Published in final edited form as:
Int J Stroke. 2010 February ; 5(1): 40–46. doi:10.1111/j.1747-4949.2009.00405.x.

Design of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)

Alice J. Sheffet, PhD[1], **Gary Roubin, MD**[2], **George Howard, DrPH**[3], **Virginia Howard, PhD**[3], **Wesley Moore, MD**[4], **James F. Meschia, MD**[5], **Robert W. Hobson II, MD**[1,*], and **Thomas G. Brott, MD**[1,5]

[1]Department of Surgery, UMDNJ-New Jersey Medical School, Newark, NJ

[2]Department of Interventional Cardiology, Lenox Hill Hospital, New York, NY

[3]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL

[4]Department of Surgery, University of California Los Angeles

[5]Department of Neurology, Mayo Clinic, Jacksonville, FL.

Abstract

Rationale—Carotid endarterectomy (CEA) and medical therapy were shown superior to medical therapy alone for symptomatic (≥50%) and asymptomatic (≥60%) stenosis. Carotid angioplasty stenting (CAS) offers a less invasive alternative. Establishing safety, efficacy, and durability of CAS requires rigorous comparison with CEA in symptomatic and asymptomatic patients.

Aims—The objective is to compare the efficacy of CAS versus CEA in patients with symptomatic (≥50%) or asymptomatic (≥60%) extracranial carotid stenosis.

Design—The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) is a prospective, randomized, parallel, two-arm, multi-center trial with blinded endpoint adjudication. Primary endpoints are analyzed using standard time-to-event statistical modeling with adjustment for major baseline covariates. Primary analysis is on an intent-to-treat basis.

Study Outcomes—The primary outcome is the occurrence of any stroke, myocardial infarction, or death during a 30-day peri-procedural period, and ipsilateral stroke during follow-up of up to four years. Secondary outcomes include restenosis and health-related quality of life.

Keywords

carotid stenosis; carotid stenting; carotid endarterectomy; stroke prevention; randomized trial

Introduction

Carotid endarterectomy (CEA) is a standard treatment for prevention of stroke depending upon severity of carotid stenosis and other preoperative factors.[1, 2] Carotid artery stenting (CAS) is an alternative to CEA, but the relative efficacy of these procedures is not well described. Early randomized clinical trials (RCTs) were criticized for inadequate sample size, sub-optimal interventionalist experience, inconsistent use of anti-platelet medications, absence of an anti-embolic device, and incomplete enrollment.[3-5] The Carotid

Correspondence: Thomas G. Brott, MD, Mayo Clinic, Griffin Building 3rd Floor, 4500 San Pablo Road, Jacksonville, FL 32224. Ph: 904-953-0556, Fax: 904-953-0277, brott.thomas@mayo.edu.
*Deceased

Revascularization Endarterectomy vs. Stenting Trial (CREST) was designed to minimize the impact of these issues, and is the only RCT to enroll symptomatic and asymptomatic patients.

METHOD

Design

CREST is a prospective, randomized, multi-center trial, with blinded endpoint adjudication, designed to compare the efficacy of CAS versus CEA. All institutions received Institutional Review Board or equivalent ethics committee approval before trial initiation, and all participants provided written informed consent.

Surgical and Interventional Management Committees (SMC & IMC) approved participation of surgeons and interventionalists. For interventionalists, a lead-in phase included a credentialing period, during which each interventionalist performed up to 20 stent procedures using ACCULINK™ and ACCUNET™ devices.6 The IMC reviewed the results and approved interventionalists prior to their participating in the randomized phase. For surgeons, the SMC used approaches proven successful in the Asymptomatic Carotid Atherosclerosis Study (ACAS)7 where approximately the past 50 procedures for each surgeon were reviewed prior to approval for participation in the trial.8

Patient Population

Tables 1 and 2 show the eligibility criteria. Asymptomatic patients were added March 2, 2005. Shortly before, the Asymptomatic Carotid Surgery Trial9 reported benefit for CEA in individuals with high-grade asymptomatic stenosis. In the United States the majority of revascularization procedures are performed for asymptomatic carotid artery disease.10 All potential CREST participants were evaluated by the study team's neurologist, interventionalist, vascular surgeon or neurosurgeon, and coordinator, to verify eligibility.

