Role of carotid endarterectomy in asymptomatic carotid stenosis. A Veterans Administration Cooperative Study

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Research in Progress

Role of Carotid Endarterectomy in Asymptomatic Carotid Stenosis

A Veterans Administration Cooperative Study

SUMMARY **A multi-centered cooperative study is being undertaken to determine the role of carotid endarterectomy in the treatment of asymptomatic carotid stenosis. The primary objective is to compare the incidence of transient ischemic attacks, stroke, and death in previously asymptomatic patients with arteriographically confirmed internal carotid stenoses (≥ 50%) randomly allocated to carotid endarterectomy and aspirin therapy versus aspirin therapy alone. Ten Veterans Administration Medical Centers (VAMC) in the United States are participating. The study will be conducted over a period of eight years. The first three years will be devoted to acquiring and randomizing patients, after which all patients will be followed clinically for a minimum of five years. It is anticipated that approximately 500 patients will be recruited into the study.**

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THE value of carotid endarterectomy in the management of asymptomatic carotid stenosis remains controversial and poorly documented.[1, 2] Central to this controversy was the early emphasis which was placed on the significance of a carotid bruit. In a retrospective study, Thompson and associates[3] concluded that the asymptomatic carotid bruit was associated with an increased risk of stroke (17%), which could be reduced significantly (2.3%) by prophylactic endarterectomy. However, two subsequent population studies have failed to confirm this initial observation. The annualized stroke rate for patients with a carotid bruit was only 2.3% in the Evans County, Georgia study[4] and 1.7% in the Framingham study.[5]

Unlike a carotid bruit, a carotid stenosis may be defined hemodynamically and arteriographically. Experimentally, a significant carotid stenosis is characterized by a decrease in the mean flow or pressure distal to the stenosis. Arteriographically, it has been suggested that such a hemodynamically significant flow reduction is associated with a stenosis which narrows the arterial lumen by 50% of its diameter or 75% of its cross-sectional area. Data on significant asymptomatic carotid stenoses contralateral to symptomatic lesions suggest that most patients will have antecedent transient neurological events before developing stroke. In 178 patients with arteriographically documented asymptomatic carotid arterial stenoses, contralateral to symptomatic carotid arterial disease, Humphries et al[6] observed only one stroke (0.6%) during a 32 month follow-up period. However, 27 patients (16%) had transient ischemic attacks during the period of observation. Levin et al[7] reported similar data, suggesting that asymptomatic but hemodynamically significant stenoses could be followed clinically and that carotid endarterectomy could be deferred until the patient became symptomatic.

Noninvasive diagnostic techniques have made it possible to accurately identify hemodynamically significant carotid occlusive disease without arteriography. While the natural history of this population has not been well defined, several recent reports have suggested that patients with noninvasively identified high grade stenoses may be at an increased risk of stroke. Busuttil and associates[8] observed a 6.6% incidence of stroke during a 2.5 year follow-up period in patients with noninvasively defined hemodynamically significant occlusive disease. There were no strokes in those patients with negative noninvasive studies. Chambers and Norris[9] reported a 15% annualized neurological event rate in patients with carotid stenoses of at least 75%, compared to a 3% annualized rate in patients with lesser stenoses. In a longitudinal study, utilizing B-mode ultrasonography and spectral analysis to identify and follow significant carotid stenoses, Roederer and colleagues[10] reported a higher incidence of neurological events among those patients with stenoses exceeding 80%.

While previous reports have been confusing, recent studies employing noninvasive diagnostic techniques suggest that hemodynamically significant or high grade stenoses may be associated with an increased risk of subsequent stroke. Consequently, a prospective clinical trial was proposed to compare the efficacy of carotid endarterectomy and aspirin therapy versus aspirin therapy alone in patients with asymptomatic, hemodynamically significant carotid stenoses. In addition to the data which has already been reviewed, the need for such a prospective study has been reflected in a number of previous reports:

> "The diversity of reported experience is clear evidence that the question of prophylactic endarterectomy in asymptomatic patients is not answered. . . . We believe that a properly supervised, probably multi-centered, randomized prospective study should be undertaken."[6]

Ten Veterans Administration Medical Centers (VAMC) in the United States (see Appendix: Participating Centers).

