Carotid Artery Stenting
Initial Public Comments
CAG-00085R
June 18-July 18, 2004

Comment #1:
Submitter: Peter Fail
Organization: Cardiovascular Institute of the South
Date: June 28, 2004
Comment:

As an investigator of cartoid stenting in high risk patients, I feel that coverage of these patients will become a necesseity. The high risk patients not only has Carotid disease but usually a whole host of other vascular co-morbidiities that makes a surgical option "high risk". There are also those patients that the surgical option is non-existant due to anatomy weather a high or low lesions or because of prior radiation or surgery, etc. The proper training will difficult to access. Even those physicians in trial some of them have low numbers. (It is assumed that their numbers to get in to the trial was adequate). I am not sure what should be considered as an "adequate" number to be considered "trained". As the trials evolved the advent of embolic protection made the procedure "safer". There have been a number of times that I found debris in a filter and was thankful for it. The clinical event may not be that different with or without filters how ever I would argue that any debris in the brain is bad. It may not result in a clinically evident stroke, only a memory of a friend or something else that "can't" be tested for. I feel that using the current critera that were put forth as "high risk" by both SAPPHIRE and ARCHER some be atleast the baseline that can be used as a CAS requirement for "coverage". Thank you for your consideration
Organization:

Comment #2:

Submitter: Stanley Barnwell
Organization: Oregon Health and Sciences University
Date: June 28, 2004
Comment:

The Sapphire trial and numerous other publications, as well as our own large personal experience with this technique, have shown it to be a safe and effective treatment for carotid artery disease. Approving wider indications will be beneficial to patient care.

Comment #3:
Submitter: Jon Matsumura
Organization: Northwestern university
Date: July 1, 2004
Comment:

i am a vascular surgeon in full time academic practice who does medical therapy, endarterectomy, and stenting. i think the stent procedure is the preferred treatment for some patients with carotid stenosis and should be a covered benefit. the difficulty is in defining these selected patients separately from those patients where we are not sure how CBAS compares with CEA. while it is tempting to use the sapphire, archer, or other registry entry criteria, this is impractical. many of these criteria are subjective, require other testing that may not be clinically indicated, or involve data which is not available at the time the patient decision-making occurs. the AHA policy statement recommends that symptomatic carotid stenosis be worked up and treated within a week. for example, if a patient is prepared for a stent procedure based on home oxygen, but there are no recent PFT's, should they be repeated just to document FEV1? what if the new PFT's show a better than expected FEV1, but the patient has been loaded on plavix, and now a CEA must be delayed for it to wear off? i must confess that i do not have a solution to offer, but there needs to be a "safe harbor" where clinicians and patients can act based on the information

available, and not delay therapy or perform medically unnecessary testing in order to document research-associcated entry criteria. what was possible in a research study is not practical in every day clinical environment.

my second comment is in regards to training. i think there can not be too much training. what may have worked (or failed depending on your opinion) in 1999 with AAA endografts, is not enough in 2005. of course, every specialty also has their "dibs" and exclusionary suggestions. my suggestion is that you let the societies determine criteria for their own specialty, but then hold them to audited results--like liver transplantation. if a clinician doesn't meet certain thresholds, then they don't get reimbursement.

Comment #4:
Submitter: Malcolm Foster
Organization: ETHC/BHET
Date: July 2, 2004
Comment:

Our practice has been involved with carotid stenting since 1997. We have treated several hundred patients. Costs have been low, compared to endarterectomy. Outcomes have been excellent, with few complications, lower than the published rates. From our experience carotid stenting should be the procedure of choice to prevent stroke in high risk patients. Please extend coverage to appropriate medicare patients.

Comment #5:
Submitter: Angelo Makris
Organization: Midwest Heart Specialists
Date: July 2, 2004
Comment:

The SAPPHIRE trial clearly proves superiority of Carotid Stenting compared to Carotid Endarterectomy in high risk patients. The FDA panel agrees. It is up to Medicare to take note of these results and issues and approve

coverage. Medicare patients would be poorly served if they are high risk and have to go for endarterectomy instead of stenting.

Comment #6:
Submitter: Russell Rotondo
Organization: East Tennessee Heart Consultants
Date: July 2, 2004
Comment:

I agree that National coverage for carotid stenting should be extended to the populations requested.

Comment #7:
Submitter: Gregory Mishkel
Organization: Prairie Cardiovascular Consultants
Date: July 5, 2004
Comment:

I am writing as a busy interventional cardiologist, who has participated in IDE trials of carotid stenting from the original Wallstent trial on through the NIH CREST trial. I was the local PI for both the Sapphire, BEACH & Archer trials.
I believe the weight of evidence from these clinical trials demonstrates that CAS is at least as effective as CEA, but can be performed in high risk populations with less cardiac mordity, and clinically acceptable risks (no difference with respect to minor/majory strokes). The cumulative weight of multiple studies now supports the clinical release and reimbursement for this procedure. Within my own practice many patients have benefitted via reductin in subsequent strokes and hopefully with clincal release, others will have access to this durable procedure.
The clinical rationale for approval is quite simply that surgical endarterectomy is often prohibitively risky for many patients or indeed may not be possible without considerably increased risk. Many patients are either too old (age>80) or have so many medical comordities

which may compromise their postoperative course (advanced cardiac disease, severe pulmonary insufficiency, uncontrolled hypertension are probably the most common). Many anatomical features add risk to surgery, and these include previous neck irradiation, a contralateral carotid occlusion or laryngeal nerve palsy, previous ipsilateral failed endarterectomy and a high carotid lesion above the angle of the jaw)or the need for concommitant cardiac surgery.
Clearly as this procedure moves from the realm of investigation (and usage by high volume operators) to the clinical arena, care will have to be paid to appropriate indications and training. I believe that evidence supports the use of CAS in high risk symptomatic patients with >60% stenosis and asymptomatic patients with >80% stenosis. Operators to should be well versed in the field of peripheral interventions, and will come from the disciplines of neurosurgery, cardiology, radiology and vascular surgery. It is imperative that they have a wide variety of technical skills to include knowledge of carotid anatomy and cereberal physiology as well as hands on skills with guiding catheters and small wires as well as embolic protection devices. Potential operators will have to have facility managing the hemodynamic and cardiac instability which may follow CAS, as well as have access to an interested neurologist and radiologist for post procedural evaluations if necessary.
Initial training can be provided via didactic learning on line or through printed material. Ultimately potential operators will have to travel to regional training centers for technical education.
Personally I believe that the procedure should be restricted to high volume cardiac or vascular centers. In the endarterectomy literature, it is well established that there is increasing mortality and morbidity relative to a sites endarterectomy volume. I have committed 9 years of my professional life to participating in FDA/IDE trials and has shepparded this program through our my own medical community and IRB, I am quite concerned about the potential for

practitioners to take commercially available systems "off the shelf" and cobble together a carotid stent program without appropriate training or oversight once this procedure becomes "commercially available". There are very substantial economic/competitve forces at play between individual practitioners, hospitals and specialities here that could destroy the field, and very adversely effect patient outcomes. For the last decade I have been involved in training predominantly cardiologists, but also vascular surgeons in advanced vascular interventions, and although the vast majority are thoughtful, competant and well intentioned, it is incomprehensible to me that all of them are going to be capable of safely performing this procedure in a widespread capacity.

Comment #8:
Submitter: Harvey M. Wiener, DO, FSIR, FCIRSE, FAHA
Organization:
Date: July 1, 2004
Comment:

Dear Dr. Chin -

I am an Interventional Radiologist with sixteen years experience practicing in Phoenix, Arizona. I applaud the deliberations by your organization in reference to Carotid Artery Stenting. While I have not participated in any clinical trails, I have personally performed thousands of carotid arteriograms and placed thousands of stents in a multitude of arteries.

This new technology is unique as it may ultimately supplant carotid endarterectomy; a mainstay procedure of the Vascular Surgeon. The downside is that patients may be harmed by those that will perform this procedure without adequate training or an appropriate knowledge base. If you haven't already done so, I would like to refer you to the Journal of Vascular and Interventional Radiology, October 2003, in which a position paper was published about the topic of carotid intervention and the need for appropriate training and credentialing guidelines. In addition, the American Society of Interventional and Therapeutic Neuroradiology is holding its first annual meeting this summer and will include a 16 hour CME course on carotid intervention, patient selection, and problem solving (www.asitn.org <http://www.asitn.org/>). The ASITN has worked closely with

the Society of Interventional Radiology (www.sirweb.org <http://www.sirweb.org/>) to make this course a foundation for those physicians who desire to perform carotid intervention.

While the device manufacturers will be required to provide training on their products, CMS/HHS may want to consider that physician operators also demonstrate an appropriate knowledge base prior to undertaking care of these patients. It may also be essential to consider how the manufacturer will train the operator. For example, the Guidant Corporation has considerable experience in physician training based on their aortic stent graft experience. The Cordis Corporation, while an excellent company, has limited experience in physician training. The aforementioned journal article and CME course may provide you with solid, unbiased information about some of the ancillary issues that need to be considered prior to inserting a stent into a carotid artery. A deliberate plan, orchestrated in concert between CMS/HHS and the device manufacturers will only benefit patient safety and the ultimate total acceptance of this procedure as the standard of care for patients with carotid stenosis.

Thank you for you time and consideration. I would be happy to continue a dialogue with you, if you think it appropriate.

Harvey M. Wiener, DO, FSIR, FCIRSE, FAHA

Comment #9:
Submitter: Scott Smith
Organization:
Date: July 6, 2004
Comment:

Based of the clinical data on carotid stenting. I feel CMS should reimburse carotid stenting.

Comment #10:
Submitter: Mark H. Wholey, M.D. and Roseanne R. Wholey
Organization: Pittsburgh Vascular Institute and Roseanne R. Wholey and Associates
Date: July 14, 2004
Comment:

Dr. Steve Phurrough c/o Rana Hogarth
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Blvd.
Mail Stop C1-09-06
Baltimore, MD 21244

Dear Dr. Phurrough,

We are interested in providing our comments for carotid artery stenting procedures (CAG-00085R).

Regarding the topics that we viewed on the tracking sheet our responses are as follows:

Definition of patients at "high risk" for carotid endarterectomy:
The subset of patients with a high risk from surgery includes patients who have had prior endarterectomy and present with restenosis, patients who have had laryngeal nerve damage from prior surgery, or who have a history of radiation therapy to the head/neck, or who have high grade stenosis in one carotid artery and total occlusion of the opposite. Octagenarians are high risk. Patients with renal failure or patients who need urgent bypass surgery, patients with unstable angina, and patients with any other significant comorbidities. The trial patients all had 80% stenosis or greater.

Provider qualification and training:
Providers have to be experienced interventionists who have performed at least 100 diagnostic arteriograms. Te be credentialed you would have to have participated in the trials or have experience with at least 25 carotid stents with favorable outcomes with less than 5% peri-procedural stroke.

Efficacy of embolic protection devices:
The literature in the trials support the efficacy of embolic protection devices and procedures should not be done without them unless there is a rare case where it is technically not possible to deploy and carotid stenting is mandatory.

Results from other carotid stenting trials:
The carotid stent trials have met their endpoints and have shown equivalency or non-inferiority to endarterectomy. The randomized SAPPHIRE trial had event rates that were superior to carotid endarterectomy in several parameters namely peri-procedural and one year stroke event rates, myocardial infarction, cranial nerve palsy, and procedural bleeding. Archer met it's non-inferiority end point against historic weighted control studies. Without question it is appropriate for the high risk patient population. If one looks at the diabetic population high risk subset there is clearly a significant difference in stenting vs. endarterectomy.

Degree of facility experience:
Trained personnel for peripheral vascular procedures (including physicians, technical staff and lab facilities) are necessary.

Types of provider training programs to be developed:
On-line didactic training programs prior to participate at an educational carotid center where case discussion, techniques and patient selection is thoroughly discussed, followed by taped or live case presentations and finally proctoring of the trainee in his own laboratory.

Supporting staff and specialty requirements:
All procedures should be screened by a neurologist and preferably a stroke neurologist. Periodic post procedure follow-up should occur at 30 days, 6 months and one year.

Stipulations in place to ensure appropriate use:
Procedural outcome analysis similar to what existed in the trials.

Thank you for considering our comments. Hopefully the outcome will be a complete overturn of the national non-coverage policy established in 1984 with reimbursement of the new 2005 stent codes at a rate similar to that of carotid endarterectomy.

Sincerely,

Mark H. Wholey, M.D.
Chairman Pittsburgh Vascular Institute

Roseanne R. Wholey
President, Roseanne R. Wholey and Associates

Comment #11:
Submitter: Barbara Calvert
Organization: Guidant
Date: July 15, 2004
Comment:

Guidant Corporation welcomes the opportunity to comment on the reconsideration of coverage for carotid artery stenting (CAS) by CMS. Guidant fully supports modification of the current national policy to permit coverage of carotid stenting for patients at "high risk" for carotid endarterectomy (CEA). Our comments will address information requested by CMS in the NCA tracking sheet including the definition of high-risk patients, results of the ARCHeR clinical trials, the efficacy of embolic protection systems, and provider qualification and training.

Headquartered in Indianapolis, Indiana, with manufacturing and/or research facilities in the states of Minnesota, California, and Washington, as well as in Puerto Rico and Ireland, Guidant Corporation is a leader in the research, development, and manufacturing of medical technologies primarily in treatment of cardiovascular and vascular illnesses.

Definition of High-Risk Patients

Guidant recommends that CMS revise the current coverage policy [Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting (#CAG-00085A)] as follows:

Coverage shall include the high-risk patient as defined by clinical evidence:

- Carotid stenosis ≥ 50% and recent neurological symptoms referable to the lesion or stenosis ≥ 80% without recent neurological symptoms
- Significant co-morbidities: examples but not limited to coronary, renal, and pulmonary diseases, uncontrolled diabetes or angina, essential hypertension
- Anatomical factors precluding surgical access or increasing surgical risks
- Restenosis of prior CEA or other previous neck surgeries
- Contralateral carotid occlusion

Clinical Evidence Supporting Coverage

Guidant believes that evidence from the ARCHeR, SAPPHIRE, and other high-risk carotid stenting trials clearly demonstrates the benefit of CAS coverage for patients at high risk for surgical treatment. Guidant sponsored the ARCHeR (ACCULINK™ for Revascularization of Carotids in High Risk patients) Trials. Inclusion criteria, rigor, 30-day data and 12-month clinical results and protocols were presented to the Coverage and Analysis Group August 2003 and April 2004. Therefore, the following only summarizes the clinical evidence.

Overview of ARCHeR Trials

Guidant‘s ARCHeR Trials (ARCHeR 1, 2, and 3) were a series of three prospective, non-randomized, multi-center clinical trials of patients deemed at high-risk or unsuitable for CEA. The ARCHeR trials were conducted to evaluate the safety and effectiveness of CAS using the ACCULINK™ Carotid Stent System and the ACCUNET™ Embolic Protection System (EPS) for the treatment of carotid artery disease. These patients were considered at high risk for CEA due to the presence of surgical/medical co-morbidities or anatomy unfavorable for CEA. Of the 657 enrolled patients, 73% of participants were Medicare beneficiaries.

Objective:
The objective of the ARCHeR trials was to establish non-inferiority of carotid stent therapy using ACCULINK with or without ACCUNET in high-risk patients to an historical control of the standard of care (CEA and/or medical management) in a similar patient population. The primary endpoint was a composite of 30-day death, stroke, and MI, plus ipsilateral stroke to one year. The comparative outcome rates for the standard of care were derived from analysis of the literature on CEA and medical therapy, and are

defined as the "weighted historical control (WHC)". The WHC comparison rate for ARCHeR 1 and 2 was 14.5%. ARCHeR 3 evaluated a modified delivery system and was designed to show equivalence with the results in ARCHeR 2 at 30-days.