Randomization

Randomization was stratified by clinical center and symptomatic status, and permuted block 1:1 randomization was performed within strata using block size randomly chosen from small multiples of two. Randomization occurred when the patient, surgeon, and interventionalist were able to schedule the procedure within two weeks.

Treatment

CAS procedures were performed using ACCULINK® and ACCUNET® devices where feasible. CAS patients received aspirin 325 mg b.i.d. and clopidogrel 75 mg b.i.d 48 hours prior to the procedure, or alternatively two aspirin (325 mg) and six clopidogrel (75 mg) given at least four hours pre-procedure.

Post-procedure, CAS patients received 1-2 aspirin 325 mg daily for 30 days and one daily thereafter. During the 30 days post-procedure, CAS patients were to receive either one clopidogrel (75 mg) or one-two ticlopidine (250 mg) daily.

Forty-eight hours before CEA, patients were to receive aspirin (325 mg) daily and remain on aspirin (325 mg) daily indefinitely (at least one year). For those intolerant at this dose, alternatives included ticlopidine (250 mg) b.i.d., clopidogrel (75 mg) daily, aspirin (81 mg) daily, or Aggrenox® b.i.d.

Primary Outcome

The primary endpoint is the composite of any stroke, MI, or death during a 30-day peri-procedural period, or ipsilateral stroke through follow-up of up to four years. Separate analyses for the Food and Drug Administration (FDA) device evaluation will assess treatment differences in the one-year composite of stroke, MI, or death during a 30-day peri-procedural period and stroke ipsilateral to the study artery between 31 days and one year. Suspected endpoint events were reviewed by two Adjudications Committee reviewers masked for treatment group, with disagreements resolved by a third reviewer.

Recurrent or new ischemic stroke is defined as an acute neurological event lasting ≥ 24 hours with focal symptoms and signs. The endpoint review process is initiated in the case of a significant neurological event, a positive TIA/Stroke questionnaire, or a two-point or greater increase in the National Institutes of Health Stroke Scale (NIHSS) score (Table 3). Peri-procedural MI is determined by symptoms, electrocardiography (ECG), and enzyme abnormalities. ECGs are centrally read using the Novacode11 modification of the Minnesota Code for MI classification. A patient will be considered to have experienced a MI when there is confirmatory evidence of myocardial ischemia plus elevation of cardiac biomarkers (CK-MB or troponin) to a value two or more times the individual clinical center's laboratory upper limit of normal. Confirmatory evidence of myocardial ischemia includes any one of the following:

- Chest pain or equivalent symptoms consistent with myocardial ischemia
- ECG evidence of ischemia including new ST segment depression or elevation > 1 mm in two or more contiguous leads.

For death, efforts are made to obtain relevant records from the hospital or the patient's primary physician, including death certificates, to determine cause.

Secondary Outcomes

Secondary aims are to describe the differential efficacy of CAS and CEA by symptomatic status and by sex, contrast peri-procedural (30-day) and post-procedural morbidity and mortality, contrast the restenosis rates of CAS and CEA, evaluate differences in health-related quality of life (QOL) and cost, and identify subgroups of participants at differential risk for procedural morbidity and mortality.

Health-related QOL and functional status are assessed using the Medical Outcomes Study 36-item health status questionnaire (SF-36) and Frenchay Activities Index at baseline, one month, and one year and the Health Utilities Index (HUI) at one year. The SF-36 and several disease-specific scales are administered two weeks after the initial revascularization procedure by a trained telephone interviewer from the QOL center.

Medical resource utilization and cost data are collected for subsequent hospitalizations, medical procedures, long-term care, and outpatient care through one year. Hospital summary bills (UB-92 forms) and detailed billing statements are obtained for each patient's index hospitalization. These data are converted into measures of medical-care cost. At completion of the study, cost and QOL data will be integrated to perform a formal cost-effectiveness analysis.