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"An adequate answer to the questions posed in the title of this review will be forthcoming only when the natural history of asymptomatic carotid artery stenosis is studied and the opportunity provided for evaluating the results of prophylactic operation in altering this natural history."[11]

"A prospective randomized trial comparing the follow-up data on patients undergoing prophylactic endarterectomy with data on those not receiving operation is clearly needed to resolve this question."[12]

"The results of a surgical versus medical randomized clinical trial, however large and difficult to carry out, should provide either the welcome opportunity to sail with the tide or the firm anchor to ride it out."[13]

"Justification of prophylactic surgery ultimately requires a randomized trial since the single study purporting to show benefit is obfuscated by nonrandom selection bias."[14]

With this background, a Veterans Administration Cooperative Study was developed and evaluated during 1979–82 and initiated in April, 1983.

Summary and Design Methods

1. Ten VA Medical Centers throughout the United States were selected by the Planning Committee to participate in this study. The vascular surgeon at each hospital was required to submit narrative summaries from a previous 24 month experience with carotid endarterectomy, performed for all indications in symptomatic patients. The final selection of these study centers was approved only after review for adequacy of clinical experience and demonstrated acceptability of morbidity and mortality.

2. At each VA Medical Center, the study team consists of the vascular surgeon (Principal Investigator, PI), a collaborating neurologist (Co-Principal Investigator, Co-PI) and a nurse vascular specialist.

3. Patients are randomized from one of two groups: asymptomatic stenosis detected in the carotid artery contralateral to a symptomatic carotid lesion and asymptomatic carotid stenosis accompanied or unaccompanied by cervical bruit. In both groups, the patients must be identified as having a hemodynamically significant carotid stenosis. Hemodynamic significance is defined as stenosis reducing the diameter of the arterial lumen by 50% or more as measured arteriographically (comparing the least transverse diameter at the stenosis with the diameter of the cervical carotid artery once its diameter has become uniform). Calculation of the luminal area of a 50% diameter stenosis results in a 75% reduction in luminal area.

4. To determine eligibility, a patient will be screened using ocular pneumoplethysmography.[15] B-mode ultrasonic imaging and Doppler spectral analysis may be used in addition if available.[16, 17]

5. If the noninvasive evaluation of the patient suggests a significant carotid stenosis and medical exclusionary criteria (see Patient Enrollment and Management) do not apply, an informed consent is obtained by the PI.

6. The informed consent is reviewed with the patient and if accepted, conventional or digital subtraction arteriography is performed. If a significant and surgically accessible stenosis is identified, patients are randomized to one of the two methods of treatment: carotid endarterectomy plus aspirin or aspirin therapy alone.

7. Representative x-ray films are sent to the Study Chairman's office for review by a Consultant Radiologist who is unrelated to the study.

8. The table of randomization is managed from the office of the Study Chairman.

9. Once the patient has been randomized, he begins receiving aspirin 650 mg, b.i.d.[18, 19]

10. If a patient is allocated to the surgical group, carotid endarterectomy is performed within ten days of randomization.

11. After randomization, the patient is followed for a period of 5 years. At each follow-up visit, he is seen by the vascular surgeon and collaborating neurologist for assessment of his general physical and neurological status. The study medication is dispensed at each clinic visit. Suspected neurologic endpoint events require inpatient evaluation for confirmed diagnosis.

12. The endpoints of this study are transient ischemic attacks (TIA), stroke or stroke death. If the patient experiences a TIA or stroke, he will still be followed clinically for the duration of the study. The goal of this study is to enter about 500 patients. Acquisition thus far is near or in excess of predicted goals for each group.

Study Methods

Study Objective

The primary objective of this cooperative research study is to compare the results of carotid endarterectomy plus aspirin therapy versus aspirin therapy alone in the treatment of patients with hemodynamically significant asymptomatic carotid stenosis. After noninvasive screening, hemodynamic significance is confirmed arteriographically in accordance with the established definition.