Inclusion criteria:
Inclusion criteria and stent design were identical in all trial phases.
However, ARCHeR 1 did not include the ACCUNET. ARCHeR 2 and 3 both included the EPS device with only a modification in the delivery system for ARCHeR 3.

Patients with a recent neurological event and stenosis ≥ 50% by angiography or asymptomatic patients with stenosis ≥ 80% by angiography were eligible. Patients enrolled were required to be at high risk for surgery based on the presence of one or more medical or surgical co-morbidity or unfavorable anatomical features. Medical/surgical co-morbidities included significant coronary disease, pulmonary disease, renal failure, uncontrolled diabetes,

restenosis after previous CEA, unstable angina or contralateral occlusion. Unfavorable anatomy included post-radical neck surgery, surgically inaccessible lesions, and contralateral laryngeal nerve palsy. Most characteristics would have excluded the patient from earlier CEA trials such as NASCET and ACAS. Nearly 86% of patients met criteria for medical/surgical co-morbidities; the remainder were categorized as anatomy not favorable for CEA.

Primary Endpoint Results for ARCHeR 1 and 2:
The endpoint was a composite of all death, stroke, MI at 30 days plus ipsilateral stroke between 31 days to 1 year. The study hypothesis of non-inferiority (equivalence) in a high-risk population was proven since the composite endpoint rate at 365 days was less than the 14.5% WHC in both ARCHeR 1 (8.3%) and ARCHeR 2 (10.2%).

Primary Endpoint Results for ARCHeR 3:
The ARCHeR 3 composite of all death, stroke, and MI at 30 days (8.3%) was non-inferior (equivalent) to the rate observed in ARCHeR 2 (8.6%).

Hierarchical Data	ARCHeR 1 N = 158	ARCHeR 2 N = 278	ARCHeR 3 N = 145
30-day event rates			
Major and Fatal Strokes	1.9%	1.4%	1.4%
Death & All Strokes	6.3%	6.8%	7.6%
Death / All Stroke / MI	7.6%	8.6%	8.3%
Composite Endpoint rates vs WHC of 14.5% for ARCHeR 1 and 2			
30-day death, stroke and MI, **plus** ipsilateral stroke between 31 and 365 days	8.3%	10.2%	N/A

Summary:
Results from the ARCHeR trials have demonstrated that the ACCULINK Carotid Stent System and the ACCUNET EPS are safe and effective in treating carotid artery disease for patients with high-risk surgical/medical and anatomic co-morbidities.

Efficacy of Embolic Protection (EP)

The purpose of EP is to capture debris that may be dislodged during a stenting procedure. During the ARCHeR 3 clinical trial, the ACCUNET™ EPS deployed in all but 2 cases. Of 136 devices examined by the pathology core lab, 58% of the baskets collected atherosclerotic debris of various types. The summary pathology report from Armed Forces Institute of Pathology Chairperson, Renu Virmani M.D. concluded "the ACCUNET™ filter device appears to be effective for safeguarding distal cerebral vasculature from potentially harmful embolic debris during invasive procedures in carotid arteries. … The average particle area was

0.04-mm^2, which, if left alone, could place the distal cerebral tissue at risk for ischemia/necrosis." There was no statistical difference between composite death/stroke/MI endpoints of the ARCHeR trials with or without embolic protection. The three ARCHeR trials were not powered or designed to show a difference between CAS with or without EP. We anticipate EP will be used in the majority of cases unless it is technically unfeasible or judged to have undue patient risk.

Training

The Guidant plan for provider device training was presented to the CMS Coverage and Analysis Group on May 27th and Guidant is considering CMS suggestions for incorporation into the final plan. Discussions with the FDA regarding this post-approval training program should be finalized by the end of July 2004.

The Guidant training plan will include a controlled release of ACCULINK and ACCUNET to specific physicians and hospitals. Physician training will be in three levels. Level 1 is for physicians who gained experience in Guidant carotid clinical trials and will focus on an updated device training and approved indications. Level 2 training will be for providers who participated in non-Guidant clinical trials and/or were trained via approved training programs by other carotid device manufacturers and have experience with their devices. The Level 3 program will be for physicians with extensive endovascular experience but minimal experience in carotid artery stenting. Level 3 training agenda includes didactics, case reviews, performing cases on simulators, and hands-on experience via anatomical models. Upon completion, physicians will receive documentation of participation. Hospitals will also be educated on the stent system, approved indications, and the procedure prior to release of product to their site. A Guidant carotid trained field representative will be present to support the first three cases and additional cases at the request of the physician.

Conclusion

Given the strong clinical evidence supporting the benefits of carotid stenting, widespread support in the medical community, and the critical need for endovascular treatment options for Medicare beneficiaries, we urge CMS to act expeditiously and implement CAS coverage for Medicare beneficiaries at high risk for surgical treatment.

We also request that CMS take steps to assure adequate inpatient CAS payment concurrent with coverage. Specifically, we recommend that CMS consider, on an interim basis for FY 2005, assigning to DRG 533 (Extracranial Vascular Procedures with CC) all carotid stenting cases that otherwise could have been paid under the DRG pair 533/534. Adequate payment is essential to ensure patient

access following FDA approval and coverage and for ongoing carotid stenting clinical trials.

Please let us know if you have questions or require additional information.

Comment #12:
Submitter: Gary M. Ansel, MD
Organization: Riverside Methodis Hospital
Date: July 18, 2004
Comment:

I would like to comment on the coverage for carotid stenting. I and my two partners have been active in this field since the early Wallstent Trials. We have participated in every FDA trial to date.

Definition of high risk
Procedural = previous neck radiation, previous carotid endarterctomy or lateral neck surgery, bilateral disease, contralateral occlusion, altered anatomy of surgical access site, difficult surgical access, high cervical lesion, intra-thoracic lesion
Significant comobidities = 2 vessel coronary disease with either angina or ischemia on noninvasive testing, COPD, CHF, need of abdominal or thoracic surgery within 30 days, advanced age >75 years old.

Provider qualification and training= Having trained other individuals from multiple specialties the common denominator is catheter skills. No matter the specialty preceeding catheter skills by training or experience allows for learning the procedure. Metrically controlled testing of cognitive and procedure performance must be demanded due to the varied specialties to undertake this procedure. From a cognitive standpoint the physician should undergo an extensive training module in carotid disease and management prior to approval.

Efficacy of embolic protection: Though the first 125 procedures performed at our institution were not associated with a neuro event (neurologist controlled) patient selection was utilized. Since the use of embolic devices we have been less restrictive on our patient selection with the same results. We visually find debri in approximately

25% of the devices. Some of these debri are quite large and undoubtly would have been associated with severe neuro compromise. The world carotid registry we are involved in has shown a consistent decrease in neuro events since the addition of the devices. The new protection devices I feel will allow for even less risk as they are smaller and easier to utilize.

Evidence of efficacy and appropriateness of the procedure: The SAPPHIRE trial clearly demonstrates both immediate decreased risk as well as increasing benefit over surgery periprocedurally as well as at the 1 year time frame. This trial did not even include the intrathoracic common carotid lesions that are now not treated surgically due to the high rish and invasive nature of the surgical treatment which is off set by the relative ease of stenting.

Degree fo facility experience: Though we started with a multispecialty approach this was out of fear strokes and the perceived need for the potential need of rescue procedures for distal emboli. This has not been the case. Our institution has never needed to perform surgical rescue and have dropped the mutlitspecialy requirment. As stated previously catheter skills are a common denominator for successful procedure learning and allow for low risk institution of the procedure. We do feel that an extensive training program is needed for institution of this procedure. Previous cerebral vascular angiography training does not appear necessary and can be instituted into the carotid stent training. Neurology consultation must be available on site to allow for successful program initiation.

Types of training: Due to the multiple specialties involved, all with their own deficiencies I would recomend that a comprehensive program with metrics on cognitive and procedural aspects be tested. Training to only the device will not be sufficient for physicians.

Supporting Staff: The supporting staff should be trainined on neurological patient assessment as
well as on the device.
Stipulations: Providers should be required to successfully complete industry training as well as have a
primary catheter based practice. This would require endovascular credentials
at their institution.

Comment #13:
Submitter: Stephen F. Daugherty, MD, FACS, RVT
Organization: Clarksville Surgical Associates, PLC
Date: July 18, 2004

Comment:

I write to you as a private vascular surgeon with a long and broad experience performing endovascular procedures in multiple vascular beds. The hospital in which I practice has four vascular surgeons on staff, all of whom are skilled and experienced with complex endovascular procedures, the most common of which are angioplasty and stenting procedures. We perform carotid endarterectomy (CEA) on a regular basis and we have a modest experience performing carotid angioplasty/stenting (CAS).

PATIENT SELECTION

I am very eager for carotid stenting to become available for my patients who I consider high risk for CEA. The initial clinical trial results are convincing even to many of the most reluctant vascular surgeons that we should be using CAS for selected patients who are at high risk for CEA. I am troubled that we cannot yet offer the technology to carefully selected patients who I deem to be better served by CAS. High risk patients include:

Severe chronic obstructive pulmonary diseae
Ischemic heart disease with baseline ischemia
Recurrent carotid stenosis
History of neck irradiation or ipsilateral radical neck dissection
Severe congestive heart failure
Common carotid or internal carotid artery stenosis in locations not accesssible through the standard
neck incision

As you know, data from trials of CEA versus medical therapy have supported CEA for pateints with a greater than 50% carotid stenisis who are

symptomatic for ipsilateral carotid embolic events and for patients who have a greater than 80% stenosis and are asymptomatic. I believe this group of patients should be considered for CAS if they have one or more of the risk factors listed above.

PROVIDER QUALIFICATIONS AND TRAINING

CAS should be performed only by physicians who have considerable experience performing endovascular procedures in the non-coronary vascular beds such as the iliac, renal, subclavian, upper and lower extremity, and mesenteric arteries. The skill sets required for performing carotid arteriograms and for CAS are all identical or only minimally different from the skill sets possessed by experienced endovascular physicians. Only very modest additional hands-on training is necessary for a skilled endovascular physician to safely perform CAS. While some willl encourage you to require a large volume of CAS experience in an effort to impede other skilled endovascular physicians from providing the service to their patients, the emphasis should be on assuring that the physician has a broad range of endovascular skills and experience which transfer very easily to performance of CAS.I believe that a physician should have an absolute minimum of 100 major non-coronary endovascular procedures as a prerequisite to training for CAS.
Provider training by means of a didactic course with sophisticated simulator training and a short hands-on course in CAS should be adequate for physicians who ALREADY POSSESS A HIGH LEVEL OF ENDOVASCULAR SKILLS.

A basic prerequisite to performing CAS is thorough knowledge of cerebrovascular disease, the ability to evaluate the patient clinically, and to interpret relevant vascular ultrasound, arteriograms, and other cerebrovascular imaging tachniques. The physician must be able to evaluate treatment options thoroughly and to provide appropriate long-term follow-up for the patient. A physician who is not able to provide this evaluation and long-term follow-up should not be doing the procedures. The long term follow-up is essential to assess early and late complications of the procedure and to detect recurrent stenosis or contralateral disease in a timely manner.

Physician training should include didactic training and review of:

Patient selection criteria,
Clinical and anatomic indications for CEA or CAS,
Device selection and use,
Perioperative care,
Management of complications,
Troubleshooting of device or equipment malfunctions,

Short and long term floow-up of patients.

FACILITY QUALFICATIONS

A facility planning to do CAS should use a high-quality fixed digital fluoroscopy unit with a C-arm capable of providing multiple views of the cerebrovascular anatomy. Staff circulating or scrubbing for the procedure should possess excellent knowledge of the various endovascular devices which might be used in a complicated case. A facility experience of at least 100 non-coronary endovascular procedures per year is desirable before undertaking CAS. Hospital staff need specific exposure to the CAS devices and training in preparation and use of the devices.

SPECIALTY REQUIREMENTS

Historically, vascular surgeons evaluate patients with carotid artery disease and make decisions with the patients regarding medical or surgical management; vascular surgeons also provide long term follow-up of patients who do not have severe enough disease to undertake surgery and for post-op CEA patients. Vascular surgeons routinely evalute their patients neurologically on many occasions during the course of their care and follow-up and , in most cases, do not need other specialties for routine care. Nonetheless, patients who have carotid disease often have coronary artery disease and high risk patients for CEA who are to undergo CEA or CAS should have a consulting cardiologist available should they be needed.

We believe strongly that a patient who is under consideration for CAS should be evaluated by a vascular surgeon as part of the pre-op work-up to assure that both options of CEA and CAS are presented to the patient who must decide which procedure to request. There is legitimate concern that some patients may be encouraged to undergo a specific procedure because it is the only option a particular clinician can offer. Some vascular surgeons will only be able to offer CEA, but most will be able within the next several years to offer CEA or CAS to appropriate patients. Physicians in other specialties will be able to offer only CAS. This will become an even larger issue if CAS proves to be a reasonable alternative to CEA in moderate risk patients.

In conclusion, some of our patients need the CAS technology available to them; the physicians and facilities providing the services need to be experienced and skilled with non-coronary endovascular procedures before undertaking training to perform CAS. Thank you for your review of these comments.

Comment #14:

Submitter: Gregorio Sicard
Organization: Society for Vascular Surgery
Date: July 18, 2004
Comment:

The Society for Vascular Surgery (SVS) represents 2,000 vascular specialists in the United States. Our society has 40-years experience in the evaluation and treatment of extracranial cerebrovascular disease. SVS members have participated in all major carotid endarterectomy and carotid stent trials performed in the United States and Canada. Importantly, SVS represents the only specialty society with a substantial proportion of members who are *experts at both treatment options*, open carotid endarterectomy and carotid stenting. This provides SVS a uniquely objective perspective to address the coverage issue. SVS offers the following comments regarding reconsideration of the Medicare National Coverage Policy for percutaneous transluminal angioplasty of the carotid artery concurrent with stenting (CAG-00085A, dated March 19, 2001).

SVS did not favor Medicare coverage for carotid stenting in prior years because published safety and efficacy data were mostly from single centers. There were no multicenter prospective trials comparing carotid stenting to the standard of practice, carotid endarterectomy (CEA). In contrast, CEA has been one of the most studied surgical operations in the world over the past 3 decades, and large prospective trials of CEA vs. medical therapy continue to be published. SVS now believes that data collected under auspices of SAPPHIRE, CREST (lead-in data), and CARESS trials provide sufficiently convincing safety and efficacy information on carotid stenting (CS) to allow expansion of coverage to the Medicare beneficiaries in certain high-risk categories. SVS would like to offer the following comments and recommendations for Medicare coverage of carotid stenting in specific proposed high risk indications, based on (1) our interpretation of the available data comparing safety and efficacy of CS to CEA, and (2) our collective judgment regarding superiority of these therapies over medical treatment. Please note that in the following table, the definition of “symptoms” is limited to clear-cut lateralizing hemispheric transient ischemic attacks, unilateral transient monocular blindness and non-disabling strokes.