Data Safety and Monitoring Board (DSMB)

The NINDS-appointed DSMB is responsible for assuring that study participants are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards. The DSMB is responsible for advising early termination of the trial in the event of unexpected safety concerns or if treatment

differences were apparent at the pre-specified interim analyses using O'Brien-Fleming boundaries.12

Sample Size

The sample size of 2,500 subjects was selected to provide 90% power to detect a hazard ratio of >1.49 or <0.54 in the composite endpoint event rates, which corresponds to greater than 1.2% per year absolute differences, a difference similar to that shown in ACAS7.

Statistical Analyses

Analyses are based on an intention-to-treat survival analysis and standard time-to-event statistical modeling with adjustment for major baseline covariates. A traditional difference assessment will be performed as described in the original NIH protocol, and a non-inferiority analysis for submission to the FDA.

The primary goal for the NIH analysis is to identify differences between CAS and CEA in preventing endpoint events over a multi-year follow-up. Survival analyses will allow for varying lengths of follow-up. Kaplan-Meier estimates of the proportion of patients remaining free of the composite endpoint at 30-days, six-months, one-year and annually thereafter, and the associated confidence intervals will be constructed. The hazard ratio between groups will be estimated after adjustment for important covariates.

A number of secondary analyses will be conducted:

- The potential for a differential treatment efficacy between symptomatic and asymptomatic participants, and between men and women, will be assessed by the inclusion of interaction terms in the proportional hazards models. A hazard ratio difference of 2.22 or greater can be detected with 90% power.
- Differences in the morphology of the treated carotid artery segment reflecting potential restenosis of the target lesion will be assessed in both groups at six months and one year by analysis of the covariance with adjustment for velocities assessed at one-month post index procedure.
- Differences in peri-procedural event rates will be assessed using logistic regression (logistic regression employed because of the low censoring rate in the short peri-procedural period). The anticipated event rate (stroke, death, MI) in the CEA arm of the study is 5.7%; there will be 90% power to detect differences between treatments if the CAS complication rate is <3.2% or >9.3%.
- Differences in post-30 day event rates will be assessed among those participants who are event-free during the first 30 days post-procedure. Unlike the peri-procedural period, the outcome for the post-procedural period is time-to-event survival analysis. Differences between groups will be assessed using the proportional hazards model; there will be 80% power to detect differences if the hazard ratio is <0.50 or >2.00.
- Differences in other major and minor complications will be assessed using standard methods including Chi-square testing. Power to detect differences is a function of the incidence of specific complications; however, should a complication have approximately a 5% incidence, statistical power would be similar to that for peri-procedural events.
- Finally, the potential for other factors that may influence the relative efficacy of CAS and CEA in subgroups will be assessed in exploratory analyses using a proportional hazards analysis. A hazard ratio >2.20 can be detected with 90%

power; however, findings will be interpreted with caution because of the exploratory nature of these analyses.

In secondary analysis of the primary endpoint, data will be imputed in order to ensure that participants who withdrew from the study early could not have biased estimated treatment effects. For each participant who withdrew from the study, the outcome for a patient matched for age and symptomatic status will be substituted. Multiple imputations will then be employed to introduce appropriate variance to the estimated treatment effects.

Two protocol-specified interim analyses were reviewed by the DSMB: after approximately 500 patients and again after approximately 1/2 of the patients were enrolled. In order to maintain maximum power for the final analysis while simultaneously protecting the overall alpha of the study, O'Brien-Fleming12 adjustments were made to the alpha for each of these tests. The statistical costs of these adjustments have been incorporated in the power calculations. After each DSMB review, the study was recommended for continuation.

Study Organization and Funding

The trial was funded January 15, 1999 by the NINDS with support from Abbott Vascular, Inc. (originally Guidant). In May, 2003, the Investigational Device Exemption (IDE) sponsorship, with reporting responsibility to the FDA, was transferred from Guidant to CREST. Enrollment began in December 2000 and ended in July 2008 with 2,522 participants.