Study Groups

It was originally planned to randomize patients from each of three clinical categories (fig. 1): Group I, patients scheduled for major vascular or general surgical procedures who had asymptomatic but hemodynamically significant stenoses; Group II, patients with unilateral symptomatic lesions combined with contralateral asymptomatic carotid stenosis noted on arteriography; and Group III, patients with incidental cervical bruits, with or without global symptoms, and positive noninvasive screening tests. Although sample size expectations have been achieved for Group II and III patients during the first 12 months of the study, rate of acquisition of patients for Group I was unacceptably low due to exclusion criteria designed for the study. (See Patient Enrollment and Management Section). As a result, the Executive Committee determined that the projected sample size would not be adequate to test the

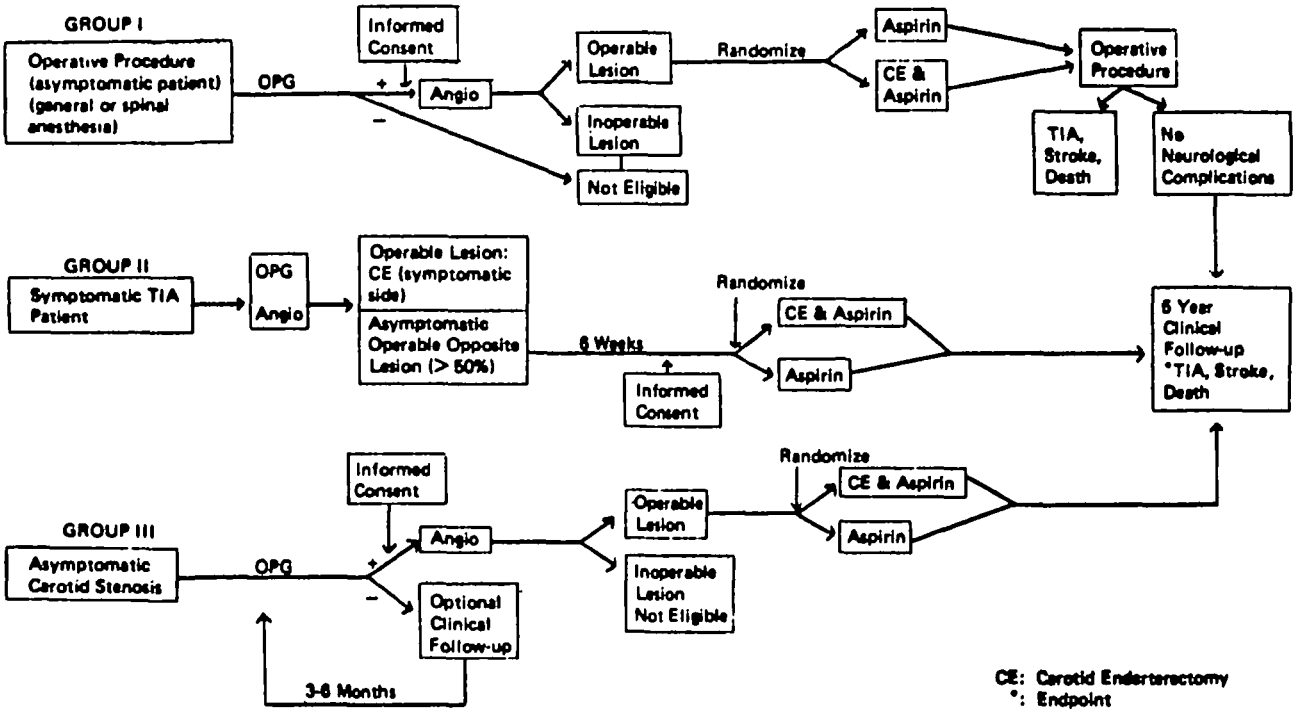

FIGURE 1. *This algorithm outlines procedures in the clinical groups of this protocol. Acquisition of patients for Group I has been discontinued.*

hypothesis in this group of patients and therefore deletion of Group I was approved.