Risk Factor	**Symptoms?**	**Carotid Stenosis**	**Indication / Comments**	**SVS Support**
Previous CEA with recurrent stenosis	Symptomatic	>50%	CEA perioperative complication rate above baseline	YES
Previous CEA with recurrent stenosis	Asymptomatic	>80%	CEA perioperative complication rate above baseline	YES
S/P radiation therapy to neck	Symptomatic	>50%	CEA perioperative complication rate above baseline	YES

S/P radiation therapy to neck	Asymptomatic	>80%	CEA perioperative complication rate above baseline	YES
Contralateral laryngeal nerve palsy	Symptomatic	>50%	CEA carries low incidence of catastrophic bilat laryngeal nerve palsy	YES
Contralateral laryngeal nerve palsy	Asymptomatic	>80%	CEA carries low incidence of catastrophic bilat laryngeal nerve palsy	YES
Contralateral carotid occlusion	Symptomatic	>50%	Literature supports higher stroke risk than baseline for CEA	YES
Contralateral carotid occlusion	Asymptomatic	>80%	Literature supports higher stroke risk than baseline for CEA	YES
Cervical ICA lesion above C2	Symptomatic	>50%	Difficult surgical access	YES
Cervical ICA lesion above C2	Asymptomatic	>80%	Difficult surgical access	YES
Intrathoracic Carotid lesion	Symptomatic	>50%	Surgery requires thoracotomy	YES
Intrathoracic Carotid lesion	Asymptomatic	>80%	Surgery requires thoracotomy	YES
Pulmonary disease documented FEV1<30%	Symptomatic	>50%	CEA may be associated with increased pulmonary complications	YES
Pulmonary disease documented FEV1<30%	Asymptomatic	>80%	CEA may be associated with increased pulmonary complications	YES

Risk Factor	**Symptoms?**	**Carotid Stenosis**	**Issues / Comments**	**SVS Support**
Open heart surgery required within 2 wks	Symptomatic	>50%	CEA may be associated with increased perioperative cardiac complications	YES
Open heart surgery required within 2 wks	Asymptomatic	>80%	CEA may be associated with increased perioperative cardiac complications	YES
Documented NYHA Class	Symptomatic	>50%	CEA may be associated with increased perioperative	YES

III or IV CHF **and** documented LVEF<30%			cardiac complications.	
Documented NYHA Class III or IV CHF **and** documented LVEF<30% **and** life expectancy > 5 years	Asymptomatic	>80%	CEA may be associated with increased perioperative cardiac complications. More data would be useful to demonstrate superiority over medical therapy.	YES
Recent MI <4 weeks	Symptomatic	>50%	Elevated cardiac risk for CEA. Medical treatment for symptomatic carotid lesion not adequately efficacious	YES
Recent MI <4 weeks	Asymptomatic	>80%	Need more data. Medical treatment may be best option until cardiac status stabilizes	NO
Unstable angina documented CCS class III/IV	Symptomatic	>50%	Elevated cardiac risk for CEA. Medical treatment for symptomatic carotid lesion not efficacious	YES
Unstable angina documented CCS class III/IV	Asymptomatic	>80%	Elevated cardiac risk for CEA, but need more data needed to demonstrate CS superiority over medical therapy.	NO

Risk Factor	Symptoms?	Carotid Stenosis	Issues / Comments	SVS Support
Severe tandem lesions	Symptomatic	>50%	Literature does not indicate CEA is high risk in this setting. Nature & severity of second lesion lack definition	NO
Severe tandem lesions	Asymptomatic	>80%	Literature does not indicate CEA is high risk in this setting. Nature & severity of second lesion lack definition	NO
Age > 80 yrs	Symptomatic	>50%	CREST lead in data shows elevated stroke risk for stent. Need more data before approving stent	NO
Age >80 yrs	Asymptomatic	>80%	CREST lead in data shows elevated stroke risk for stent. Need more data before approving stent	NO

SVS would like to emphasize that our goal is to endorse carotid stenting as a covered treatment option for those specific high-risk patient subsets in whom CS is proven equivalent to CEA, but as noted in our table, we believe some proposed high-risk subsets require more investigation. Withholding stent treatment from individuals who would benefit is as undesirable as allowing it for subsets who don't meet these criteria, and we encourage CMS to revisit any coverage decisions that are made as more high quality data become available.

Although noninvasive methods including quality-controlled carotid duplex ultrasound, MRA, CTA, and CTA with three-dimensional reconstructions are diagnostic techniques suitable for entry in a carotid treatment algorithm, all patients undergoing carotid stent will necessarily have an ipsilateral diagnostic carotid arteriogram as an initial step. For standardization purposes of inclusion under this policy, we recommend that the final determination of carotid stenosis required for CS coverage must be calculated from the angiographic images using the methodology defined in NASCET.

SVS wishes to address a second crucial issue, which is the absolute need for CMS to monitor delivery of this new therapy to individuals proven to derive benefit. We are extremely concerned that carotid stenting will be offered to a wide range of individuals falling well outside proven indications. Carotid stenting indications that we endorse are based on tested "high-risk" indications, either anatomic or medical. *For "normal-risk" patients we believe it is absolutely crucial to withhold coverage until prospective randomized studies such as CREST have tested the equivalence of CS to CEA.* We

cannot overemphasize the importance of continued data collection, powered sufficiently to test appropriateness of expanded and subset indications with independently adjudicated medium and long-term outcome data. We understand that the task of assuring appropriate application of the new CS technology on a patient-by-patient basis will be a challenging task, but we believe CMS has the skill to execute accurate monitoring, the power to ensure compliance, and the obligation to do so. For instance, post-payment audits could be conducted at medical centers where the frequency of CS compared to CEA far exceeds expectations.

Carotid stenting is an exciting new treatment modality. We urge CMS to consider all available data during reconsideration of the current non-coverage policy, and we are entirely willing to meet with members of the Agency at any time should you believe our expertise in cerebrovascular disease may be helpful. We appreciate the opportunity to submit comments.

Comment #15:
Submitter: Boston Scientific Corporation
Organization: Boston Scientific Corporation
Date: July 16, 2004
Comment:

Boston Scientific

One Scimed Place
Maple Grove, MN 55311-1566

BY ELECTRONIC SUBMISSION

July 16, 2004

The Centers for Medicare and Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244-1850

ATTN: Joe Chin MD
RE: (CAG-00085R) Coverage Request to Revise Current Policy

Dear Dr. Chin:

Boston Scientific Corporation (Boston Scientific) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Service's (CMS's) Notice of Review of Coverage for Carotid Artery Stenting (CAG-00085R). We are pleased CMS has decided to revisit this important policy matter and encourage the Agency to revise its current policy in order to extend coverage beyond FDA Category B IDE designated clinical trials. Toward that end, we offer the following comments on some of the questions posed in the Notice.

Definition of Patients at "High Risk" for Carotid Endarterectomy

We believe that there are a significant number of similarities between the trials that examined/are examining the safety and efficacy of stents to treat stenosis of carotid arteries. We encourage the Agency to build on this substantial consensus and include the full range of the patient inclusion/exclusion criteria utilized in these trials to define patients at high risk for surgery (carotid endarterectomy).

A number of the criteria that were used to define high risk patients in the BEACH, ARCHER, SAPPHIRE, CABERNET and other clinical trials are similar, and to the extent there were additional criteria, there were minor variations in them. The criteria that were utilized in all trials include the following items.

Altered Anatomy:

- Total occlusion of contralateral carotid artery
- Previous radiation treatment to neck or neck dissection
- Treatment lesion at or above 2nd vertebral body C2
- Restenosis of a previous CEA
- Laryngeal nerve palsy
- Target lesion below clavicle or C2
- Inability to extend head

In addition the majority of the trials included Tracheostomy or tracheal stoma.

Complicating co-morbid conditions:

- Heart Failure defined by LVEF<30%
- CHF, NYHAA Class III/IV
- MI within previous 6 weeks or defined as acute
- TIA within 180 days
- Patient on anti-coagulants (Warfarin)
- Unstable Angina
- Uncontrolled Diabetes
- Patient requiring CABG, cardiac valve or peripheral vascular surgery or abdominal aortic aneurysm repair
- Asymptomatic patients greater than or equal to 80 percent of stenosis on angiographic results.
- Symptomatic patients greater than or equal to 50 percent stenosis on angiographic results.

In addition, the majority of the trials included: COPD qualified as moderate to severe; dialysis dependent renal failure; two or more proximal major coronary arteries with greater than 70% stenosis at the time of the index procedure.

Age:

- Minimum requirement on age was 70years of age or greater. (Some trials age requirement was 80 years of age.)

Multiple or Bilateral lesions:

- Multiple or tandem lesions
- Bilateral stenosis

Provider Qualification and Training

Boston Scientific believes it is important that the Agency recognize the overall effectiveness that established entities and procedures have played in ensuring that health professionals and institutions competently provide care. While carotid artery stenting (CAS) is a significant procedure, there is no reason why these established entities and procedures will not protect the public health. CMS should not duplicate their efforts, nor impose additional regulation on the practice of medicine in this area. By doing so, the Agency will help to ensure that beneficiaries have timely, geographically reasonable and appropriate access to this procedure.

Whether considering the role of FDA in ensuring that manufacturers have an appropriate training program to ensure that physicians and staff can safely use a device, the role of specialty societies in setting competency standards for their members, the ability of local hospital credentialing committees to control service delivery, or JCAHO's responsibility to continuously improve the safety and quality of care provided in hospitals, it is clear that there are a number of ways that the public's interest in competent providers will be addressed.

We recognize that the Agency's call for comments on provider competency will no doubt elicit comments from a number of stakeholders with varying perspectives. It seems likely that there will be a lack of complete consensus on the specifics (e.g. number of previous procedures performed, etc.) surrounding what makes a physician competent to provide this procedure. We encourage the Agency to not let this lack of complete consensus serve as a stimulant to the need for regulation in this area.

Boston Scientific realizes the need for specialized training for this procedure and has committed to a comprehensive training program. In essence, we believe it is important that we do all we can to provide a fund of knowledge to physicians and staff so that they can be credentialed. Toward this end, we will build on our long-standing and extensive PVD training courses. We will do this with courses on correctly diagnosing peripheral and carotid cases, making appropriate patient selection decisions, engaging in simulation training, and learning how to use our specific devices.

Efficacy of Embolic Protection Devices
Boston Scientific utilized an embolic protection device in its trials. A copy of slides providing an early overview of the 30-day pivotal safety data is attached for the Agency's consideration of the role of embolic protection devices.

The fact that AMA has created a CPT code to describe a CAS procedure with embolic protection, and that CMS initiated a request for (and soon will be making effective) a unique ICD-9-CM procedure code to capture CAS with embolic protection, would seem to indicate that a host of stakeholders believe that embolic protection will play an important role in the provision of CAS. Boston Scientific is of this opinion as well.

Results from Other Carotid Stenting Trials with High Risk Population
As the Agency may be aware, Boston Scientific has completed enrollment of our "BEACH" CAS clinical trial. As mentioned above, we have enclosed an early overview of our 30-day pivotal data. We are currently estimating that the analysis of our 1-year BEACH IDE clinical data will be available in April of 2005 when it is submitted to the FDA.

Evidence of the Efficacy and Appropriateness of Carotid Stenting for this Target Population
Based on the presentations related to CAS clinical trial status and data that have been made at various scientific meetings and our discussions with clinicians it appears that this technology is beginning to demonstrate its efficacy and appropriateness for the type of patients on whom it has been performed.

Over the last several years, peer-reviewed journals have looked at distinct target populations and the benefit of CAS over CEA with embolic protection. Enclosed are several of the peer-reviewed published articles with references and summary of endpoints.
(See Attachment A).

Degree of Facility Experience Requirements

As mentioned above, Boston Scientific believes it is important that the Agency recognize the overall effectiveness that established entities and procedures have played in ensuring that hospitals have the necessary experience to competently provide care. In addition, the Agency has its own standing methods of approving hospitals. While CAS is a significant procedure, these established entities and procedures will protect the public health. By relying on the existing mechanisms, the Agency will help to ensure that beneficiaries have timely, geographically reasonable and appropriate access to this procedure.

We would also suggest that the Agency utilize the February 3, 2004 letter to Dr. Sean Tunis from nine different specialty societies on the dimensions of specialty collaboration that will be necessary to ensure that facilities have the appropriate set of clinical resources in place. Assuming that this complement is in place, CMS should allow this service to be provided on an inpatient basis in any Medicare-approved hospital.

Types of Provider Training Programs to be Developed

First, manufacturers, specialty societies and clinical centers are engaging each other in many ways to ensure that health professionals are in a position to become competent to carrying out this procedure. Reinforcing this activity is the fact that any manufacturer of stents or embolic protection devices that are going to be used in conjunction with a carotid procedure will need to gain FDA acceptance of their educational plan. In addition, specialty societies and various clinical centers will be developing and implementing training programs.

To reiterate our earlier comment, Boston Scientific is committed to providing comprehensive and substantive educational programs that will provide physicians and staff with a knowledge bank to draw on to appropriately select patients and the safe use of the stent, embolic protection and appropriate accessories we will sell to treat carotid arteries. In addition, given the interest in the health professional community, we would expect that various societies and centers of care would pursue relevant training programs as well. Some of our training is already underway, while we expect other elements to be implemented in 2005.

Supporting Staff Required for the Procedure

Assuming that a hospital has the inter-disciplinary team (called for in the multi-society letter) in place, we believe that the staff that is commonly found in an inpatient hospital suite will be adequate for the provision of this service.

Specialty Requirements for the Procedure

Boston Scientific does not believe that this procedure should be limited to a specific specialty. Again, we encourage the Agency to look at the multi-society recommendations on inter-specialty consultation to determine appropriate patient selection for this procedure.

Stipulations to Ensure the Appropriate Use of the Procedure in the Indicated Patient Population

Appropriate patient selection will be achieved by the patient inclusion criteria the Agency will be describing in its coverage regulation. In addition, given the cross-specialty collaboration that is likely to be present around the determination of the appropriateness of this procedure, we encourage the Agency to stay with its practice of not requiring some sort of prior authorization.

We appreciate the opportunity to provide comment on this important coverage decision. Please contact me (763-494-2016; tom.meskan@bsci.com) if you have questions or need additional information. We look forward to working with CMS and others to achieve beneficiary access to this procedure.

Sincerely,

Thomas L. Meskan
Director of Reimbursement and Outcomes
Boston Scientific Corporation

Attachment A

1. Katzen BT, Laird JH, Ohki T, The SAPPHIRE and ARCHeR Updates. *Endovascular Today.* 2003;Sept.:77-80.
2. Ramazanali A, Schillinger M, Lang W, et. al. Carotid Artery Stenting in Older Patients: Is Age a Risk Factor for Poor Outcome? *J.Endovascular Therapy.* 2002;9:559-565.
3. Brooks WH, McClure R, Jones MR, et al. Carotid Angioplasty and Stenting Versus Carotid Endarterectomy: Randomized Trial in a Community Hospital. *Journal of the American College of Cardiology.* 2001;38:6:1589-1595.
4. Brajesh KL, Hobson RW, Goldstein J, et. al. In-stent recurrent stenosis after carotid artery stenting: Life table analysis and clinical relevance. *Journal of Vascular Surgery.* 2003; 38:6:1162-1168.
5. Hobson RW,Brajesh KL, Chaktoura E, et. al. Carotid artery stenting: Analysis of data 105 patients at high risk. *Journal of Vascular Surgery.* 2003; 37:6: 1234-1239.
6. Cho JS, Pandurangi K, Conrad MF, et. al. Safety and durability of redo carotid operation: An 11-year experience. *Journal of Vascular Surgery.* 2004; 39:1:155-160.
7. Kastrup A, Groschel K, Krapf H, et. al. Early Outcome of Carotid Angioplasty and Stenting With and Without Cerebral Protection Devices. *Stroke.* 2003;34:813-819.
8. Dangas G, Laird JR, Mehran R, et. al. Carotid Artery Stenting in Patients With High Risk Anatomy for Carotid Endarterectomy. *J.Endovascular Ther.* 2001;8:39-43.
9. Angelini A, Reimers B, Barbera M, et. al. Cerebral Protection During Carotid Artery Stening Collection and Histopathologic Analysis of Embolized Debris. *Stroke.* 2002;33: 456-461.
10. Al-Mubarak N, Colombo A, Gaines P, et. al. Multicenter Evaluation of Carotid Artery Stenting With A Filter Protection System. *Journal of the American College of Carodiology.* 2002; 39:841-846.
11. Houdart E, Mounayer C, Chapot R, et. al. Carotid Stenting for Radiation-Induced Stenois A report of 7 cases. *Stroke.* 2002; 32:118-121.