Summary

CREST is a prospective, randomized, parallel, two-arm, multi-center trial, designed to compare the efficacy of CAS versus CEA in preventing stroke. The primary comparison outcome is the occurrence of any stroke, MI, or death during a 30-day peri-procedural period, and ipsilateral stroke during the follow-up period of up to four years in patients with extracranial carotid stenosis. Conventional-risk participants with symptomatic carotid stenosis (≥ 50% by angiography, ≥ 70% by ultrasound, or ≥70% by CTA/MRA) or asymptomatic carotid stenosis (≥60% by angiography, ≥70% by ultrasound, or ≥80% by CTA/MRA) are randomized to CEA or CAS in a 1:1 ratio. Secondary aims contrast CAS and CEA by symptomatic status, in men and women, by restenosis rates, by health-related quality of life, and by cost. With 2,522 randomized patients at 117 U.S. and Canadian sites, CREST has been designed to have 90% power to detect annual treatment differences of 1.2% in CEA and CAS primary endpoints.

Acknowledgments

Additional funding provided by Abbott Vascular Solutions, Inc., Santa Clara, CA. The CREST Publications and Presentations Committee approved this manuscript.

Funding: National Institute of Neurological Disorders and Stroke (NINDS) (RO1 NS 038384)

CREST Principal Investigators (in order of number of participants randomized)

Wayne Clark -Oregon Health & Science University, Portland, OR

William Brooks -Central Baptist Hospital, Lexington, KY

Ariane Mackey -Centre Hospitalier Affilie´ universitaire de Que´bec-Ho^pital de l'Enfant-Je´sus, Que´bec City, QC Canada

Michael Hill -University of Calgary/Foothills Medical Centre, Calgary, AB Canada

Pierre Leimgruber -Deaconess Medical Center/Northwest Cardiovascular Research Institute, Spokane, WA

Vito Mantese -St. John's Mercy Medical Center, St. Louis, MO

Carlos Timaran -University of Texas Southwestern Medical School, Dallas, TX

Nelson Hopkins -SUNY at Buffalo, Buffalo, NY

David Chiu -Methodist Hospital, Houston, TX

Richard Begg -Tri-State Medical Group, Beaver, PA

Zafar Jamil -St. Michael's Medical Center, Newark, NJ

Robert Hye -Kaiser Permanente -San Diego Medical Center, San Diego, CA

Bart Demaerschalk -Mayo Clinic, Scottsdale, AZ

O.W. Brown –Beaumonts Hospitals, Royal Oak, MI

Gary Roubin -Lenox Hill Hospital, New York, NY

Donald Heck -Forsyth Medical Center, Winston-Salem, NC

Richard Farb -Toronto Western Hospital, Toronto, ON Canada

Irfan Altafullah -North Memorial Medical Center, Golden Valley, MN

Gary Ansel -MidWest Cardiology Research Foundation, Columbus, OH

Albert Sam, II -Vascular Specialty Associates, Baton Rouge, LA

Nicole Gonzales -University of Texas Medical School, Houston, TX

Peter Soukas -St. Elizabeth's Medical Center, Boston, MA

Lawrence Wechsler -University of Pittsburgh Medical Center/ Shadyside Hospital and Presbyterian Hospital, Pittsburgh, PA

Daniel Clair -Cleveland Clinic, Cleveland, OH

Mark Reisman -Swedish Medical Center, Seattle, WA

John Eidt -University of Arkansas for Medical Sciences/Central Arkansas Veteran's Healthcare System, Little Rock, AR