Sample Size and Statistical Design

Patients who have surgically accessible stenotic lesions and who consent are randomly assigned to endarterectomy plus aspirin therapy or aspirin therapy alone. The occurrence of transient ischemic attack, stroke, or death due to stroke constitutes a treatment "failure" for purposes of statistical analysis. The estimated sample size required for this study was based on a statistical test for the difference of two proportions as described by Fleiss.[20] Based on clinical experience the study's Planning Committee decided that a failure rate of 20% might be anticipated in patients receiving aspirin alone during the five year clinical follow-up. To establish efficacy for surgical intervention, the Committee estimated that endarterectomy should reduce the failure rate to 5% or less during the same time. The primary objective of this study is to establish the superiority of surgical intervention relative to medical therapy alone. This objective is consistent with adopting a "one-tailed" test in assessing statistical significance, an approach supported by Taylor and colleagues[21] for clinical trials in which the experimental treatment entails greater cost, immediate risk, or major side effects. For a Type I error of 0.05, and Type II error of 0.10 (power = 0.9), the required sample size for a one-tailed test of significance for the difference of two proportions is 81 cases in each group. It is anticipated that there will be a 10% loss to follow-up during the 8 year study. The estimated sample size adjusted for this loss is 90 per group. The total sample size for the study over the three patient strata is 540 patients or for the revised two strata study a minimum of 360 patients. However, acquisition of nearly 500 patients is anticipated to cover loss of patients to follow-up which may be greater than the expected 10%. Based on initial screening in the study centers, a reasonable estimate of the accrual rate is 16–20 patients per year at each institution. Consequently, a three year intake period was planned for each of ten participating VA Medical Centers. Including the five year clinical follow-up for each patient, the proposed study will extend over a period of eight years.

In addition to the simple dichotomy of the major outcome variable (success or failure), other information, namely time until failure, will be available. Statistical analyses which exploit this additional information can be more efficient than a simple test for proportions and, hence, the sample size computed above must be considered conservative. Such analyses could include the estimation of survival curves by some parametric model possibly with inclusion of one or more covariants or the estimation of survival curves by usual nonparametric life table approaches.[22–24] In the analysis of the major outcome variables, life table methods will be used to estimate five year survival curves and to compare treatment groups. Other data to be recorded on each patient include baseline demographic history and lab data and noninvasive studies at each clinic visit. These data are reviewed at 6 month intervals through the Operations Committee, which would allow identification of any untoward trends in patient management.

It is recognized that the proposed reduction in event rates from 20% to 5% may be considered as too severe a test of surgical management by some clinicians. Al-

though this requires a 75% reduction in endpoint events, the Planning Committee theorized that reductions of this magnitude would be necessary to convince physicians and surgeons of the value of carotid endarterectomy in asymptomatic patients. Since several authors have recommended close clinical follow-up awaiting development of symptoms before intervening surgically in patients with asymptomatic carotid stenoses, we believe that a substantial advantage for carotid endarterectomy would be required before recommending it in preference to conservative management.

Noninvasive Testing

Patients belonging to one of the two study groups are identified as candidates for study eligibility on the basis of noninvasive testing: ocular pneumoplethysmography, OPG[15] which measures systolic pressure in the ophthalmic arteries and obtains calibrated pulse volume changes from the ocular globes simultaneously. The technique requires application of a vacuum suction cup on the sclera of each eye, lateral to the cornea as a means of elevating intraocular pressure. When intraocular pressure exceeds systolic pressure in the ophthalmic artery, blood flow to the eye ceases and the eye itself no longer pulsates. With reduction in the vacuum, the systolic endpoint is determined by the return of the ocular pulse. The vacuum measurement is converted to mmHg ophthalmic artery pressure using an established relationship between the two parameters. Differences of 5 mmHG or more between the eyes correlates with stenoses of greater than 75% or occlusion of the internal carotid artery. This method of testing was supplemented at most centers with B-mode ultrasonography and Doppler spectral analysis, using equipment recently acquired by all VAMC's. Although it is acknowledged that these techniques will characterize stenosis more satisfactorily and assist in identifying significant stenosis and occlusion, these tests are not required by the study protocol. If ocular pneumoplethysmography is positive, the patient is then scheduled for either conventional or digital subtraction arteriography after informed consent has been obtained.