BEACH TRIAL

"Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients"

30-Day Pivotal Group Results

Christopher J. White, MD
on behalf of the BEACH Investigators
Chairman, Department of Cardiology
Ochsner Clinic Foundation

BEACH Trial Objective

To evaluate the outcomes of patients with carotid artery stenosis at high-risk for carotid endarterectomy (CEA) using the Carotid Wallstent® and the FilterWire EX/EZ ™ distal protection system.

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Primary Endpoint

- One-Year Composite Endpoint
  - ✓ Cumulative morbidity and mortality:
    - ≤ 24 hours: Non Q-wave MI.
    - ≤ 30 days: Q-MI, All Death, All Stroke.
    - > 30 days & ≤ 1 year.
      - Ipsilateral stroke.
      - Neurological death.

30 Day Results

Benchmark is Objective Performance Criteria (OPC).

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Study Design

Patients at High-Risk for CEA
Stenosis in ICA, CCA or Bifurcation
↓
Prospective, Single-Arm Trial

Roll-In Group
n =189

Bilateral Group
n = 78

Pivotal Group
n = 480

30 Day
Results

Follow Up (Clinical, Duplex US, Neurologic):
30 Day; 6 month; One Year; Annually x 4

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Study Organization

Co-Principal Investigators	Christopher J. White, MD Sriram S. Iyer, MD
Data Management and Analysis	Harvard Clinical Research Institute (HCRI)
Site Monitoring and Compliance	J.Tyson and Associates, Boston Scientific Corporation
Angiographic Core Lab	Brigham and Women's Hospital
ECG Core Lab	Harvard Clinical Research Institute (HCRI)
Vascular Core Lab	Vascular Ultrasound Core Lab., Cardiovascular Research Foundation
CT/MRI Core Lab	Perceptive Informatics, Inc.

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BEACH: Unique Trial Oversight

- Executive Steering Committee (ESC)
  - ✓ Physician Committee Members:
    - Christopher J. White, MD – Barry Katzen, MD
    - Sriram S. Iyer, MD – L.N. Hopkins, MD
    - Mary E. Russell, MD
  - ✓ Review overall conduct of study / DMC recommendations
- Clinical Steering Committee (CSC)
  - ✓ 6-10 BEACH study physicians
  - ✓ Oversee study enrollment & quality performance at sites
  - ✓ Participate as reviewer for site transition from Roll-In to Pivotal phase of trial
- Clinical Events Committee (CEC)
- Data Monitoring Committee (DMC)

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Investigational Sites (47 U.S.)

Christopher White, MD (trial co-PI)
Ochsner Clinic Foundation

Sriram Iyer, MD (trial co-PI)
Lenox Hill Heart and Vascular Institute

Gary Ansel, MD / Barry George, MD
Riverside Methodist Hospital

William Bachinsky, MD / Rajesh Dave, MD
Pinnacle Health at Harrisburg Hospital

Tanvir Bajwa, MD
Aurora St. Luke's Medical Center

William Brooks, MD
Central Baptist Hospital

Mark Burket, MD
Medical College of Ohio

Wayne Clark, MD
Oregon Health Sciences University

Edward Diethrich, MD
Arizona Heart Institute & Foundation

Douglas Ebersole, MD
Lakeland Regional Medical Center

Richard Fessler, MD
Wayne State University - Harper Univ. Hospital

Malcolm Foster, MD
Baptist Hospital of East Tennessee

Thomas Grobelny, MD
St. Luke's Hospital of Kansas City

Patrick Hall, MD
Providence Hospital

Louis Heller , MD
Piedmont Hospital

L.N. Hopkins, MD
Kaleida Health/Millard Fillmore Hospital

John Jacobs, MD
LDS Hospital

James Joye, DO
El Camino Hospital

William Julien, MD
Northwest Medical Center

Barry Katzen, MD
Miami Cardiac and Vascular Institute

William Knopf, MD
St. Joseph's Hospital of Atlanta

Robert Koenigsberg, DO
MCP - Hahnemann University

Pierre Leimgruber, MD
Deaconess Medical Center

Demetrius Lopes, MD
Rush Presbyterian-St. Luke's Med.Ctr.

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BEACH Investigational Sites (47 U.S.)

Cameron McDougall, MD
St. Joseph's Hospital and Medical Center

Gregory Mishkel, MD
St. John's Hospital

Ali Mortazavi, MD / Mark Skolkin, MD
St. Luke's Episcopal Hospital - Texas Heart Institute

Subbarao Myla, MD
Hoag Memorial Hospital

Takao Ohki, MD, PhD
Montefiore Medical Center

George Petrossian, MD
St. Francis Hospital

Kenneth Rosenfield, MD
Massachusetts General Hospital

John Rundback, MD
New York Presbyterian Hospital

Michael Rush, MD
North Ridge Medical Center

Robert Safian, MD
William Beaumont Hospital

Souheil Saddekni, MD
University of Alabama - Birmingham

Lowell Satler, MD
Washington Hospital Center

Michael Silva, MD
Texas Tech University Health Sciences Ctr.

Richard Smalling, MD, PhD
Memorial Hermann Hospital

Anthony Smith, MD
Duke University Medical Center

Scott Standard, MD
Skyline Medical Center

James Swischuk, MD
St. Francis Medical Center

Jay Yadav, MD
Cleveland Clinic & Foundation

Ajay Wakhloo, MD, PhD
Univ. of Miami-Jackson Memorial Hospital

Lawrence Wechsler, MD
UPMC - Pittsburgh Vascular Institute

Michael Wholey, MD / William Wu, MD
Baptist Hospital

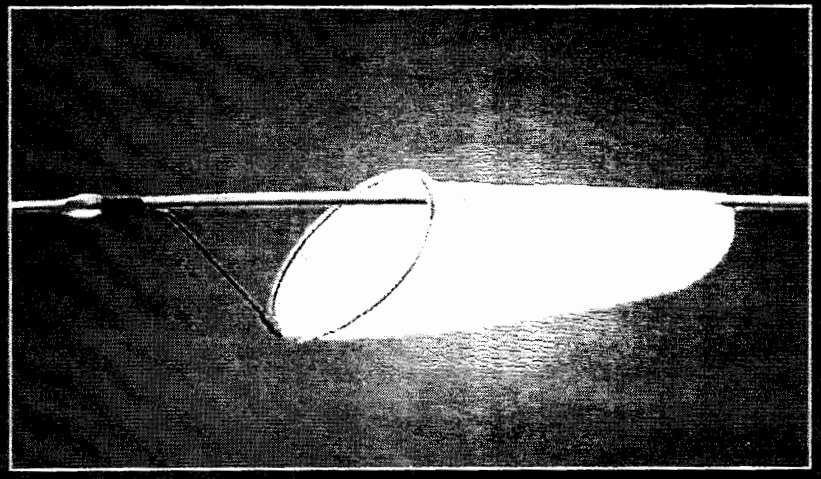
Charles Zacharias, MD
St. Mary's Hospital

Richard Zelman, MD
Cape Cod Hospital

CAUTION: Investigational device. Limited by federal law to investigational use.

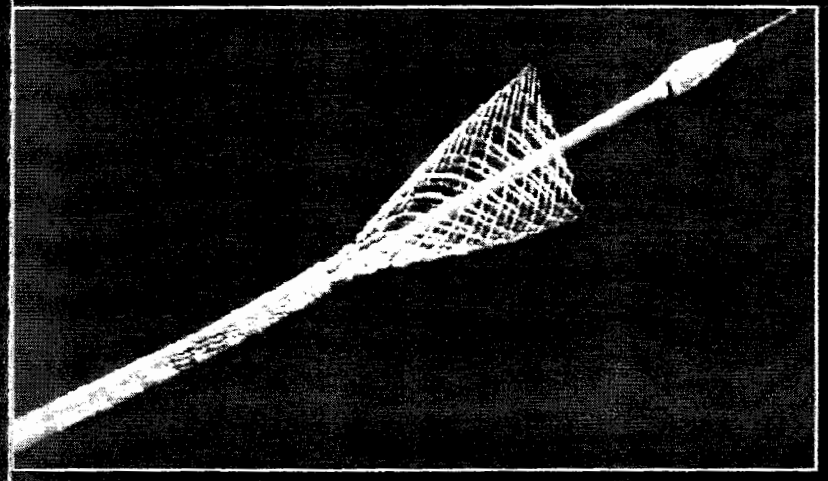
BEACH Investigational Study Devices

FilterWire EX/EZ™



- Monorail delivery system
- Suspended radiopaque nitinol loop
- 0.014" Embolic Protection Guidewire
- Filter pore size = 110 microns
- Fits 3.5–5.5 mm vessels
- 190cm & 300cm lengths

Carotid Wallstent® Monorail®



- Monorail delivery catheter
- Self-expanding stainless steel
- 5.0–5.9 F
- Diameters: 6, 8, 10 mm
- Lengths: 20, 30, 40 mm
- Closed cell design

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Enrollment Criteria

Inclusion

- Patients either:
  - Symptomatic: Stenosis ≥50% by angiography
  - Asymptomatic: Stenosis ≥80% by angiography
- Target lesion: CCA, ICA, or bifurcation
- Target segment reference diameter: ≥4.0mm and ≤ 9.0mm
- Vessel diameter distal to target lesion: ≥3.5mm and ≤5.5mm as an optimal FilterWire landing zone

Exclusion

- Patient experienced evolving, acute or recent stroke within 21 days of study evaluation
- Known cardiac sources of emboli
- Myocardial infarction <72 hours prior to the index procedure
- Any surgery ≤30 days preceding stent procedure
- Total occlusion of ipsilateral carotid artery
- Pre-existing stent in ipsilateral carotid artery

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Enrollment Criteria: Surgical High-Risk Categories

Anatomic Risk (1 criteria)	Comorbid Risk (1 or 2 criteria)
• Surgically inaccessible lesions at or above C2 or below the clavicle	• Age ≥75 years
• Previous neck or head radiation therapy/surgery	• CHF (NYHA Class III/IV)
• Spinal immobility of the neck	• Unstable angina
• Restenosis after a prior CEA	• COPD with FEV ≤30%
• Laryngeal palsy or laryngectomy	• LVEF ≤30%
• Tracheostoma	• Recent MI ≥24 hours and ≤30 days
• Contralateral total occlusion	• ≥2 major diseased coronary arteries with ≥70% stenosis
	• Planned CABG or valve replacement surgery post-CAS
	• Planned peripheral vascular surgery, or other major surgeries

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Pivotal Group Population

Symptomatic
≥ 50% stenosis

n = 113 (23.5%)

Asymptomatic
≥ 80% stenosis

n = 367 (76.5%)

→

Pivotal Group
n = 480

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Pivotal Group

Demographics	n = 480
Mean Age (years)	70.9 ± 9.4
Male gender	65.2 %
History of Hypertension	89.6 %
History of CHF	22.1 %
Prior MI	36.0 %
Prior CABG	34.8 %
History of Hyperlipidemia	87.6 %
History of Smoking	75.4 %
Diabetes Mellitus	33.8 %
- Insulin dependent	10.0 %

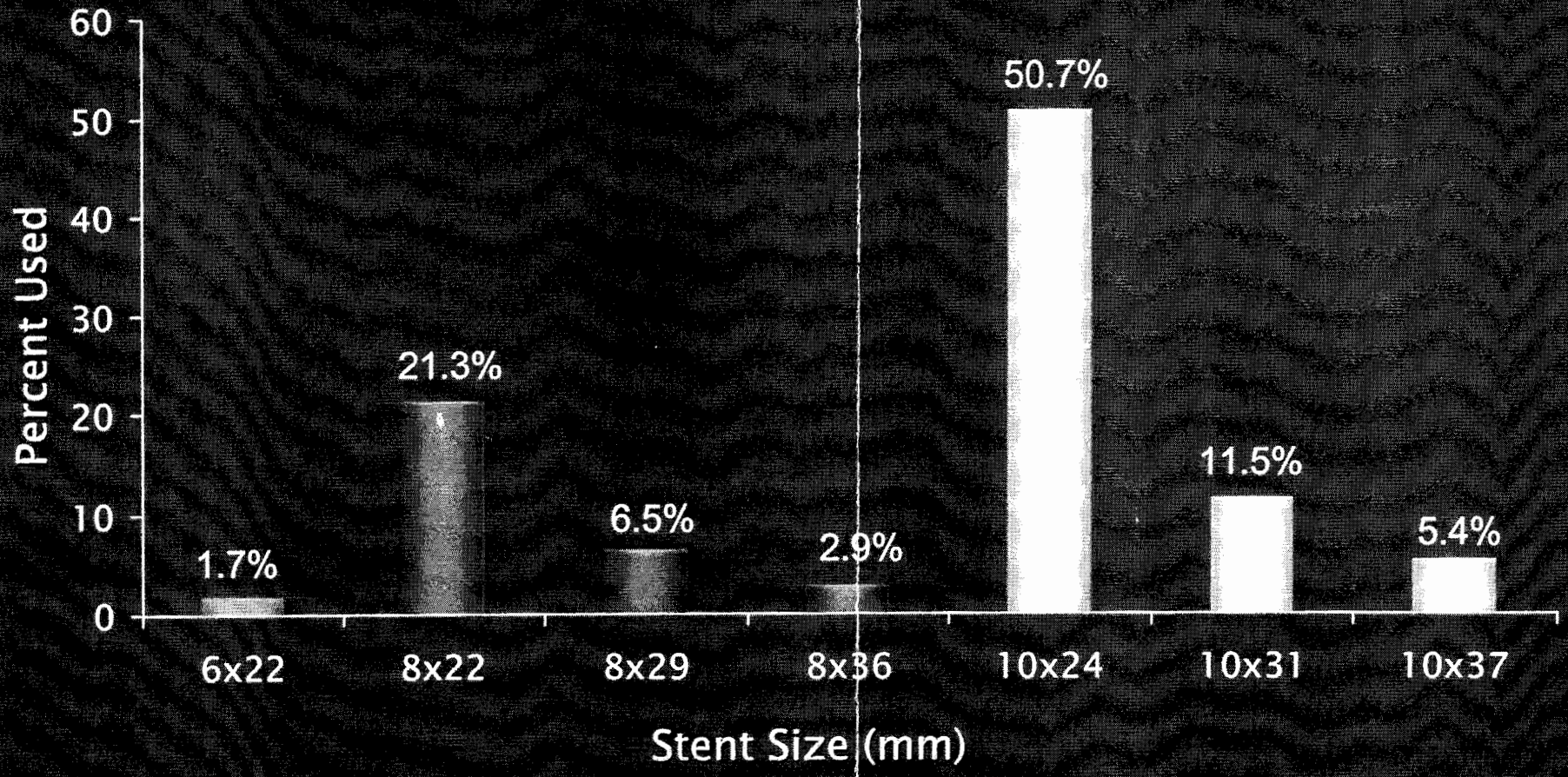
CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Pivotal Group: Procedural Characteristics

Procedural Characteristics	Patients n = 480
GP IIb/IIIa used during procedure	3.1%
Patients that maintained ACT ≥275 sec. or ≥200 sec. if patient received GP IIb/IIIa	90.2%
Post-stent balloon dilatation performed	97.7%
• Maximum inflated pressure- atm (mean)	10.2
• Site reported Final % Stenosis (mean)	6.0%
Aspiration of vessel performed prior to FilterWire retrieval	0.6%

CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Pivotal Group: Carotid Wallstents Used in Treatment



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BEACH Pivotal Group: All Strokes through 30 Days

	Ipsilateral % (n)	Contralateral % (n)
Ischemic–Major	1.0 (5)	0.0 (0)
Ischemic–Minor	1.9 (9)	0.6 (3)
Hemorrhagic	0.2 (1)	0.4 (2)
Total	3.1 (15)	1.0 (5)

