least one artery. Secondary objectives are 1) to determine the surgical success in lesion removal and the incidence of recurrent carotid stenosis after carotid endarterectomy, 2) to determine the rate of progression or regression of carotid atherosclerosis in the medically treated group, and 3) to determine incidence of all other cerebrovascular events, angina pectoris, nonfatal myocardial infarction (MI), and cardiac death in follow-up years.

For all the above reasons, ACAS has been initiated to supplement other multicenter studies in progress, including North American Symptomatic Carotid Endarterectomy Trial (NASCET)[32] and Veterans Administration asymptomatic trial[33] and symptomatic trial (M.R. Mayberg, personal communication) designed to evaluate the effectiveness of carotid endarterectomy in specific populations.

In the planning stages since 1981, partial funding was provided by The Upjohn Company in 1984, and ACAS obtained a planning grant from the National Institute of Neurological Disorders and Stroke (NINDS) in September 1985. The main phase protocol was approved by NINDS on November 25, 1987, but initiation of patient acquisition for each center varied, based on successful completion of training and certification requirements. By March 1988, most centers had been approved and as of November 11, 1988, 145 patients had been randomized.

Study Design

All patients receive 325 milligrams of aspirin daily plus risk factor–reduction counseling, and one half are randomly assigned to carotid endarterectomy. Candidates may be eligible who are between the ages of 40 and 79 years and who have unilateral or bilateral surgically accessible stenosis of the region of the bifurcation of the common or internal carotid artery of at least 60%, confirmed by at least two of the following three procedures: ocular pneumoplethysmographic (OPG-Gee) examination with a difference in ophthalmic artery systolic pressures $\geq$ 5 mm Hg or with a ratio [(ophthalmic artery systolic pressure minus 39) divided by (brachial artery systolic pressure)] less than 0.43; Doppler sonography showing a peak systolic frequency shift greater than the institutional cutpoint determined by correlation of Doppler flow velocities with arteriography in 50 consecutive cases; and/or conventional or arterial digital subtraction angiography indicating diameter stenosis $\geq$60% using minimal residual lumen (MRL) and the distal lumen (DL) for the equation $1-(\text{MRL}/\text{DL})\times 100$.

Patients are excluded for conditions that are likely to produce significant mortality or morbidity or otherwise render follow-up difficult within the 5-year period, confound future evaluation of the patient for end points, or contraindicate treatment.

The end points for evaluation of the two treatments will be TIA or infarction in the distribution of the randomized artery. In the 30-day perioperative period or 42 days postrandomization for the medical group, any TIA, stroke, or death will be a study end point. Thereafter, any ipsilateral TIA or stroke during the 5-year follow-up is an end point. The primary analysis variable will be the time between intervention and end point.

This is not a population-based study. Potential study candidates are identified by the ACAS patient coordinator's daily monitoring of intake points such as physicians' offices, ultrasound laboratories, and angiography suites. Patients who seem to fulfill the minimum eligibility criteria are entered in the recruitment log. If informed consent is obtained from the patient, further workup is performed to determine if the patient is in fact eligible. If determined eligible, the patient is asked when he/she would be available for surgery should he/she be randomized to the surgery arm. Randomization is not done until surgery can be scheduled within 2 weeks. This process is controlled by the statistical coordinating center and includes stratification by clinical center, sex, surgery for contralateral stenosis, and bilateral hemodynamically significant stenoses. If two arteries are eligible, the one selected for randomization will be the artery with the greater degree of stenosis.

CT scan and the Folstein Mini-Mental State examination[34] will be performed on all subjects at entry, exit, and at end points, but CT findings will

not be considered in the decision regarding eligibility or end points.

Thirty days postsurgery or 42 days postrandomization for the medical group, there will be follow-up for medical history, physical and neurologic examinations, cognitive function, TIA/stroke questionnaire, event detection, and drug adherence.

At subsequent 3-month intervals throughout the study, the patient receives a medical history questionnaire, TIA/stroke questionnaire, event detection, review of risk reduction, and drug adherence questionnaire. Telephone interviews alternate with clinic visits, at which time physical, neurologic, and Folstein Mini-Mental State examinations are done. Carotid Doppler studies are repeated at 3 months, then every 6 months during the first 24 months and yearly thereafter and at verified end point. CT is performed at entry and repeated when an end point is diagnosed or when a patient exits from the study. Electrocardiogram (ECG) is performed when clinically indicated.

Data will be collected on recurrence of stenosis in the surgical group and on the progression of stenosis in the medical group. Coronary events will be evaluated in both. In addition to identification of events from the clinic visits and telephone contacts, other medical events information will be gathered from death certificates and hospital discharge diagnosis. Also recorded are the occurrences of a number of nonhospitalized, nonfatal events.