Patient Enrollment and Management

A patient becomes a candidate for study when noninvasive testing (OPG and optional B-mode ultrasonography/Doppler spectrum analysis) is positive and the suspected carotid lesion is asymptomatic. A patient may also be a candidate if a prior arteriogram confirmed the presence of significant asymptomatic carotid stenosis.

Once a patient has been identified as a candidate for study, his eligibility for randomization is further determined by his medical history. Medical exclusionary criteria include: previous cerebral infarction (Group III only), previous endarterectomy with re-stenosis, previous extracranial to intracranial bypass, high surgical risk due to associated medical illness, chronic anticoagulant therapy, aspirin intolerance, chronic aspirin therapy ($\geq$ 10, 325 mg tablets/day), life expectancy less than five years, non-compliance and refusal. Eligibility for enrollment is established by review of each patient's medical record and/or patient interviews by the PI and collaborating neurologist.

Arteriography is performed to establish eligibility for randomization in the study and requires that the patient agree to participate and that the informed consent be signed. If the arteriogram confirms the stenosis as both significant and operable, the patient is eligible for randomization. The patient is randomized to one of two treatments, carotid endarterectomy plus aspirin or aspirin therapy alone. The randomization codes are kept at the Office of the Study Chairman. The Coordinating Center has prepared a separate list of randomization codes for each VAMC and each group (II and III). When a patient is to be randomized, the Vascular Specialist calls the Office of the Chairman and obtains a randomization code from the Study Coordinator.

In this study, the code name given to aspirin is *SALIPRIN*. When a patient consents to participation in the study, he will start taking SALIPRIN immediately. The patient takes two tablets (aspirin, 650 mg) twice daily. Patients who are randomized to carotid endarterectomy plus aspirin are scheduled for surgery within 10 days of randomization.

All study patients are scheduled for periodic clinical visits at 13 week intervals during the first follow-up year and at 26 week intervals during follow-up years two through five. At each visit, the patients are examined by the PI and collaborating neurologist and noninvasive diagnostic tests are repeated. Blood work (complete blood count with differential and platelet count, prothrombin time and partial thromboplastin time) is repeated once every 12 months. At each clinic visit, patient compliance with the study medication is assessed by pill counts.

Neurologic events which constitute endpoints for this study are TIA, stroke, or death due to stroke. Patients and families are instructed to contact the PI, collaborating neurologist or vascular specialist immediately after the occurrence of any suspected neurologic event. Patients who experience these events will undergo appropriate clinical evaluation as in-patients. The definitions of TIA and stroke as presented by an ad hoc committee established by the Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health were reviewed and adopted by the Study Group.[5]

The Cooperative Studies Program Coordinating Center (CSPCC) at Perry Point, Maryland is the central repository for all study data on patients who are randomized. A screening form is also completed on all patients who have positive noninvasive tests, but are eliminated from randomization based either on arteriographic findings, or other medical exclusionary criteria.

Organizational Structure (see Appendix)

Ten VA Medical Centers throughout the United States are participating in the cooperative study. They

are as follows: VAMC, Atlanta, GA; VAMC, Boston, MA; VAMC, Buffalo, NY; VAMC, East Orange, NJ; VAMC, Iowa City, IA; VAMC, Little Rock, AR; VAMC (Sepulveda),* Los Angeles, CA; VAMC (Wadsworth), Los Angeles, CA; VAMC, Milwaukee (Wood), WI; VAMC, Tucson, AZ and VAMC, San Francisco, CA. The Office of the Study Chairman and Study Coordinator is located at the VAMC, East Orange, NJ. Analysis of a previous 24 month experience with carotid endarterectomy in these institutions demonstrated the following: mean number of carotid endarterectomies performed per year per center, 31 (range 19 to 55); overall mortality, 1.9% (310 procedures); and neurologic morbidity: transient, 2.2% and permanent, 1.8%.

The Coordinating Center for this VA Cooperative Study is located at the VAMC, Perry Point, Maryland. The center provides biostatistical, administrative, and data processing support.