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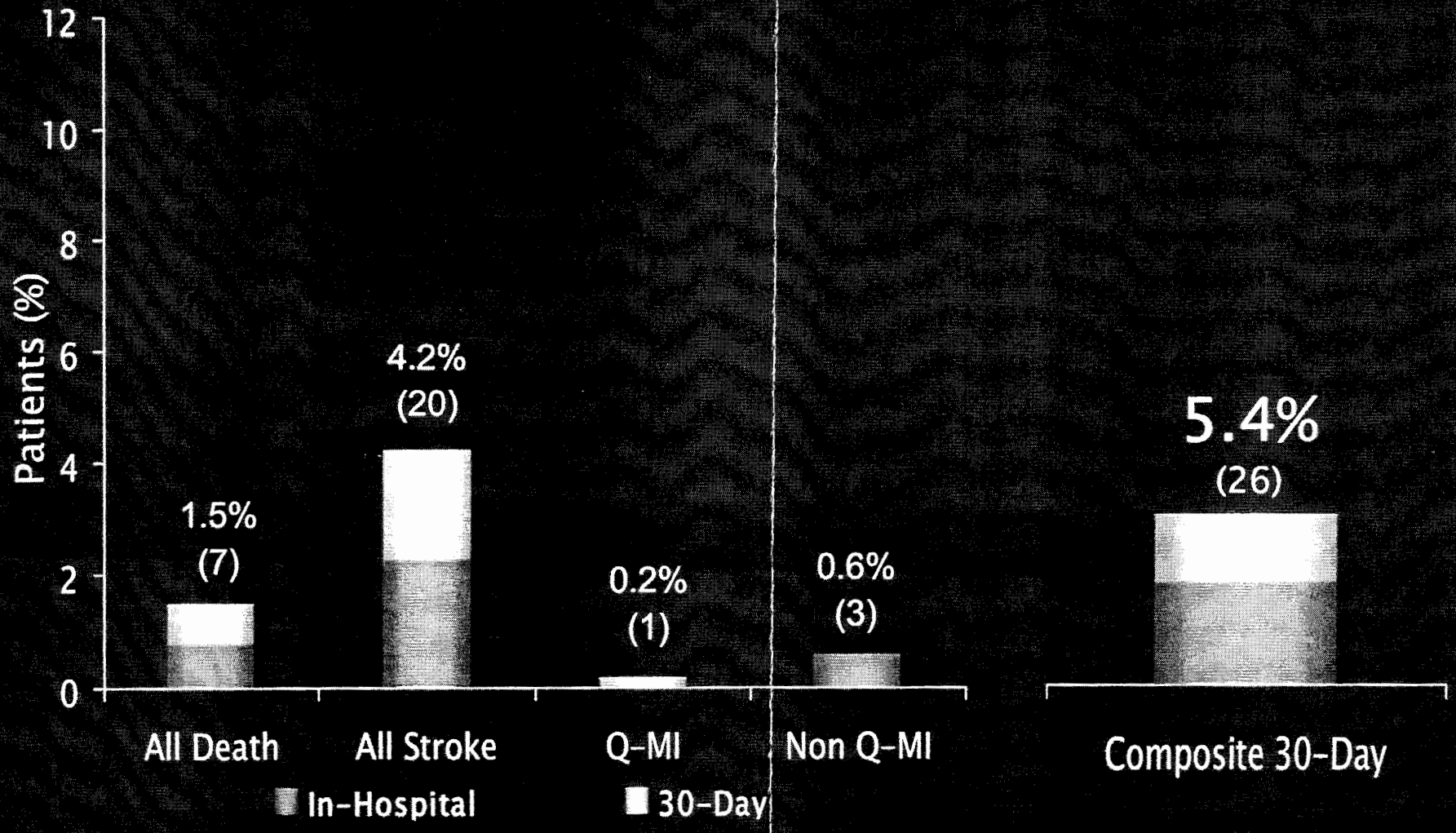
BEACH Pivotal Group: 30-Day Composite Endpoint



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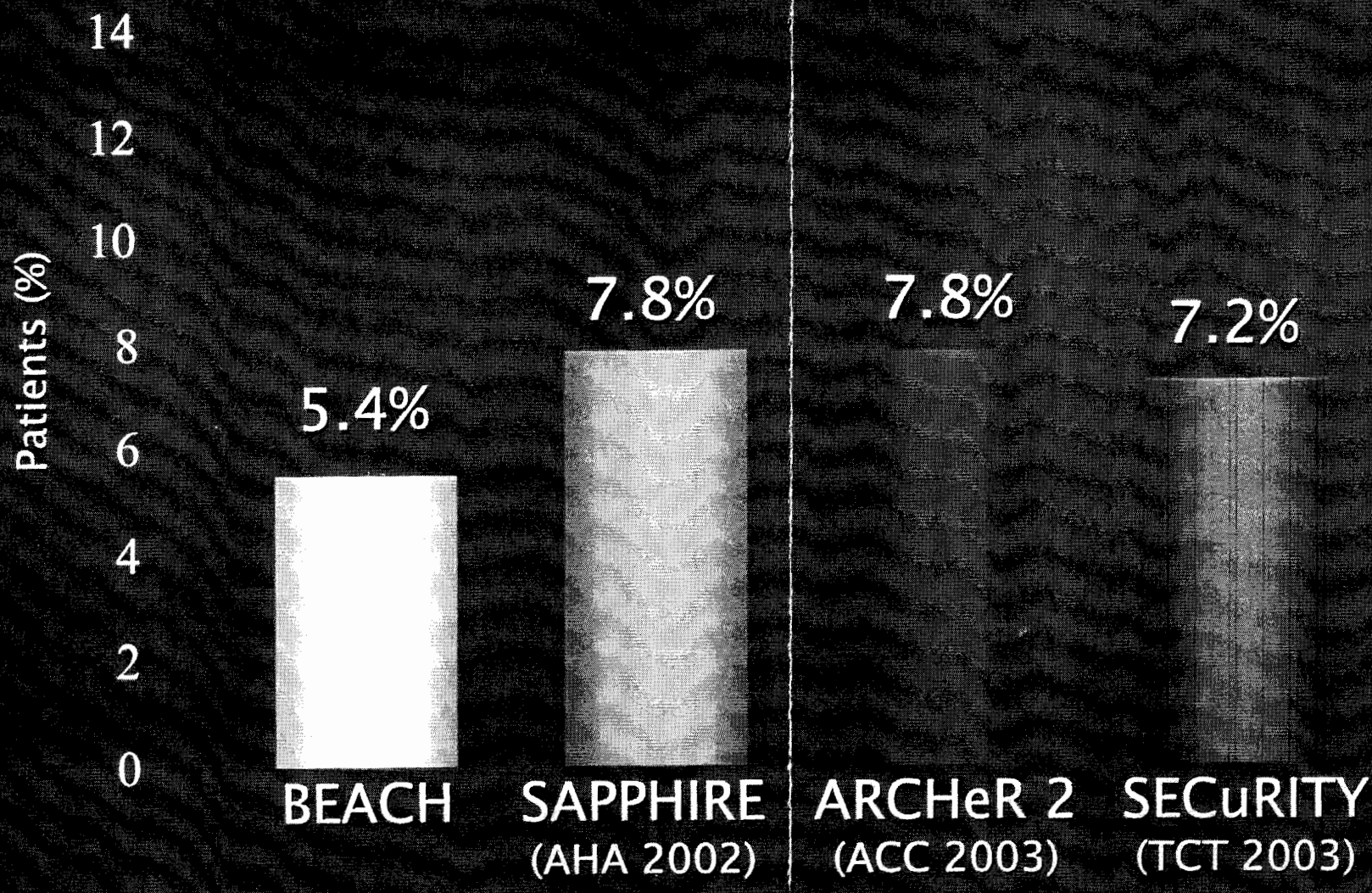
BEACH Pivotal Group: 30-Day Summary

30-Day Composite Endpoint = 5.4%

- All Death = 1.5%
- All Stroke = 4.2%
  - Minor Ipsilateral Stroke = 1.9%
  - Major Ipsilateral Stroke = 1.0%
- All MI's= 0.8%

CAUTION: Investigational device. Limited by federal law to investigational use.

30-Day Composite Endpoint in Carotid Stenting Trials



CAUTION: Investigational device. Limited by federal law to investigational use.

BEACH Pivotal Group: Conclusion

- Early safety is acceptable and comparable to other high-risk CAS trials.

- One Year results → Spring 2005

CAUTION: Investigational device. Limited by federal law to investigational use.

The SAPPHIRE and ARCHeR Updates

A report on the early progress of two trials critical to our understanding of carotid artery stenting.

BY BARRY T. KATZEN, MD; JOHN R. LAIRD, JR, MD; AND TAKAO OHKI, MD, PHD

Physicians in every endovascular specialty anxiously await the continuing results of two major clinical evaluations of the safety and efficacy of carotid artery stenting (CAS)—SAPPHIRE and ARCHeR. These trials are important because they may supply the data necessary to support an FDA decision to approve the procedure in the US. The SAPPHIRE is especially important because it compared CAS to carotid endarterectomy (CEA) in a randomized fashion. Its results will likely legitimize CAS, which has been viewed by some as a dangerous experimental procedure and which many believed could never match the results of CEA, which has withstood the test of time. CAS has even gained notice among the national media, as is evidenced by coverage on the front page of the November 20, 2002 edition of *The New York Times*, which compared the complication rate for surgery (12.6%) versus that for CAS (5.8%). If this new finding holds up, the article states, CAS may become the preferred procedure for 200,000 Americans who might otherwise choose to undergo surgery.

THE CORDIS/JOHNSON & JOHNSON SAPPHIRE TRIAL

The SAPPHIRE trial is a prospective clinical trial for CAS in high-surgical-risk patients. The 30-day preliminary results were reported at the American Heart Association

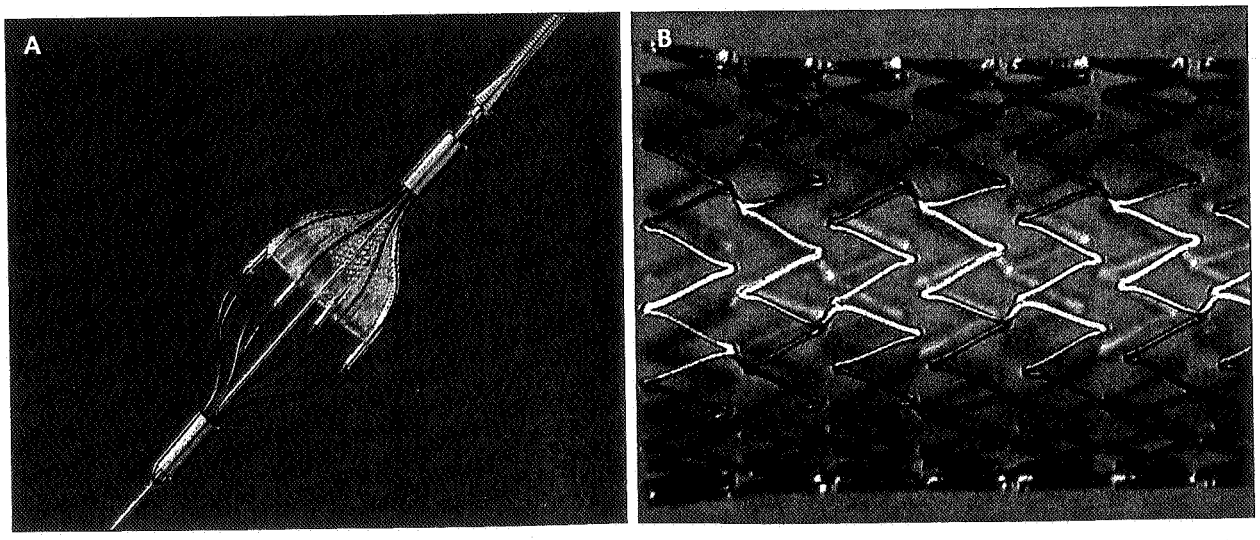


Figure 1. The Cordis Carotid Stenting System. The AngioGuard filter (A). The PRECISE is a nitinol, self-expanding stent with a 6-F delivery system (B).

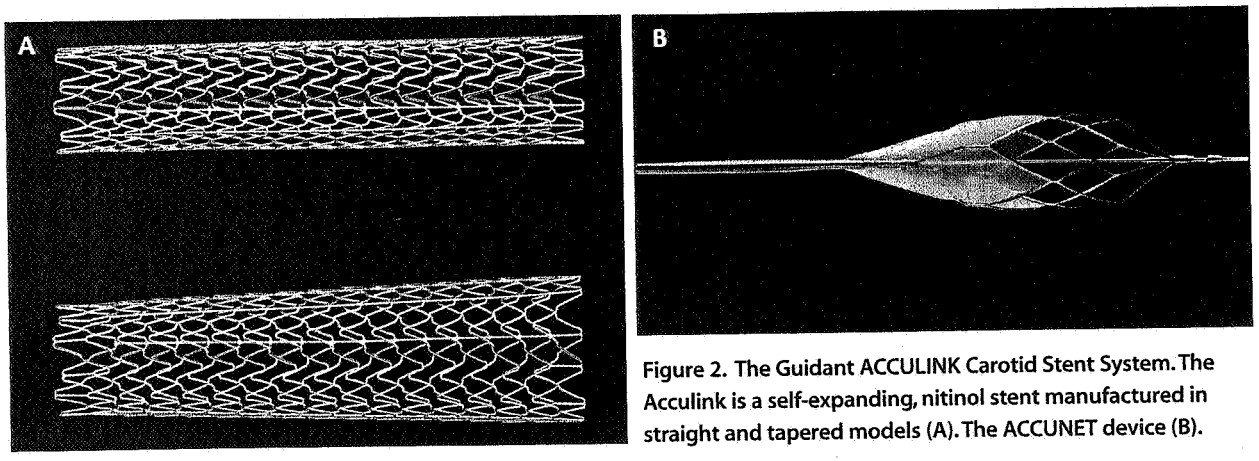


Figure 2. The Guidant ACCULINK Carotid Stent System. The Acculink is a self-expanding, nitinol stent manufactured in straight and tapered models (A). The ACCUNET device (B).

meeting in Chicago, November 2002, by Jay Yadav, MD, Co-Principal Investigator of the trial.[1] A study overview identified 29 investigational sites in the multicenter, randomized trial evaluating CAS in patients who are at high risk for CEA. All patients were evaluated by a team composed of a neurologist, a surgeon, and an interventionist. Randomization to either CEA or CAS required a team consensus; if a surgeon believed that surgery carried prohibitive risk, the patient was entered into a stent registry. Conversely, if the interventionist believed that stenting carried prohibitive risk, the patient was placed into a surgical registry.

Symptomatic patients with ≥50% stenosis determined by ultrasound, and asymptomatic patients with ≥80% stenosis, also determined by ultrasound, were eligible for enrollment, assuming they met the necessary entry criteria. Follow-up duplex and neurologic examinations were scheduled for 30 days, 6 months, 1 year, and annually for 3 years. The primary endpoint was a composite of stroke, death, and myocardial infarction at 30 days, and ipsilateral stroke or death between 31 days and 1 year. The secondary endpoints also included vessel patency (at 48 hours, 6 months, and 1, 2, and 3 years), disabling stroke (at 30 days, 6 months), composite major adverse events (at 6 months, and 1, 2, and 3 years), and safety assessment of the AngioGuard XP (Cordis Endovascular, a Johnson & Johnson company, Miami, FL) embolic distal protection device.