Risk factor reduction will include counseling and interventions for the following: hypertension, obesity, hyperlipidemia, diabetes mellitus, tobacco abuse, sedentary lifestyle, use of estrogen compounds, and polycythemia.

Endarterectomy and recruitment logs document the following nonrandomized patients: 1) All ACAS physicians' patients who are probably eligible (i.e., have an asymptomatic carotid artery with stenosis >60%); 2) all endarterectomies by non-ACAS physicians in ACAS-affiliated hospitals; 3) all ACAS physicians' endarterectomies including asymptomatic patients who are ineligible, asymptomatic patients who are probably eligible, and symptomatic patients.

Minimum eligibility/baseline data and reason for nonrandomization will be documented on all patients of an ACAS physician who are probably eligible but who for any reason are not randomized. If consent is given, these patients will be followed with a schedule corresponding to the telephone follow-up schedule of the randomized patients.

Conservative power calculation resulted in a goal of 750 patients randomized into each of the two study groups. Power calculations were based on the assumptions of an $\alpha=0.05$, two-sided test, an annual event rate of 3% per year of TIA and 1% of cerebral infarction in the worst group. The study has 90% power for detection of a 25% difference in events in a 5-year study.

Because determination of end points is initiated by questionnaires administered quarterly, the exact time of end point may be difficult to determine. Life-table methods will estimate unadjusted treatment-specific survival curves and test for differences. Analyses other than the proportional hazards model may be appropriate since survival curves are expected to cross because of the greater hazard in the surgical group in the perioperative period.[35]

Steps are being taken to ensure as much as possible that data accumulated in ACAS will be comparable to that of NASCET and the two Veterans Administration trials of carotid endarterectomy, with planning for meta-analyses.

Quality is assured by training and certification of personnel; by selection of equipment; by measures for data completeness and consistency; by monitoring event rates for surgeon and institution; by central evaluation of samples of angiograms, Doppler, CT, and OPG-Gee studies; and by external blinded verification of all putative end points. Training includes angiogram measurement, noninvasive techniques, operation of the clinic data management system, the computerized randomization system, and clinical and surgical data collection including the TIA/stroke questionnaires.

Procedures designed to enhance adherence to the protocol begin long before patients are enrolled with the training and certification of clinic personnel, the calibration of noninvasive equipment, and the checking of laboratories. These same measures continue during the study, with monitoring of personnel and clinics, retraining and recertification of personnel, and checking the quality and timeliness of data collection and submission.

Two continuous validation programs are used. The Doppler/angiogram relation determines one of the eligibility criteria, and Doppler is used for the noninvasive evaluation of change in stenosis. For each Doppler machine used, the Doppler/angiogram validation study requires retrospective data on patients who had both an angiogram and a Doppler performed within 4 weeks of each other (and OPG-Gee if it is available). For the first five of these cases, the angiogram films and the Doppler videotape/hard copy are reviewed for protocol adherence and overall quality of data. The goal is to establish the relation between the Doppler flow velocity and stenosis as defined by angiography, keeping the positive predictive value at approximately 90%.

Because the diagnosis of TIA is subjective and because TIA is both an eligibility exclusion and a study end point, the ACAS group has designed a TIA/stroke questionnaire to increase objectivity of diagnosis. For the TIA questionnaire validation, each center will recruit four normal patients, four with TIA, four who had strokes, and four with conditions that might be confused with TIA. These patients will receive the TIA/stroke questionnaire and a neurologic history and examination by both the ACAS neurologist and surgeon, and data on

suspected TIAs and stroke will be reviewed blindly by neurologists. The agreement between questionnaire and the neurologic assessments will be determined in 300 cases.

The quality control and operations of the TIA/stroke diagnosis system are under the direction of the end point verification committee comprised of three neurologic consultants not otherwise associated with the study. After a suspected end point, within 48 hours of completion of the history and examination by the neurologist and surgeon, data is submitted to an end point reviewer, excluding the physician diagnosis forms or any mention of diagnosis or treatment group. Within 24 hours, the end point reviewer will telephone his assessment to the statistical coordinating center. Unanimity among the institutional neurologist, surgeon, and the end point reviewer is necessary for the patient to have achieved an end point. When lacking, the statistical coordinating center will schedule a telephone conference. If a consensus cannot be reached or if it is agreed that an end point has not occurred, the patient will be placed under increased surveillance without change in treatment. If new symptoms occur, the entire end point review process described above must be repeated before the patient may be withdrawn from the study and alternative therapy initiated. When data consistent with diagnosis of stroke are collected, the stroke will be classified on the basis of the NINDS Stroke Data Bank criteria and stroke severity scale.[36]

From its beginning, ACAS established guidelines for minimum annual experience and maximum surgical morbidity/mortality. For approval, a surgeon must perform an annual minimum of 12 carotid endarterectomies with a mortality/morbidity rate no greater than 3% in the last 50 cases. During the study, each clinical center's perioperative and postoperative mortality and morbidity will be monitored. Should an institution have two events of a stroke and/or death, that center will be temporarily suspended from further randomization until a committee investigation of the circumstances can be carried out. Appropriate action will be taken that could include dropping a surgeon or center from the study.