The Executive Committee includes two participating investigators, two permanent consultants (one in Neurology and one in Vascular Surgery), the Study Biostatistician and the Study Chairman. This Committee serves as the management group and major decision-making body for the operational aspects of the study. It reviews any proposed changes in the study or its protocols, other use of study data or publication of study results, and actions regarding medical centers in which performance is considered unsatisfactory.

The Operations Committee consists of four members: two vascular surgeons, one neurologist and one biostatistician. None is related directly to the cooperative study. The purpose of this Committee is to provide continuing critical and unbiased evaluation of the study's progress and to formulate operational policy consistent with current accepted biomedical research practices.

The Human Rights Committee is composed of seven members. This committee is responsible for review of informed consent and for ensuring that the patient's rights and safety are protected during the course of the study.

The Cooperative Studies Program Clinical Research Pharmacy Coordinating Center of the VA is located at the VA Medical Center, Albuquerque, New Mexico and will provide administrative support for supply study medications for each participating medical center for the duration of the study.

Appendix

Study Organization

VA Medical Center, East Orange, NJ; Study Chairman, Robert W. Hobson II, M.D. formerly VAMC East Orange, N.J., currently VAMC Boston, MA.; Study Coordinator, Sandi G. Rossos, M.S.; Study Secretary, Lorraine McClendon, 2/83–6/85, Elaine C. Brooks, 6/85 to present.

*See, Participating Centers in Appendix.

Planning Committee: 1979–83

Robert W. Hobson II, M.D., VAMC, East Orange, NJ; William S. Fields, M.D., University of Texas Health Science Center, Houston, TX (Consultant Neurologist); Andrew Gage, M.D., VAMC, Buffalo, NY; Jerry Goldstone, M.D., VAMC, Tucson, AZ; (Currently at University of California, San Francisco, CA); Wesley Moore, M.D., UCLA, Los Angeles, California; Creighton B. Wright, M.D., VAMC, Iowa City, IA; (Currently at Cincinnati, OH); and David G. Weiss, Ph.D. (Biostatistician), Cooperative Studies Program Coordinating Center, Perry Point, MD.

Participating Centers

VA Medical Center, Atlanta (Decatur), GA. Principal Investigator, Robert B. Smith, M.D.; Co-Principal Investigator, John Ammons, M.D.; Vascular Specialist, Rita Gianetti, R.N.

VA Medical Center, Boston, MA. Principal Investigator, Rudolph W. Vollman, M.D., 4/83–9/84; Willard Johnson, M.D., 9/84-Present; Co-Principal Investigator, Russell Butler, M.D. 4/83–8/85, Carlos Kase, M.D. 9/85–present; Vascular Specialist, Janis Hamilton, R.N.

VA Medical Center, Buffalo, NY. Principal Investigator, Andrew A. Gage, M.D., 4/83–8/85, C. Steven Powell, 9/85-Present; Co-Principal Investigator, Emilio Soria, 4/83–4/84, Walter A. Olszewski, M.D., 5/84–Present; Vascular Specialist, Delores E. Young, R.N.

VA Medical Center, East Orange, NJ. Principal Investigator, Thomas G. Lynch, M.D.; Co-Principal Investigator Said Shanawani, M.D.; Vascular Specialist, Dolores A. Johnson, R.N., 4/83–4/85, Carolyn Clark, R.N., 5/85–Present.

VA Medical Center, Iowa City, IA. Principal Investigator, Loren F. Hiratzka, M.D.; Co-Principal Investigator, William T. Talman, M.D.; Vascular Specialist, Cheryl Martin, R.N., 4/83–5/84; Vickie B. Griffith, R.N., 5/84–Present.

VA Medical Center, Little Rock, AR. Principal Investigator, Bernard W. Thompson, M.D.; Neurology Service VAMC; Vascular Specialist, Diane Morgan, R.N.

VA Medical Center, Los Angeles (Sepulveda), CA. Principal Investigator, J. Dennis Baker, M.D.; Co-Principal Investigator, E. Jeffrey Metter, M.D., Vascular Specialist, Nadine Rabey, A.S., 4/83–8/84, Diette Dix, P.A., 5/84–Present. (Participated in study 4/83–8/84).