The stent utilized in the SAPPHIRE trial was the self-expanding nitinol PRECISE stent (Cordis Endovascular), available in dimensions of 5 mm to 10 mm in diameter and 20-, 30-, and 40-mm lengths (Figure 1). Also available for use in this trial were 8 mm to 6 mm, 9 mm to 7 mm, and 10 mm to 7 mm tapered self-expanding PRECISE stents. The AngioGuard distal protection device consists of a polyurethane filter over a nitinol basket with a diameter of 6 mm to 8 mm and and a pore size of 100 μm to maintain satisfactory perfusion during the endovascular procedure (Figure 1).[2]

Assuming the patient met the key inclusion criteria of degree of stenosis, he was also evaluated and had to meet at least one of the high-risk criteria:

- Congestive heart failure (class III/IV) and/or known severe left ventricular dysfunction LVEF <30%
- Open heart surgery within 6 weeks
- Recent myocardial infarction (>24 hours and <4 weeks)
- Unstable angina (CCS class III/IV)
- Coexistent severe coronary artery disease requiring carotid and coronary revascularization
- Severe pulmonary disease (FEV <1.0)
- Contralateral carotid occlusion
- Contralateral laryngeal palsy
- Postradiation treatment
- Previous CEA recurrent stenosis
- High cervical ICA lesions
- CCA lesions below the clavicle
- Severe tandem lesions
- greater than 80 years of age

Seven hundred twenty-three patients were enrolled; 307 were randomized, 409 patients were in the stent registry, and seven patients were in the CEA registry (patients not suitable for CAS).

AngioGuard device delivery placement and retrieval success was reported to be 98.6%. The 30-day, combined death, stroke and/or myocardial infarction rate for the randomized CAS arm was reported to be 5.8% versus 12.6% for the randomized CEA arm ($P = .047$). Subanalysis showed that in the group of symptomatic patients treated, the death, stroke, and myocardial infarction rate was 4.2% for the randomized stent arm and 15.4% for the randomized CEA arm, whereas it was 6.7% and 11.2%, respectively, for asymptomatic patients. The 30-day death, stroke, and myocardial infarction rate for the stent registry group was reported to be 7.8%.

Conclusions

The SAPPHIRE trial is the first randomized study comparing CAS with embolic protection to carotid endarterectomy. It is also the only high-risk randomized study with stent and surgical registries defined by vascular surgeons. This study provides a surgical complication rate for a large group of high-risk patients who were previously excluded from prior CEA trials. Also, the SAPPHIRE study demonstrates a high technical success rate for CAS using distal protection technology. The remaining primary endpoint (ipsilateral stroke or death between 31 days and 1 year) will be presented at the upcoming 2003 TCT conference. According to a credible source, the benefit of stenting that was apparent at 30 days is expected to hold up at 1 year.

Cordis will soon file their PMA application to the FDA for market clearance. They have also initiated negotiations with the Centers for Medicare & Medicaid Service (CMS) to revise their national "noncoverage policy" for CAS. FDA approval is expected in the second quarter of 2004, and CMS reimbursement is expected in early 2005. Whether CAS will only be approved and reimbursed strictly for high-risk patients is unknown at this time.

THE GUIDANT ARCHeR TRIAL

The ARCHeR trial is a prospective clinical trial for CAS in high-surgical-risk patients and nonsurgical patients. The 30-day preliminary results were reported at the recent American College of Cardiology meeting in Chicago, March 2003, by Mark Wholey, MD, Co-Principal Investigator of the trial, and at the Society of Interventional Radiology conference in Salt Lake City, March 2003, by Gus Eles, MD.[3] A study overview identified 41 investigational sites in the multicenter, single-arm trial evaluating CAS in patients who were at high risk for CEA. All patients were seen by an independent neurologist for assessment prior to enrollment and for continued follow-up. Symptomatic patients with ≥50% stenosis determined by angiography, and asymptomatic patients with ≥80% stenosis, also determined by angiography, were eligible for enrollment assuming they met the necessary entry criteria.

Clinical follow-up examinations are scheduled for 30 days, 6 months, 12 months, 18 months, 24 months, and 30 months. The primary endpoint is a composite of stroke, death, and myocardial infarction at 30 days, and ipsilateral stroke between 31 days and 1 year. Another primary endpoint is the acute success with the ACCUNET Embolic Protection System (Guidant Corporation, Indianapolis, IN). The key secondary endpoints are target lesion revascularization at 6 and 12 months; duplex carotid ultrasound evaluation at 6, 12, and 24 months, and the ACCULINK Carotid Stent System success (Guidant Corporation).

The device evaluated in the ARCHeR trial was the self-expanding, nitinol ACCULINK stent, available in dimensions of 5 mm to 10 mm in diameter, with 20-, 30-, and 40-mm lengths (Figure 2). Also available were 8-mm to 6-mm and 10-mm to 7-mm tapered self-expanding stents. The ACCUNET filter consists of a polyurethane filter over a nitinol basket with a diameter of 4 mm to 8 mm and a pore size of 120 microns to maintain satisfactory perfusion during the endovascular procedure (Figure 2).[2]

Assuming the patients met the key inclusion criteria for degree of stenosis, they were also evaluated as to the high-risk inclusion criteria. Patients were determined to be high risk by meeting criteria in one of two classification systems (Table 1).

Five hundred thirteen patients were enrolled. Seventy-six of these patients represented a lead-in prior to the registry.

TABLE 1. ARCHeR TRIAL HIGH-RISK CRITERIA

1. Patients having two or more of the following high-risk criteria:

a. Two or more coronary vessels with ≥70% stenosis
b. Myocardial infarction within 30 days of the carotid stent procedure
c. Concurrent requirement for aortocoronary bypass or valve surgery within 30 days of the carotid stent procedure
d. Unstable angina
e. Contralateral occlusion of the internal carotid artery

2. Patients having one of the following high-risk criteria:

a. Ejection fraction <30% or NYHA functional Class ≥ III
b. FEV of <30% predicted
c. Dialysis-dependent renal failure
d. Uncontrolled diabetes
e. Restenotic lesions after previous endarterectomy
f. Patients with previous radical neck surgery and/or radiation therapy
g. Surgically inaccessible lesions
h. Spinal immobility
i. Tracheostomy stoma
k. Contralateral laryngeal nerve paralysis
l. On list for major organ transplantation

Major exclusion criteria included:

- An evolving stroke
- Previous major ipsilateral stroke
- Recent stroke of <7 days
- Neurological deficits simulating stroke
- History of intolerance or allergic reaction to both ticlodipine and clopidogrel, and history of intolerance or allergic reaction to any study medications or materials

Four hundred thirty-seven patients in the registry were enrolled. The demographics in this subset included a history of stroke in 28% and transient ischemic attacks in 24%. The mean age was 69.4 years; 66.6% of the patients were male, and 33.4% were female. Diabetes was present in 39.1% of the patients and 83.9% had hypertension and 68.8% had hyperlipidemia. Other patient data included 32.2% of the patients had restenotic lesions after previous CEA, 28.6% of the patients had ejection fractions of <30% or New York Heart Association classification of III or higher, 27.5% had two or more diseased coronary arteries, and 14.6% had contralateral internal carotid artery occlusion. The remainder was composed of patients with unstable angina, surgically inaccessible lesions, previous radiation therapy, dialysis-dependent renal failure, and contralateral laryngeal nerve damage.

Results

Successful ACCUNET device delivery, placement, and retrieval were reported for 92% of the patients. Debris, either macroscopic or microscopic, was present in the filter baskets in 57% of the patients.

The incidence of 30-day stroke events was minor ipsilateral stroke (3.7%), major ipsilateral stroke (1.4%), and major contralateral stroke (0.2%). Non–stroke-related deaths were 1.6%, and stroke-related death was 0.7%. Myocardial infarction, both Q wave and non-Q wave, accounted for 2.1% of the 30-day events. The overall stroke and death rate was 6.6%, and stroke, death, and myocardial infarction rates were 7.8%. There were 141 patients with restenotic lesions from previous endarterectomy, and in that subset, stroke and death accounted for only 0.7% of patients undergoing CAS. Patients with contralateral ICA occlusions (n = 66) had a stroke, death, and myocardial infarction rate of 7.6% (the combined stroke and death rate was 4.5%). Both of these patient subsets had significantly lower event rates than historical controls. For example, in contralateral ICA occlusions in the NASCET study (North American Symptomatic Carotid Endarterectomy Trial), a 14% periprocedural stroke and death rate was reported. Two or more comorbidities were present in 187 patients; the combined stroke and death rate was only 4.8%, and the combined stroke, death, and myocardial infarction rate was 6.4%.

What was quite significant, however, was that dialysis-dependent renal failure had a stroke, death, and myocardial infarction rate of 28.6%. Only 14 patients were represented in that subset, but it does raise the question in this subset of patients that renal failure may indeed be a predictor for complication.

Conclusions

The ARCHeR trial, representing one of the high-risk trials, demonstrated that CAS with filter protection can be safely performed in high-risk patients in a multicenter trial. The data appear to compare favorably with the historical CEA outcomes in high-risk cohorts. The data are also consistent with the previously presented SAPPHIRE trial results and are additional evidence that CAS is a viable and possibly better alternative to CEA in select high-risk patients. The availability of alternative treatment options may improve the overall outcome of treating carotid stenosis.

SUMMARY

Two important controlled clinical trials have been completed and provide data and clinical experience in a specific cohort of patients who can benefit from CAS, namely those with clearly defined increased risk for CEA. Whereas some dispute the definition of "high-risk" from a surgical point of view, very specific definitions were established based on published data. The randomized data seem particularly powerful, and given the difficulty in successfully completing randomized trials in this area, it is likely that it will be some time before we see other randomized data. These data also support what we are seeing in the community, namely acceptance by physicians involved in the medical and surgical care of patients with carotid occlusive disease, who increasingly rely on CAS for treatment of high-risk patients. ■

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◆ CLINICAL INVESTIGATION ◆

Carotid Artery Stenting in Older Patients: Is Age a Risk Factor for Poor Outcome?

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Purpose: To assess the impact of age on technical success and complications of carotid stenting in a prospective single-center cohort study.
Methods: One hundred eleven consecutive patients (74 men; median age 70 years) with ≥70% symptomatic (n=33) or ≥90% asymptomatic (n=78) internal carotid artery (ICA) stenosis underwent carotid artery stent implantation. Primary technical success and periprocedural complications were compared in patients aged >75 years (n=28) to patients <75 years (n=83).
Results: Patient groups below and above 75 years compared well with respect to baseline demographic and clinical data. Successful stenting was achieved in 108 (97%) patients. The combined neurological complication rate was 7% (n=8), with 1 (1%) major stroke, 1 (1%) minor stroke, and no 30-day mortality. Technical angiographic complications occurred in 8 (7%) patients. No significant differences between patients >75 years and those <75 years were observed for primary success rates (100% [28/28] versus 96% [80/83]; p=0.8), overall complications (14% [4/28] versus 16% [13/83]; p=1.0), neurological complications (7% [2/28] versus 7% [6/83]; p=1.0), or technical complications (7% [2/28] versus 4% [3/83]; p=0.6).
Conclusions: Elective carotid stenting can be performed safely in older patients with several comorbidities. Patient age does not seem to be an independent risk factor for poor outcome after endovascular treatment of internal carotid artery stenosis.

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Key words: internal carotid artery, stenosis, Wallstent, complication, stroke

Prevention and treatment of stroke is a significant socioeconomic problem.[1] Large-artery thromboembolism, which accounts for about 35% of strokes, originates most frequently from atherosclerotic lesions of the internal carotid arteries (ICA).[2] Carotid angioplasty and stenting appear to be feasible and safe for the treatment of high-grade ICA stenosis.[3–14] The procedure can be performed with periprocedural complication rates varying between 1% and 11%,[3–11,13–16] similar to those of carotid endarterectomy, and the ongoing multicenter prospective randomized trials should provide evidence concerning the equivalency of the techniques.

Older patients often exhibit relative contraindications to surgical treatment due to underlying cardiovascular risk factors and comorbidities; they are, therefore, prime candidates for minimally invasive endovas-

Both Drs. Ahmadi and Schillinger contributed equally to the study.

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J ENDOVASC THER
2002;9:559–565

cular procedures. However, reports suggest that increasing age has a negative impact on the rate of complications in carotid stent patients.[13,17,18] It remains unclear so far if older age per se is associated with a higher incidence of periprocedural complications. Hence, we investigated the effect of increasing age on the rate of technical success and the incidence of complications of elective carotid stenting in our university-based practice.

METHODS

Study Design

The study was designed as a prospective cohort study including all consecutive patients who were scheduled for elective carotid stenting from March 2000 to March 2001. The study complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave their written informed consent.

Candidates were initially identified based on clinical status and a high-grade ICA stenosis identified by duplex ultrasound examination and/or computed tomography (CT) of the head. The indications for carotid stenting were based on an angiographically documented ≥70% stenosis determined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. In symptomatic patients, there also had to be high clinical suspicion that the neurological manifestations were due to microembolization from the carotid plaque, and the time interval between onset of hemispheric symptoms and the procedure had to be ≤6 months. A time frame of at least 6 weeks was used to treat patients who suffered major stroke.

In the asymptomatic patient, fulfillment of any one of several criteria supported stent treatment: rapid lesion progression within the last 6 months, documented by duplex ultrasound; silent cerebral infarction on CT scan consistent with thromboembolism from the carotid plaque; very high-grade stenosis (>90%); contralateral carotid occlusion or severe stenosis; or request of a surgeon before major (cardiac or neck) surgery.

Patients severely disabled as result of stroke or dementia were excluded, as were patients with severe acute disease, such as intensive care unit patients on mechanical ventilation, acute cardiac decompensation, or acute metabolic dysfunction or renal insufficiency without dialysis. Other exclusion criteria were intracranial tumor or a cerebral hemorrhage documented by CT, peripheral arterial occlusive disease that prevented femoral artery access, and inability to give consent.

Patient Evaluation

Duplex grading of the carotid stenosis was done in accordance with the principles of the consensus meeting on the quantification of stenosis of the extracranial carotid artery[19] and the proposals of Nicolaides et al.[20] The scans were performed before treatment and 1 day after the intervention with an Acuson XP 10 system (Acuson Corporation, Mountain View, CA, USA) using a 5-MHz linear probe.

A complete neurological history, including the National Institute of Health Stroke Scale status (NIHSS),[21] were routinely performed by an independent neurologist before the intervention. Baseline cranial CT was mandatory. The clinical neurological state prior to stenting in conjunction with a recent cranial CT and the carotid duplex ultrasound formed the basis for the neurologist's explicit consent to carotid stenting. Routine neurological examinations were scheduled the day before intervention, the day after, and on day 30. In cases of suspected neurological events, clinical evaluation with cranial CT and angiography as necessary were performed immediately.

A diagnostic 4-vessel angiogram was performed in all patients prior to the intervention to document anatomical variations, stenoses at the origin of the great vessels, severely diseased aortic arches, intracranial pathology, and any vertebral and posterior circulatory problems.