ACAS comprises the following groups: the funding institute, the NINDS, the operations center at Bowman Gray School of Medicine, the statistical coordinating center at the University of North Carolina at Chapel Hill, and 18 clinical centers (see Appendix). Additional and replacement centers are reviewed on a regular basis. A steering committee consisting of two principal investigators, a neurologist and a surgeon from each of the 18 clinical centers, as well as personnel from the operations center, the statistical coordinating center, consultants and representatives from NINDS, controls the study and considers possible changes in the protocol or methodology vis à vis new developments in the field. In the interim between annual steering committee meetings, the executive committee is the policy and decision-making committee for ACAS, providing ongoing direction at the operational level. This committee shares with the principal investigator the responsibility for overseeing performance in the study.

Appendix I. Study Organization

Operations Center

Bowman Gray School of Medicine, Winston-Salem, NC: James F. Toole, MD, principal investigator; Virginia Howard, MSPH, project director; Dee Dee Vernon, administrative manager; and Karla Essick, study secretary.

Statistical Coordinating Center

University of North Carolina at Chapel Hill, Chapel Hill, NC: Lloyd Chambless, PhD, principal investigator; James Grizzle, PhD, O. Dale Williams, PhD, Jeff Johnson, MS, Kay Paton, J.J. Nelson.

Participating Centers

Bowman Gray School of Medicine, Winston-Salem, NC: David Lefkowitz, MD, principal investigator; Michael McWhorter, MD, coprincipal investigator; Roger Wood, PA-C, 6/87–10/87, Jean Satterfield, LPN, 1/88–present, patient coordinator; Robert Cordell, MD, Richard Dean, MD, George Plonk, MD, surgeons; James F. Toole, MD, neurologist; Cathy Nunn, sonographer.

University of Cincinnati, Cincinnati, OH: Tom Brott, MD, principal investigator; John Tew, MD, coprincipal investigator; Chris Blum, MS, patient coordinator; Richard Fowl, MD, Richard Kempczinski, MD, L.R. Roedershiener, MD, Richard Welling, MD, surgeons; Joseph Brodereick, MD, Robert Reed, MD, neurologists; Bill Schomaker, sonographer; Thomas Tomsick, radiologist.

Columbia University, New York, NY: J.P. Mohr, MD, principal investigator; James Correll, MD, coprincipal investigator; Anilda Cabrera, MD, patient coordinator; Donald Quest, MD, surgeon; George Petty, MD, John Brust, MD, Laura Lennihan, MD, neurologists; Lorraine Oropeza, sonographer.

Henry Ford Hospital, Detroit, MI: Calvin Ernst, MD, principal investigator; Michael Welch, MD, coprincipal investigator; Wendy Robertson, PA-C, 6/87–8/88, Shelia Daley, RN, 8/88–present, patient coordinator; Joseph Elliot, MD, Daniel Reddy, MD, Alexander Sheppard, MD, Roger Smith, MD, Charles Ryan, MD (non-operating surgeon), surgeons; Steven Levine, MD, neurologist; Micky McPharlin, RN, RVT, sonographer; Serish Patel, MD, radiologist.

Milton S. Hershey Medical Center, Hershey, PA: Brian Thiele, MD, principal investigator; Robert Brennan, coprincipal investigator; Florence Smith, RN, patient coordinator; Robert Atnip, MD, surgeon; Brad Duckrow, MD, neurologist; Marsha Neumyer, RVT, sonographer; Maureen Sullivan, MD, Cindy Janesky, MD, radiologists.

University of Iowa, Iowa City, IA: José Biller, MD, principal investigator; Loren Hiratkza, MD, 2/84–9/86, John Godersky, MD, 9/86–present, coprincipal investigator; Karla Banwart, RN, patient coordinator; Christopher Loftus, MD, John D. Corson, MD, surgeons; Harold Adams, MD, E. Eugene Marsh III, MD, neurologists; Ed Miller, BS, RVT, sonographer.

Kansas University, Kansas City, KS: Arthur Dick, MD, principal investigator; George Pierce, MD, coprincipal investigator; Linda Reger, RN, patient coordinator; Arlo Hermreck, MD, surgeon; Louis Giron, MD, neurologist; Joyce Nutt, sonographer.