Steven Orlow -Northern Indiana Research Alliance, Fort Wayne, IN

James Burke -Intermountain Medical Center, Salt Lake City, UT

Mahmoud Malas -Johns Hopkins Medical Institutions, Baltimore, MD

Michael Rinaldi -Sanger Heart and Vascular Institute, Charlotte, NC

Kenneth Rosenfield -Massachusetts General Hospital, Boston, MA

Charles Sternbergh, III -Ochsner Health System, New Orleans, LA

Richard McCann -Duke University Medical Center, Durham, NC

Charles O'Mara -Mississippi Baptist Medical Center, Jackson, MS

Albert Hakaim -Mayo Clinic, Jacksonville, FL

Barry Katzen -Baptist Cardiac and Vascular Institute, Miami, FL

Robert Spetzler -Barrow Neurological Institute, Phoenix, AZ

Anthony Pucillo – Westchester Medical Center, Valhalla, NY

James Elmore -Geisinger Medical Center, Danville, PA

William Jordan -University of Alabama at Birmingham, Birmingham, AL

David Lew -Leesburg Regional Medical Center, Leesburg, FL

Richard Powell -Dartmouth Hitchcock Medical Center, Lebanon, NH

Robert Bulas -The Christ Hospital, Cincinnati, OH

Bryan Kluck -Lehigh Valley Hospital, Allentown, PA

Joseph Rapp -San Francisco VA Medical Center, San Francisco, CA

Gregory Mishkel -Prairie Education and Research Cooperative, Springfield, IL

Fred Weaver -University of Southern California, Los Angeles, CA

Munier Nazzal -University of Toledo Medical Center, Toledo, OH

Craig Narins -University of Rochester Medical Center, Rochester, NY

Robert Molnar -Michigan Vascular Research Center, Flint, MI

Mark Eskandari -Northwestern Memorial Hospital, Chicago, IL

Herbert Aronow -Michigan Heart & Vascular Institute, Ann Arbor, MI

Fayaz Shawl -Washington Adventist Hospital, Takoma Park, MD

Robert Rosenwasser -Thomas Jefferson University, Philadelphia, PA

Hollace Chastain -Parkview Research Center, Fort Wayne, IN

Malcolm Foster -Baptist Hospital West, Inc., Knoxville, TN

Rodney Raabe -Providence Medical Research Center, Spokane, WA

David Pelz -London Health Sciences Centre, London, ON Canada

Grant Stotts -Ottawa Hospital, Ottawa, ON Canada

Harry Cloft -Mayo Clinic, Rochester, MN

Louis Heller -St. Joseph's Hospital of Atlanta, Atlanta, GA

Bhagat Reddy -Piedmont Hospital/Fuqua Heart Center, Atlanta, GA

Kim Hodgson -Southern Illinois School of Medicine, Springfield, IL

Ken Fraser -OSF Saint Francis Medical Center, Peoria, IL

William Gray -Columbia University Medical Center/New York Presbyterian Hospital, New York, NY

Alexander Shepard -Henry Ford Hospital, Detroit, MI

Walter Montanera -St. Michael's Hospital, Toronto, Canada

Wes Moore -University of California, Los Angeles, CA

Elliot Chaikof – Emory University Hospital/Atlanta VAMC, Atlanta, GA

Sarah Johnson -Cardiovascular Research Foundation/Cardiovascular Associates, Elkgrove, IL