Patient Population

Within the 12-month study period, 111 patients (74 men; median age 70 years, interquartile range 64–75) were enrolled in the study. At admission, the medical history and

TABLE 1
Comparison of Baseline Data for 111 Carotid Stent Patients Grouped by Age

	<75 Years Old (n=83, 75%)	>75 Years Old (n=28, 25%)	p
Men	54 (65%)	20 (71%)	0.6
Body mass index, kg/m^2	25.8 (24.2–28.1)	24.9 (23.5–27.4)	0.2
Current smokers	31 (37%)	3 (11%)	0.009
Hyperlipidemia	68 (82%)	23 (82%)	1.0
Medication with statins	54 (65%)	17 (61%)	0.8
Arterial hypertension	62 (75%)	25 (89%)	0.1
Diabetes mellitus	33 (40%)	6 (21%)	0.1
Peripheral artery disease	46 (55%)	10 (36%)	0.08
Coronary artery disease			0.8
CCS I	18 (22%)	7 (25%)	
CCS II	15 (18%)	4 (14%)	
CCS III	1 (1%)	1 (4%)	
Myocardial infarction	14 (17%)	5 (18%)	1.0
Symptomatic ICA stenosis			0.6
Ipsilateral TIA	17 (21%)	7 (25%)	
Ipsilateral minor stroke	1 (1%)	1 (4%)	
Ipsilateral major stroke	6 (7%)	1 (4%)	
Contralateral stroke	19 (23%)	8 (29%)	0.6
ICA stenosis, %	90 (85–90)	90 (85–95)	0.6
ICA stenosis, mm	10 (10–20)	10 (10–18)	0.8

Continuous data given as median (interquartile range). CCS = Canadian Cardiovascular Society, ICA = internal carotid artery, TIA = transient ischemic attack.

data from physical examination were recorded using a standardized questionnaire. Standard laboratory examination included assessment for complete blood count, global coagulation tests, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, lipoprotein (a), and serum uric acid. Diabetes mellitus was defined as fasting blood glucose levels >110 mg/dL measured 3 times, pathological oral glucose tolerance tests, and HbA1c >6.5%. Hyperlipidemia was defined as fasting total serum cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, or serum triglycerides >180 mg/dL; all patients on lipid-lowering medication (inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase [statins] are the standardized treatment for hyperlipidemia at our department) were also considered hyperlipidemic. Arterial hypertension was diagnosed according to the WHO criteria. Patients who were smoking more than 3 cigarettes per day were regarded as current smokers. The diagnosis of peripheral artery disease was assessed by clinical evaluation, ankle-brachial index measurements, duplex sonography, and angiography in selected cases. Coronary artery disease was classified according to the Canadian Cardiovascular Society (CCS) classification and was evaluated by echocardiography, stress exercise testing, myocardium scintigraphy, and angiography in selected cases.

Seventy-eight (70%) patients had a >90% asymptomatic carotid artery stenosis and 33 (30%) patients had a ≥70% symptomatic ICA stenosis with preceding ipsilateral transient ischemic attacks (n=24, 22%), minor strokes (n=2, 2%), and major strokes (n=7, 6%). In 10 (12%) patients, a recurrent stenosis after endarterectomy was the target lesion. Baseline demographic data in patients aged <75 years (n=83) and above 75 years (n=28) are given in Table 1.

Carotid Stent Procedure

One physician who had experience with >300 carotid interventions performed all stent implantations.[14] Procedures were begun with transfemoral access under local anesthesia. After placement of an 8-F sheath, every patient received 5000 units of heparin intra-

J ENDOVASC THER
2002;9:559–565

arterially. An overview angiogram of the supra-aortic arteries from the aortic arch was followed by a selective angiogram (in at least 2 planes) of the carotid artery and its intracranial branches. Length and grade of the lesion were documented, and a road map was then established.

After crossing the stenosis to the distal ICA with a gold-tip wire, a 3.5-mm × 40-mm Bijou balloon (Schneider, Bülach, Switzerland) was placed at the site of the stenosis for primary dilation at 10 atmospheres for 5 to 10 seconds. The catheter was exchanged, and 1 mg of atropine was given intravenously immediately before deploying an OTW Wallstent (Boston Scientific Corp., Natick, MA, USA), which was sized according to an estimation of the diameter of the carotid artery on the selective angiogram. Stent deployment was followed by dilation within the stent using a 5- to 6-mm-diameter balloon catheter and a pressure of 8 to 10 atmospheres for 5 to 10 seconds.

After stenting, selective control angiography in at least 2 planes was done to evaluate the local result and to examine the intracranial arteries for changes in hemodynamics and embolization. If a suboptimal result was seen on the control angiogram, a second stent was implanted. An intervention was considered successful when the residual diameter reduction calculated from the final angiogram was <30%.

Standardized antiplatelet therapy was clopidogrel (75 mg/d) plus aspirin (100 mg/d) for 4 weeks. The same dose of clopidogrel without aspirin was administered thereafter because of the suggested beneficial effect in atherothrombotic patients with cerebrovascular disease.[22,23]

Definitions

Neurological events were categorized as transient ischemic attacks (TIA): a focal ischemic neurological deficit with abrupt onset that resolved completely within 24 hours; minor stroke: focal neurological deficit lasting >24 hours with NIHSS score <4; and major stroke: focal neurological deficit lasting >24 hours with NIHSS score >4. "Combined neurological complications" included TIAs and all strokes.

Statistical Analysis

Continuous variables are presented as the median and interquartile range (25th to 75th percentile). Percentages were calculated for dichotomous variables. To assess the effect of age on primary technical success and periprocedural complications, patients were divided into quartiles of age, and patients in the oldest quartile were compared to the 3 younger quartiles. The chi-square test or, if appropriate, Fisher exact test was used to compare proportions; the nonparametric Wilcoxon rank sum test was applied to compare continuous variables. All tests were 2-sided, and $p<0.05$ was considered statistically significant. All analyses were performed using SPSS for Windows, version 10.0 (SPSS, Chicago, IL, USA).

RESULTS

The 2 age groups compared well with respect to their demographic and clinical characteristics, with the exception of current smoking habits (Table 1). Ten patients underwent bilateral stenting during the study period with at least 6 weeks between interventions; no patient was stented bilaterally within the same session. Primary technical success rate was 97% (108/111). In all, 95 (86%) patients received a single stent; 9 (8%) patients had 2 stents implanted bilaterally, and 1 (1%) ICA had 3 overlapping stents implanted.

Intimal dissection after predilation occurred in 3 (3%) patients. No prolonged hypotensive states were observed, but 1 (1%) patient had a transient decline in blood pressure below 90 mmHg for <30 minutes. No residual stenosis ≥50% after stent implantation was found in any patient. Improved intracerebral runoff was documented in 104 (94%) patients on the final angiogram. One patient who mistakenly did not receive clopidogrel within the first 48 hours postintervention developed early occlusion and suffered a TIA; however, no thrombophilic disorder or technical procedure-related problem was found in this patient. The reocclusion was treated successfully by intra-

TABLE 2
Comparison of Technical Success and Complications in 111 Carotid Stent Patients Grouped by Age

	<75 Years Old (n=83, 75%)	>75 Years Old (n=28, 25%)	p
Primary technical success	80 (96%)	28 (100%)	0.8
Improved intracranial runoff	77 (93%)	27 (96%)	0.7
Overall complications	13 (16%)	4 (14%)	1.0
Intimal dissection after predilation	3 (4%)	0	0.6
Early reocclusion	1 (1%)	0	1.0
Neurological complications	6 (7%)	2 (7%)	1.0
TIA	4 (5%)	2 (7%)	
Minor stroke	1 (1%)	0	
Major stroke	1 (1%)	0	
Pseudoaneurysm/hematoma	3 (4%)	2 (7%)	0.6

TIA = transient ischemic attack.

venous administration of abciximab for 24 hours in combination with low-molecular-weight heparin.

The combined neurological complications rate was 7% (n = 8) with no 30-day mortality. A TIA was recorded in 6 (5%) patients after the intervention; there was 1 (1%) minor and 1 (1%) major stroke. Five (5%) access-site complications were observed: 3 small, localized hematomas, 1 arteriovenous fistula, and 1 pseudoaneurysm; all these sequelae were managed conservatively.

Comparing the 2 age groups (below and above 75 years), there were no significant differences for any parameter of technical success or any category of complications (Table 2) in this patient series. Symptomatic and asymptomatic patients in the 2 age groups showed similar neurological event rates (Table 3). A further investigation between the 4 groups of patients according to the age quartiles again found no significant difference in complications with increasing age (p=0.7, chi-square test for trend). The 8 (7%) patients over the age of 80 did not show a higher frequency of overall complications (p=0.4) or neurological events (p=0.1) compared to the 103 patients <80 years.

TABLE 3
Combined Neurological Event Rates After ICA Stenting in Symptomatic and Asymptomatic Patients

	Combined Neurological Events	
	Symptomatic	Asymptomatic
Age <75 years	2 (8%)	4 (7%)
Age >75 years	1 (11%)	1 (5%)
p	1.0	1.0

DISCUSSION

In our study, patient age per se was not associated with an increased risk for neurological or technical complications after ICA stenting. It seems unlikely that underlying confounding factors influenced the association of patient age and outcome after endovascular treatment in our analysis, as the patient groups were comparable in both demographic and clinical variables. Immediate results in our few octogenarians were similar to those in patients below 80. It is important to note that when treating asymptomatic patients, a life expectancy of at least 5 years is reasonable to justify the procedural risk in relation to the expected benefit of cumulative stroke risk reduction.

The high rate of successful stenting in the present series is in accord with previous findings,[9,14,24,25] and the rate of neurological complications is slightly lower.[13,25] For comparison, the data published by Wholey et al.[25] on the global carotid stent experience of 36 centers in over 5000 cases were 2.7% minor strokes, 1.5% major strokes, a 0.9% 30-day death rate, and 5.1% for any stroke or death.

Our 1% rates for major and minor strokes, respectively, may be due to patient selection or the fact that the interventionist had performed over 300 carotid interventions before this study, so the learning curve was not a factor as it has been in some earlier studies. In fact, a considerable effect of learning has been observed during the first 50 to 80 procedures,[14] which significantly influences the complication rate. Moreover, our outcomes were achieved without a device for cerebral protection. While further improvement may be achieved with cerebral protection[26] irrespective of patient age, there are no data on this issue at present.

Surgical revascularization of symptomatic patients was associated with a perioperative risk of death or major stroke of 2.8% in NASCET[27] and 7% in the European Carotid Surgery Trial (ECST),[28] but it is higher in smaller centers and in aged patients.[15,17,18] Chastain et al.[18] reported a negative impact of increasing age on the rate of complications in carotid stent patients; it was 3-fold higher in those aged >80 years. Furthermore, advanced age was identified as an independent predictor of procedural stroke during carotid stenting in other studies.[13,17] In contrast to these findings, our data support the view that age per se is not an independent risk factor for poor outcome. Older patients might be good candidates for endovascular treatment rather than surgical revascularization, particularly if several cardiovascular comorbidities and additional risk factors for surgery are found.[10,29]

Some clinical implications may be considered when treating older patients with carotid artery stenting. Low blood volume together with age-related diastolic dysfunction can lead to a low cardiac output state, which increases the susceptibility to hypotension. Stent implantation in the carotid bulb often causes a transient decline in blood pressure for hours after the intervention. Cerebral autoregulation, which maintains a constant cerebral circulation over a wide range of blood pressure changes, is altered in the presence of arterial hypertension and, possibly, also by aging. As a result, sudden mild to moderate declines in peripheral blood pressure can affect cerebral blood flow markedly and render an older person particularly vulnerable to hypotensive states after carotid stenting. Close blood pressure monitoring and careful administration of antihypertensive medication in the days after carotid interventions may therefore be recommended in these patients.

We recognize that this single operator and institution evaluation may not reflect the impact of age on carotid stent outcomes in other centers, and our patient selection criteria may have also influenced our findings. Data acquired during the ongoing multicenter trials will be necessary to finally answer this question. However, based on our experience, elective carotid stenting in older patients can be performed with excellent technical success rates and an acceptable frequency of periprocedural complications. Age per se does not appear to be an independent risk factor for poor outcome. On the contrary, technical factors, personal experience of the interventionist, and lesion morphology are more important predictors of outcome than is patient age.[14,30] Therefore, older patients, particularly if cardiovascular comorbidities are present, may be good candidates for endovascular stent implantation rather than for carotid endarterectomy.

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CLINICAL STUDIES **Interventional Cardiology**

Carotid Angioplasty and Stenting Versus Carotid Endarterectomy: Randomized Trial in a Community Hospital

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OBJECTIVES The goal of this study was to determine whether carotid angioplasty and stenting (CAS) is equivalent to carotid endarterectomy (CEA) in patients with symptomatic carotid stenosis >70% by a randomized, controlled trial in a community hospital.

BACKGROUND Carotid angioplasty and stenting has been suggested to be as effective as CEA for treatment of symptomatic carotid artery stenosis.

METHODS A total of 104 patients presenting with cerebrovascular ischemia ipsilateral to carotid stenosis were selected randomly for CEA or carotid stenting and followed for two years.

RESULTS Stenosis decreased to an average of 5% after CAS. The patency of the reconstructed artery remained satisfactory regardless of the technique as determined by sequential ultrasound. One death occurred in the CEA group (1/51); one transient ischemic attack occurred in the CAS group (1/53); no individual sustained a stroke. The perception of procedurally related pain/discomfort was similar. Hospital stay was similar, although the CAS group tended to be discharged earlier (mean = 1.8 days vs. 2.7 days). Complications associated with CAS prolonged hospitalization when compared with those sustaining a CEA-related complication (mean = 5.6 days vs. 3.8 days). Return to full activity was achieved within one week by 80% of the CAS group and 67% of the patients receiving CEA. Hospital charges were slightly higher for CAS.

CONCLUSIONS Carotid stenting is equivalent to CEA in reducing carotid stenosis without increased risk for major complications of death/stroke. Because of shortened hospitalization and convalescence, CAS challenges CEA as the preferred treatment of symptomatic carotid stenosis if a reduction in costs can be achieved. (J Am Coll Cardiol 2001;38:1589–95) © 2001 by the American College of Cardiology

The efficacy of endarterectomy for the treatment of patients with symptomatic high-grade stenosis of the extracranial carotid artery has been established through a series of randomized, controlled trials (1–4). The absolute reduction in the occurrence of cerebral ischemic events is dependent, however, on perioperative complication rates (5,6). A combined stroke (major or minor) and death rate exceeding 6% for patients with symptomatic stenosis eliminates the benefit of stroke reduction gained through operation. Although varying according to operator and hospital experience (7), the overall incidence of major disabling stroke approaches 2% with mortality rates of <1% (8,9), thereby supporting the therapeutic advantages of carotid endarterectomy (CEA) in treating symptomatic carotid stenosis. Despite this reduction in serious complications, CEA has limitations (10–14). Minor strokes and/or complications remain significant and can be disabling. Cranial or cervical nerve palsies occur in 7.6% to 27% of patients undergoing CEA (15–17). Complications associated with concurrent cardiac disease and hypertension occur perioperatively in about 8% of patients (18). In addition, individuals with contralateral carotid occlusion or advanced coronary vascular disease are considered poor candidates for CEA (1,19–22). Other well-known anatomical considerations, which increase morbidity and mortality, include the presence of an extremely high carotid bifurcation (C1 to C2), tracheotomy, recurrent stenosis after previous CEA and radical neck dissection with or without radiation-induced carotid stenosis.

See page 1596

The advent of percutaneous endovascular techniques has the potential for being safer, less traumatic and more cost-effective in patients with symptomatic carotid occlusive disease. The therapeutic advantage of carotid angioplasty and stenting (CAS) has been demonstrated in patients with contralateral occlusion, restenosis and surgically inaccessible lesions (23–25). Although it has been suggested that CAS is an acceptable (26–30), if not preferred, alternative to CEA, the clinical experience has been less enthusiastic. Data accrued from various centers report a major stroke and death rate of 4.7% after CAS (30). Others report a "minor" stroke rate associated with CAS of 6.5% compared with a CEA-related risk of 0.6% (31). Although these complications may be lessened through operator experience after an as yet to be

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Abbreviations and Acronyms

ACT	= activated clotting time
CAS	= carotid angioplasty and stenting
CEA	= carotid endarterectomy
CVA	= cerebral vascular accident
MRI	= magnetic resonance imaging
NIH	= National Institute of Health
NASCET	= North American Symptomatic Carotid Endarterectomy Trial
TIA	= transient ischemic attack

defined "learning curve" and optimal patient selection, the theoretical benefits of endoluminal revascularization in treating symptomatic or asymptomatic carotid stenosis have not been realized fully or documented in randomized comparative trials. Indeed, the only published randomized study of CAS versus CEA was stopped because of the occurrence of strokes, three of which were considered major, in five of the seven patients who underwent CAS (32).

The purpose of this prospective, randomized trial was to compare the efficacy and benefits of CAS with CEA in the treatment of symptomatic carotid stenosis in a community hospital.