VA Medical Center, Los Angeles (Wadsworth), CA. Principal Investigator, R. Eugene Zierler, M.D., 4/83–5/84, Bruce Stabile, M.D. 5/84–6/85, Eric Wilson, M.D., 7/85–Present; Co-Principal Investigator Stanley Cohen, M.D.; Vascular Specialist, Lynne Emma, R.N.

VA Medical Center, San Francisco, CA. Principal Investigator, William C. Krupski, M.D.; Co-Principal Investigator, Frank Sharp, M.D.; Vascular Specialist, Sande Perez, R.N.

VA Medical Center, Tucson, AZ. Principal Investigator, Jerry Goldstone, M.D., 4/83–6/84; Victor Bernhard, M.D., 7/84–Present; Co-Principal Investigator, Enrique Labadie, M.D.; Vascular Specialist, Martha Nash, R.N., 4/83–4/84; Barbara Phelps, R.N., 4/84–9/85, Jenifer Vance, R.N. 10/85–Present.

VA Medical Center, Milwaukee (Wood), WI. Principal Investigator, Jonathan Towne, M.D.; Co-Principal Investigator, Varun K. Saxena, M.D.; Vascular Specialist, John Navine, R.N.

Cooperative Studies Program Coordinating Center

VA Medical Center, Perry Point, MD. Chief, C. James Klett, Ph.D.; Study Biostatistician, David G. Weiss, Ph.D.; Statistical Assistants, Peggy Jackson & Dorothy Morson; Administrative Assistant, Bertha D. Carter; Programmers, Diana Preston, Robert Kuhn, Ph.D., Barbara Miller, M.S.

Radiology Consultant

In Sook Yu Song, M.D., VA Medical Center, Bronx, New York.

Cooperative Studies Program Clinical Research Pharmacy Coordinating Center

VA Medical Center, Albuquerque, New Mexico. Study Pharmacist, Claire Haakenson, R.Ph., M.S., 1979–1984; Dennis Toussaint, R.Ph., M.S., 1984–Present.

Executive Committee

Robert W. Hobson II, M.D., VA Medical Center, Boston, MA; William S. Fields, M.D., University of Texas, Houston, Texas; Wesley Moore, M.D., University of California, Los Angeles, CA; Jonathan Towne, M.D., VA Medical Center, Wood, Wisconsin; Creighton Wright, M.D. (Ad Hoc), Christ Hospital, Cincinnati, OH; Jerry Goldstone, M.D. (Ad Hoc), University of California, San Francisco, California; David G. Weiss, Ph.D., VA Medical Center, Perry Point, MD; C. James Klett, Ph.D., VA Medical Center, Perry Point, MD.

Operations Committee

Allan Callow, M.D., Chairman; New England Medical Center, Boston, MA; Roger E. Flora, Ph.D., A.H. Robbins Co., Richmond, VA; James C. Grotta, M.D., University of Texas Health Science Center Medical School, Houston, Texas; Anthony M. Imperato, M.D., New York University Medical Center, New York, New York.

Human Rights Committee

Colleen Crigler (Chairperson), VAMC, Perry Point, MD; Mr. Samuel L. Caesar, Baltimore, MD: Ms. Susan K. Gauvey, Baltimore, MD; Rev. Maurice Moore, Ashton, MD; Mr. William Beard, Baltimore, MD; Ronald S. Limpman, Ph.D., Baltimore, MD; Lino Covi, M.D., Baltimore, MD.

Endpoint Committee

Robert W. Hobson II, M.D., Study Chairman, VA Medical Center, Boston, MA; David G. Weiss, Ph.D., Study Biostatistician, VA Medical Center, Perry Point, Maryland; Louis R. Caplan, M.D., Tufts University School of Medicine, Boston, Massachusetts; William S. Fields, M.D., University of Texas, Houston, Texas; Jerry Goldstone, M.D., University of California, San Francisco, California; Wesley Moore, M.D., University of California, Los Angeles, CA; Creighton Wright, M.D., Christ Hospital, Cincinnati, Ohio.

Cooperative Studies Program Central Administration

Chief: James A. Hagans, M.D., Ph.D.; Staff: Ping C. Huang, Ph.D.

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