Richard Zelman -Cape Cod Research Institute, Hyannis, MA

Avery Evans -University of Virginia Health System, Charlottesville, VA

David Burkart -St. Joseph Medical Center, Kansas City, MO

Dennis Bandyk -University of South Florida, Tampa, FL

Percy Karanjia -Marshfield Clinic, Marshfield, WI

Jamal Zarghami -Providence Hospital and Medical Centers, Southfield, MI

Adam Arthur -Baptist Memorial Hospital, Memphis, TN

Manish Mehta -Vascular Interventional Project, Inc., Albany, NY

Anthony Comerota -Jobst Vascular Center, Toledo, OH

Kannan Natarajan -St. Vincent Hospital, Indianapolis, IN

Jay Howington -St. Joseph/Candler Health System, Savannah, GA

Daniel Selchen -Trillium Health Centre, Mississauga, ON Canada

Marc Schermerhorn -Beth Israel Deaconess Medical Center, Boston, MA

Steven Laster -St. Luke's Hospital, Kansas City, MO

Mark Sanz -St. Patrick Hospital, Missoula, MT

Eric Lopez del Valle -Morton Plant Hospital, Clearwater, FL

Joseph Andriole -Orlando Regional Healthcare, Orlando, FL

Andrew Ringer -University of Cincinnati, Cincinnati, OH

John Martin -Anne Arundel Medical Center, Annapolis, MD

Randy Guzman -University of Manitoba, Winnipeg, MB Canada

Philip Teal -Vancouver General Hospital, Vancouver BC, Canada

Frank Hellinger -Florida Hospital, Orlando, FL

George Petrossian -St. Francis Hospital, Roslyn, NY

Mark Bates -Charleston Area Medical Center, Charleston WV

Joseph Mills -University of Arizona College of Medicine, Tucson, AZ

Michael Golden -Hospital of the University of Pennsylvania, Philadelphia, PA

Ashraf Mansour -Butterworth Hospital, Grand Rapids, MI

Andrew MacBeth -St. Joseph's Medical Center, Stockton, CA

L.A. Iannone -Iowa Heart Center, Des Moines, IA

Kimberly Hansen -Wake Forest University Health Sciences, Winston Salem, NC

Jose Biller -Loyola University Medical Center, Maywood, IL

John Shuck -Christiana Care Health Services, Newark, DE

Pierre Gobin-WeillCornell MedicalCollege of NewYorkPresbyterian Hospital, New York, NY

Kent Dauterman -Rogue Valley Medical Center, Medford, OR

Jim Melton -Oklahoma Foundation for Cardiovascular Research, Oklahoma City, OK

Daniel Benckart -Allegheny General Hospital, Pittsburgh, PA

Walter Lesley -Scott & White Memorial Hospital, Temple, TX

Michael Belkin -Brigham & Women's Hospital, Boston, MA

Tanvir Bajwa -St. Luke's Medical Center, Milwaukee, WI

Subbarao Myla -Hoag Memorial Hospital, Newport Beach, CA

Jeffrey Snell -Rush University Medical Center, Chicago, IL

Harish Shownkeen -Central DuPage Hospital, Winfield, IL

Alex Abou-Chebl -University of Louisville, Louisville, KY

References

1. Goldstein LB, Adams R, Alberts MJ, et al. Primary Prevention of Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline. Stroke. 2006; 37(6):1583–633. [PubMed: 16675728]
2. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA Recommendations for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. Stroke. 2008; 39(5): 1647–52. [PubMed: 18322260]
3. Furlan AJ. Carotid-Artery Stenting -- Case Open or Closed? N Engl J Med. 2006; 355(16):1726–9. [PubMed: 17050898]
4. Bonvini RF, Righini M, Hamon M, et al. Endarterectomy versus Stenting for Carotid Stenosis. N Engl J Med. 2007; 356(3):305–7. [PubMed: 17229961]
5. Barrett KM, Brott TG. Carotid Artery Stenting Versus Carotid Endarterectomy: Current Status. Neurosurgery Clinics of North America. 2008; 19(3):447–58. [PubMed: 18790380]
6. Howard VJ, Voeks JH, Lutsep HL, et al. Does sex matter? Thirty-day stroke and death rates after carotid artery stenting in women versus men: results from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) lead-in phase. Stroke. 2009; 40(4):1140–7. [PubMed: 19211486]
7. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995; 273(18):1421–8. [PubMed: 7723155]
8. Moore WS, Vescera CL, Robertson JT, Baker WH, Howard VJ, Toole JF. Selection process for surgeons in the Asymptomatic Carotid Atherosclerosis Study. Stroke. 1991; 22(11):1353–7. [PubMed: 1750041]
9. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet. 2004; 363(9420):1491–502. [PubMed: 15135594]
10. McPhee JT, Hill JS, Ciocca RG, Messina LM, Eslami MH. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. Journal of Vascular Surgery. 2007; 46(6):1112–8.e1. [PubMed: 18154987]
11. Rautaharju PM, MacInnis PJ, Warren JW, Wolf HK, Rykers PM, Calhoun HP. Methodology of ECG interpretation in the Dalhousie Program; NOVACODE ECG classification procedures for clinical trials and population health surveys. Methods of Information in Medicine. 1990; (29):362–74. [PubMed: 2233384]
12. O'Brien P, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979; 35(3): 549–56. [PubMed: 497341]

Table 1

Eligibility criteria randomized phase.