University of Kentucky, Lexington, KY: Byron Young, principal investigator, Michael McQuillen, MD, coprincipal investigator; Artie Norton, RN, patient coordinator; Robert Dempsey, MD, surgeon; Andrew Massey, MD, neurologist; Marcie Hauer, RVT, Jerry Sherrow, RN, RVT, sonographers; Charles Lee, MD, radiologist.

Lehigh Valley Hospital Center, Allentown, PA: John Castaldo, MD, principal investigator; Gary Nicholas, MD, coprincipal investigator; Joan Bealer, RN, patient coordinator; James Goodreau, MD, Kenneth McDonald, MD, James Rex, MD, surgeons; Peter Barbour, MD, William Pistone, MD, James Redenbaugh, MD, neurologists; Alice Madden, RN, Maggie Malik, RDMS, Judith Hutchison, sonographers; Allan Wolson, MD, Zwu-Shin Lin, MD, radiologists.

Loyola University, Maywood, IL: William Baker, MD, principal investigator; Michael Kelly, MD, coprincipal investigator; Katy Burke, RN, patient coordinator; Howard Greisler, MD, Fred Littooy, MD, surgeons; Michael Merchut, MD, neurologist.

Marshfield Clinic, Marshfield, WI: Percy Karanjia, MD, MRCP, principal investigator; Mark Swanson, MD, coprincipal investigator; Sandra Lobner, LPN, patient coordinator; M.E. Kuehner, MD, surgeon; Bradley C. Hiner, MD, neurologist; Lynn Turner, BS, RVT, Sharon R. Schaefer, LPN, RVT, John Hasenauer, RN, Ann Wlagenbach, CMA, sonographers; Robert D. Carlson, MD, J. Steven Davis, MD, Thomas Gallant, MD, John Warner, MD, radiologists.

University of Mississippi, Jackson, MS: Robert Smith, MD, principal investigator; Armin Haerer, MD, coprincipal investigator; Robin Brown, RN, patient coordinator; Robert Rhodes, MD, surgeon; S.H. Subramony, MD, neurologist.

New England Medical Center, Boston, MA: Louis Caplan, MD, principal investigator; Tom O'Donnell, MD, coprincipal investigator; Loretta Barron, RN, patient coordinator; William C. Mackey, MD, surgeon; L. Dana DeWitt, MD, Michael Pessin, MD, neurologists; Paula Heggerick, sonographer.

University of Rochester, Rochester, NY: John Ricotta, MD, 2/84–6/88, Richard Green, MD, 6/88–present, principal investigator; Richard Satran, MD, coprincipal investigator; Mollie O'Brien, RN, 2/84–6/88, JoAnne McNamara, RN, 6/88–present, patient coordinator; James DeWeese, MD, surgeon; Joshua Hollander, MD, neurologist; Sandra Roes, RT, RDMS, sonographer; Dahne Cohen, MD, radiologist.

University of Tennessee, Memphis, TN: James T. Robertson, MD, principal investigator; Patrick O'Sullivan, MD, coprincipal investigator; Nancy Ensminger, RN, 2/84–8/87, Susan Bennett, PA-C, 8/87–8/88, Terrye Thomas, RN, 6/88–8/88, Nan Stahl, RN, 8/88–present, patient coordinator; John Crockarell, MD, Clarence Watridge, MD, surgeons; Curtis Sauer, MD, Ken Vasu, MD, Kenneth Gaines, MD, neurologists; Jeanette Davis, RT, RVT, sonographer.

University of California, Los Angeles, CA: Wesley Moore, MD, principal investigator; Stanley Cohen, MD, coprincipal investigator; Candace Vescera, RN, 2/84–8/87, Jay von Rajcs, RN, 8/87–present, patient coordinator; Samuel Ahn, MD, J. Dennis Baker, MD, Ronald Busuttil, MD, Herbert Machleder, MD, William Quinones-Baldrich, MD, surgeons; Sheldon Jordan, MD, Bruce Dobkin, MD, neurologists; Vicki Canan, RN, RVT, Eugene Hernandex, RVT, sonographers; Bruce Jacobs, MD, radiologist.

University of California, San Diego, CA: John F. Rothrock, MD, principal investigator; Marc Sedwitz, MD, coprincipal investigator; Barbara Alvarez, PA-C, 6/87–1/89, Traci Babock, 1/89–present, patient coordinator; Robert Hye, MD, surgeon; Patrick Lyden, MD, neurologist; Jim Sivo, John Forsythe, Melody Adame, sonographers; Barbara Gosink, MD, Gary Press, MD, radiologists.

Virginia Mason Clinic, Seattle, WA: Hugh Beebe, MD, 7/86–3/88, Edmond Raker, MD, 3/88–present, principal investigator; James MacLean, MD, 7/86–3/88, Richard Birchfield, MD, 3/88–present, coprincipal investigator; Kathy Butler-Levy, RN, patient coordinator.

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