Clinical Inclusion Criteria

1. Age ≥18 years old
2. Symptomatic status

   • Symptomatic patient, as evidenced by transient ischemic attack (TIA), amaurosis fugax, minor or non-disabling stroke (in the hemisphere supplied by the target vessel), within 180 days of the randomization date

   • Asymptomatic patient with compatible history and findings on physical and neurological exam. Patients with eligible carotid stenosis that do not meet the definition for symptomatic carotid stenosis may be enrolled as asymptomatic patients. This includes:

   ■ No prior carotid territory symptoms or

   ■ Prior symptoms referable only to the hemisphere contralateral to the target vessel or

   ■ Symptoms in either hemisphere > 180 days prior to randomization or

   ■ Vertebrobasilar symptoms only
3. No childbearing potential or has a negative pregnancy test within one week prior to study procedure
4. Patient and patient's physician agree to have the patient return for all required clinical contacts.
5. Written informed consent.
6. Candidate for CEA and meets all other eligibility requirements.

Anatomic Inclusion Criteria

1. Discrete lesion located in the internal carotid artery (ICA) (with or without involvement of the contiguous common carotid artery (CCA)).
2. Degree of Stenosis:

   Symptomatic patients – carotid stenosis ≥ 50% defined as:

   • Stenosis ≥70% by ultrasound

   • Stenosis ≥50% by angiography (based on NASCET Criteria) **or**

   • If the ultrasound indicates 50-69% stenosis, that patient may be randomized on the basis of results from a CT angiogram (CTA) or MR angiogram (MRA) **IF** a radiologist or neuro-imaging specialist documents his/her opinion that a CTA or MRA indicate ≥ 70% stenosis and that the CTA or MRA is of acceptable technical quality. If the results of the CTA or MRA are not conclusive, the patient should undergo conventional angiography.

   Asymptomatic patients – carotid stenosis ≥ 60% defined as:

   • Stenosis ≥70% by ultrasound

   • Stenosis ≥60% by angiography (based on NASCET Criteria) **or**

   • If the ultrasound indicates 50-69% stenosis, the patient may be randomized on the basis of results from a CTA or MRA **IF** a radiologist or neuro-imaging specialist documents his/her opinion that a CTA or MRA indicate ≥ 80% stenosis and that the CTA or MRA is of acceptable technical quality. If the results of the CTA or MRA are not conclusive, the patient should undergo conventional angiography.
3. Target ICA vessel reference diameter must be measured to be ≥4.0 mm and ≤9.0 mm. Target ICA measurements may be made from angiography of the contralateral artery.
4. In the presence of bilateral stenosis treatment of the non-study artery must take place at least 30 days prior to randomization, or >30 days after the study procedure is completed.
5. Expected ability to deliver the stent to the lesion.

Clinical Exclusion Criteria

1. Evolving stroke.
2. Untoward reaction to anesthesia not able to be overcome by pretreatment with medications.
3. Intolerance or allergic reaction to any of the study medications, including aspirin (ASA), ticlopidine and clopidogrel.
4. Active bleeding diathesis or coagulopathy or will refuse blood transfusions.
5. Prior major ipsilateral stroke if likely to confound study endpoints.
6. Severe dementia.
7. Spontaneous intracranial hemorrhage within the past 12 months.

8. Recent (<7 days) stroke of sufficient size (on CT or MRI) to place patient at risk of hemorrhagic conversion during the procedure.
9. Hemorrhagic transformation of an ischemic stroke within the past 60 days.
10. Hgb <10 g/dl, platelet count <125,000/μl, uncorrected INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-associated thrombocytopenia.
11. Any condition that precludes proper angiographic assessment or makes percutaneous arterial access unsafe.
12. Neurologic illnesses within the past two years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from TIA or stroke.
13. Actively participating in another drug or device trial that has not completed the required protocol follow-up period.
14. Inability to understand and cooperate with study procedures or provide informed consent.
15. Chronic atrial fibrillation.
16 Other cardiac sources of emboli such as left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma.
17. Any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation.
18. MI within previous 30 days.
19. Recent GI bleed that would interfere with antiplatelet therapy.
20. Non-surgical or a high risk surgical candidate defined as the presence of any one of the following:
    - Knowledge of two or more proximal or major diseased coronary arteries with ≥70% stenosis that have not, or cannot be revascularized.
    - Ejection fraction <30% or New York Heart Association (NYHA) Functional Class III or higher.
    - Unstable angina defined as rest angina with ECG changes.
    - Currently on a list for major organ transplantation (i.e., heart, lung, liver, kidney) or is being evaluated for such.
    - Malignancy or respiratory insufficiency limiting life expectancy to <5 years or FEV_1 <30% (predicted).
    - Dialysis dependent renal failure.
    - Uncontrolled diabetes defined as fasting glucose >400 mg/dl and ketones > +2.
    - Concurrent requirement for any surgery requiring general anesthesia.
21. Patient may be considered a non-surgical candidate for CEA as a result of one or more anatomic conditions or features which preclude normal surgical access, or a high surgical risk defined as the presence of any one or more anatomic conditions that present an increased potential for adverse events.
    - Radiation treatment to the neck.
    - Radical neck surgery.
    - Surgically inaccessible lesions (i.e. lesions above level of C2).
    - Spinal immobility – inability to flex neck beyond neutral or kyphotic deformity.
    - Symptomatic, well-delineated carotid artery dissection below the carotid siphon.
    - Ostial lesion of LCCA/RCCA lesion below clavicle.
    - Presence of tracheostomy stoma.
    - Contralateral laryngeal nerve paralysis.
    - Previous carotid endarterectomy, extracranial-intracranial or subclavian bypass procedure ipsilateral to the carotid stenosis.

Anatomic Exclusion Criteria

Specific criteria are for patients who have angiograms available prior to randomization:

1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement.
2. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution.
3. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath.
4. An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) that is not associated with an ulcerated target lesion.

5. Abnormal angiographic findings that constitute a contraindication to CEA: ipsilateral intracranial or extracranial arterial stenosis greater in severity than the lesion to be treated, cerebral aneurysm ≥ 5 mm, AVM (arteriovenous malformation) of the cerebral vasculature, or other abnormal angiographic findings that constitute contraindication to CEA.
6. Bilateral carotid stenosis if intervention is planned within the 30-day CREST periprocedural period.
7. Occlusion [Thrombolysis In Myocardial Infarction Trial (TIMI 0)] "string sign" >1 cm of the ipsilateral common or internal carotid artery.

Table 2

Eligibility criteria by degree of carotid stenosis.

Eligibility Criteria (by imaging)	**Symptomatic** **TIA or non-disabling stroke within 180 days**	**Asymptomatic** **No ipsilateral neurological events within preceding 180 days**
Angiography* < 1 year from date of randomization	≥ 50%	≥ 60%
Ultrasound CREST certified lab	≥ 70%	≥ 70%
CTA/MRA Only If U/S 50-69%	≥ 70%	≥ 80%

* measurement with criteria used in NASCET

Table 3

Summary of testing pre- and post-randomization.

Test	Pre-Procedure	Post-Procedure (18-54 hours)	Follow-up
Carotid duplex ultrasound	√		1, 6, 12-months, annually
CT scan/MRI	√		PRN
TIA/Stroke Questionnaire	√	√	1, 3, every 3 months thereafter
Neurological exam	√	√	1, 12 months
NIH Stroke Scale (NIHSS)	√	√	1, 6 months, every 6 months thereafter
Modified Rankin Scale	√		1, 6 months, every 6 months thereafter
Barthel Index	√		1, 6 months, every 6 months thereafter
Quality of Life Scales	√		2 weeks, 1 month, 1 year
Medical History, Risk Factor Profile	√		1, 3, every 3 months thereafter
ECG	√	√[1,3]	1 month[3]
Cardiac Biomarkers (CPK, CK-MB or troponin)	√	√[2,3]	
Lipid Profile	√		6, 12 months, annually
SMAC-7	√		6, 12 months, annually
Fasting Blood Sugar	√		6, 12 months, annually

[1] 6-48 hours post-procedure

[2] 6-8 hours post-procedure

[3] And for chest pain lasting >15 minutes