METHODS

This two-arm randomized clinical trial was approved by the Institutional Review Board to include patients experiencing symptoms and/or signs of cerebral ischemia confined to the ipsilateral internal carotid artery. All patients were informed that the Food and Drug Administration has not approved deployment of stents within the carotid artery for the treatment of carotid stenosis. Patients with symptoms of vertebral-basilar insufficiency or intracranial occlusive disease shown by cerebral angiography were excluded. The inclusion criteria included those sustaining events confined to the carotid circulation within three months of evaluation; >70% stenosis of the ipsilateral carotid bifurcation as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (33); anticipated life expectancy of five years; willingness to complete treatment within two weeks and ability to sign informed consent. Exclusion criteria included: National Institute of Health (NIH) stroke scale of >4; cardiac arrhythmia; allergy and/or sensitivity to aspirin, heparin, ticlopidine or clopidogrel; history of bleeding diathesis or coagulopathy or history of intracranial hemorrhage within two months of randomization. A total of 104 individuals met these criteria, agreed to participation and were selected randomly to undergo CEA (51 individuals) or CAS (53 individuals). The presence of contralateral total occlusion and/or the angiographic appearance of the stenotic lesion were not factors in treatment selection. All patients received 325 mg aspirin and 75 mg clopidogrel before CAS or CEA. A neurologist (T. C.) and the research clinical nurse coordinator (L. B.) provided independent oversight and neurologic examination before and subsequent to each procedure.

Carotid endarterectomy was performed using standard operative techniques under general anesthesia with intraoperative electroencephalogram monitoring. All patients were observed in intensive care for 24 h.

Carotid angioplasty and stenting was performed using a standard percutaneous retrograde femoral approach via an 8F Super-S Arrowflex sheath (Arrow International, Inc., Reading, Pennsylvania). After heparinization with 100 μ/kg, carotid angiography was performed with a 5F/125-cm VTK (Cook, Inc.) catheter over a 0.035-in angled-tip glide wire. Subsequent to guiding angiography, an 0.18-in Steel-core wire (Guidant-ACS, Inc., Indianapolis, Indiana) was placed in the external carotid artery for support. The Arrowflex sheath then was advanced over either the VTK catheter or the Arrowflex dilator into the common carotid artery. Activated clotting time (ACT) was maintained >300. Distal protection was not used in any case. Although not routinely used, ReoPro (0.25 mg/kg bolus over 20 min followed by a continuous infusion of 0.125 μg/kg/min for 12 h to a maximum of 10 μg/min) was administered to three individuals who sustained cerebral vascular accidents (CVA) with persistent defects (NIH < 4) associated with ulcerative lesions and possible residual thrombus. In all cases, the stenosis was crossed using a 0.014-in Sport wire (Guidant-ACS, Inc.) and placed in the petrous portion of the internal carotid artery. All stenoses were predilated with a 4.0 × 20 mm Symmetry balloon (Medi-Tech, BSC, Inc.) inflated to 8 atms for 5 s before placement of a 10 × 20 mm Wallstent (Boston Scientific, Inc.). Postdilation was completed with an appropriately sized balloon meeting a balloon:artery ratio of 1:1 by visual estimate. Pan cerebral angiography was performed before withdrawal of the Arrowflex sheath from the common carotid artery.

A 6F femoral venous sheath was placed at the initiation of the procedure for placement of a temporary pacemaker if bradycardia was observed. Systolic arterial pressure was maintained between 120 mm Hg to 160 mm Hg throughout the procedure. All patients were admitted and observed in the neurovascular intensive care for 24 h. The sheaths were removed when the ACT was <170.

Carotid duplex scanning was performed within 24 h of either procedure and at 1, 3, 6, 12 and 24 months and expressed as the ratio of internal carotid artery/common carotid artery velocity. Sequential neurologic examinations, Rankin and Barthel scorings were performed concurrent with Duplex scanning. Magnetic resonance imaging (MRI) was obtained at 6 and 12 months to detect the presence of asymptomatic ischemic events in the distribution of the treated vessel (34).

Perception of pain was assessed in accordance with guidelines commissioned by the Agency for Health Care Policy and Research (35). No specific posthospitalization instructions were provided in reference to activities; each individual determined return to "full activity."

Table 1. Baseline Characteristics of Study Patients

	CAS (n = 53)	CEA (n = 51)
Mean age (yrs)	66.4 (36–78)	69.6 (56–81)
Presenting symptom		
Stroke (NIH < 4)	9	8
Transient ischemia	32	33
Amaurosis fugax	12	10
Risk factors		
Hypertension	45	48
Diabetes mellitus	19	12
Cholesterol (>200)	34	24
Smoking	38	40
>2 risk factors	38	32
Coronary vascular disease	39	31
Family history		
Stroke	27	31
Cardiac disease	48	48

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

Hospital variable costs included operating room or catheterization laboratory, nursing, pharmacy, laboratory and radiology. Professional charges were not assessed for stenting; hence, no physician's fees were included in determination of any costs or charges. Costs/charges for the single patient requiring amputation necessitated by complications attendant with femoral artery access were not included.

Results are expressed as average ± SEM. Statistical comparisons were performed using Student *t* test. Two-way repeated measures of analysis of variance were used to compare sequential testing of carotid duplex scanning. A p value of <0.05 was considered statistically significant.

RESULTS

Demographics. The inclusion criteria, average ages and numbers of men and women of those randomized for CEA or CAS were similar (Table 1). The most common presenting event was a TIA. Those sustaining a CVA were functionally independent (NIH scores of <4 and Barthel Index >90). No patient experienced speech or comprehension dysfunction. Risk factors for stroke included hypertension, elevated cholesterol, smoking and diabetes. More than two risk factors were observed in more than 50% (70/104) of patients.

Results of treatment. Most patients (87/104) were treated within one month (range: 7 to 42 days.) of the presenting symptom. All received definitive treatment by six weeks. Diagnostic cerebral angiography indicated the average pretreatment stenosis in the CEA group (88.2 ± 13.2%) to be similar (p > 0.05) to the CAS group (82.4 ± 7.1%). The mean cross-sectional diameter as determined by the greatest stenosis observed on anteroposterior, lateral or oblique angiographic view was 1.6 ± 1.1 mm (range: 0.8 mm to 2.4 mm) in the CAS group and 1.7 ± 0.46 mm (range: 1.0 mm to 3.0 mm) in those undergoing CEA. The contralateral, asymptomatic carotid artery was found to have <50% stenosis in 70/104 patients, although total occlusion

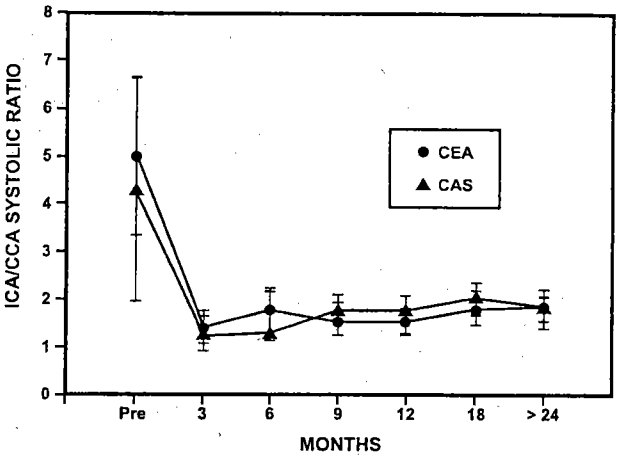

Figure 1. Patency of carotid artery before revascularization and after 3, 6, 9, 12, 18 and >24 months expressed as average internal carotid artery/common carotid artery (ICA/CCA) systolic ratio. CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

was observed in five and two individuals undergoing CAS or CEA, respectively. The average postangioplasty and stenting stenosis decreased to 5.0 ± 2.7% (range: 0% to 10%). The 24-month patency of the reconstructed artery remained satisfactory as determined by carotid ultrasound (Fig. 1). No MRI evidence of asymptomatic focal cerebral ischemia was found in any patient (data not shown).

Complications. No patient sustained a CVA, although one individual died from an immediate postoperative myocardial infarction subsequent to CEA (Table 2). This was the only procedurally related mortality experienced during this study. One patient experienced transient confusion associated with left sensory loss subsequent to postdilation of the stent that resolved within 10 min with elevation of the systolic blood pressure. Complications associated with CEA included wound hematoma requiring re-exploration (one patient) and peripheral nerve injury manifest as hoarseness (one patient) or lower facial and diminished sensations in the neck (three patients). These nerve injuries resolved within three months.

The most common occurrence associated with CAS was transient bradycardia (7/53) and/or hypotension (12/53) concurrent with angioplasty as a result of carotid body stimulation. None persisted more than 24 h. Initially, a

Table 2. Complications

	CAS	CEA
Death/cerebral ischemia		
Death	0	1
Stroke	0	0
Transient cerebral ischemia	1	0
Other		
Arterial thrombosis/amputation	1	0
Hematomas requiring treatment	3	1
Cranial/cervical nerve injury	0	4
Bradycardia (temporary pacing)	7	0
Hypotension (requiring treatment)	12	3

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

Table 3. Days Length of Hospital Stay*

	CAS	CEA
All patients	5.2 ± 11.4 days (1–68)†	3.7 ± 3.1 days (1–14)
Without complications	1.8 ± 0.58 days (1–4)	2.7 ± 1.2 days (1–13)
With complications	13.3 ± 21 days (3–68)†	3.8 ± 3.5 days (1–14)

*Avg ± SEM (range); †Exempting the single patient with major vascular complication, overall length of stay for CAS = 2.6 ± 1.6 days. Average length of stay for patients undergoing CAS who experienced other complications = 5.6 ± 3.7 days (3–11).
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

temporary pacemaker was inserted prophylactically. However, in efforts to contain cost and due to infrequent use, this has been abandoned. Currently, severe and/or prolonged bradycardia and/or flux in blood pressure were treated pharmacologically. These events are anticipated and frequently resolve without treatment. Complications associated with CAS were contingent with femoral artery access similar to other routine interventional approaches used for coronary artery disease (36). Retroperitoneal hemorrhage occurred in the three patients who received the platelet IIb/IIIa receptor antibody, abciximab (ReoPro, Eli Lilly and Co., Indianapolis, Indiana) in conjunction with heparin. This complication can be avoided by adhering closely to recommendations for the use of heparin with this monoclonal antibody provided by the Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome with Abciximab Glycoprotein IIa/IIIb Blockade (EPILOG) protocol (37). One individual with previously undiagnosed advanced generalized peripheral vascular occlusive disease sustained popliteal artery thrombosis, which necessitated below-the-knee amputation. This was the only major complication in the CAS group.

Length of hospital stay. The length of hospitalization was similar for both groups, although those undergoing CAS without complication tended to be discharged sooner (Table 3). As the study progressed, patients in the CEA group remained in the hospital for shorter periods, most being discharged the day after surgery. Forty-four patients (44/53) in the CAS group (83%) and 34 patients (34/51) in the CEA group (67%) were discharged from the hospital the day after the procedure. Excluding the single patient requiring below-the-knee amputation whose hospitalization extended to 68 days, overall hospital stays tended to be shorter in the CAS group (2.6 ± 1.6 days vs. 3.7 ± 3.1 days). Nevertheless, complications prolonged hospital care slightly more in the CAS group (5.6 ± 3.7 days vs. 3.8 ± 3.5 days). The primary complication associated with CAS was related to femoral artery access (3/53), which prolonged hospitalization because of continued bed rest and/or transfusion. Cranial/peripheral nerve injuries associated with CEA (4/51) did not prolong hospitalization. Hospitalization was extended secondary to concurrent or subsequent coronary bypass surgery in five patients. This procedure added an average of 10 ± 2 days to hospitalization. Neither CAS nor CEA afforded an advantage in terms of shortened stay in this small group of patients.

Patient's perception of pain and return to activity. The perception of pain was similar in both groups; neither experienced pain beyond a rating of 5/10 (Table 4). Most symptoms resolved by one month. Return to full activity was achieved within one week by 43 of the 53 patients undergoing CAS and 34 of the 51 patients randomized to CEA. All individuals in the CEA group resumed full activity by one month. However, complications in the CAS group significantly prolonged convalescence (57 to 120 days).

Cost/charges. Variable costs reflect the actual expenditures of performing a specific procedure, thus provide an accurate accounting of CEA and CAS. The total variable costs associated with CAS and CEA are similar ($p = 0.89$) (Table 5). As anticipated, individual hospital costs and charges resulting from the occurrence of complications varied widely, although they were higher for the CAS group secondary to prolonged hospitalization. Charges to patients, which did not include any professional fees, were higher in the CAS group ($p = 0.01$).

DISCUSSION

Endovascular technology has advanced to include treatment of carotid occlusive disease (23,24,26–29,38). Although proponents suggest that stenting may be effective in reducing carotid stenosis, its use has been recommended without testing its "clinical equipoise" (39) against the standard of care, endarterectomy. The single published randomized study designed to address this issue was suspended because of significant numbers of disabling strokes associated with

Table 4. Perception of Perioperative Pain and Activity

	CAS	CEA
Pain scale (0–10)		
24 h postprocedure (avg)	1.2 (range 0–5)	2.7 (range 0–5)
1 month postprocedure	<1.0 (0–4)	<1.0 (0–4)
Return to full activity (average days)		
Without complication	12 days (2–30)	16 days (7–30)
With complications	120 days (57–140)	21 days (9–30)

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

Table 5. Comparison of Variable Costs/Patient Charges*

	Total Costs	Nursing Costs	Cath/OR Lab	Pharmacy Costs	Lab Costs	Radiology Costs	Charges (Excluding Doctor Fees)
CAS	4,077 ± 460	327 ± 39	3,550 ± 286	66 ± 16	81 ± 26	105 ± 11	6,653 ± 367
CEA	3,415 ± 1,289	1,187 ± 101	1,159 ± 359	470 ± 229	79 ± 41	108 ± 58	5,594 ± 166

*Expressed as Avg ± SEM.
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; OR = operating room.

stenting (32). Other multicenter prospective, randomized trials comparing CAS with CEA have been suspended (40) or have yet to be initiated (41). This report presents initial observations of a clinical trial designed to investigate the safety and effectiveness of carotid stenting compared with CEA in treating symptomatic carotid occlusive disease in a community hospital.

Equipoise of stenting and endarterectomy. Our results agree that carotid stenting is equally as effective as CEA in correcting and maintaining postprocedure patency of carotid stenosis (24,26,28,42). Equipoise is further supported by MRI, indicating that no asymptomatic ischemic events occurred in the distribution of the treated vessel subsequent to either revascularization technique (data not shown). The occurrence of major or minor stroke or death associated with CAS or CEA was well within the limits of acceptable risk delineated by the NASCET (1,4) and Asymptomatic Carotid Arteriosclerosis study (43) yet markedly differed from previous reports of nonrandom series indicating a risk for major or minor stroke associated with CAS approaching 6% (31). Although the "learning curve" for CAS is about 50 cases (31,42), the occurrence rates for serious complications in series involving an excess of 100 patients is higher than those associated with CEA (26,28,31,43,44). The low number of neurologic complications observed in this trial reflects a "cerebral endovascular team" comprised of neurosurgeons possessing skills in endarterectomy and catheter-based techniques, experienced interventional cardiologists and neurologists.

Economic issues of carotid stenting versus endarterectomy. Economic evaluation of stroke prevention and treatment is an important factor in the heath care sector (45–47). Thus, the deference toward evidence-based medicine now includes a demand for "cost-effectiveness" of new and existing technologies. This trial addresses these issues as characterized by length of hospital stay, the return to full activity, patient's perception of pain associated with the procedure and hospital costs. The occurrence of major or minor stroke was not observed in this trial regardless of the revascularization procedure. Thus, in contradistinction to Jordan et al. (31), these cerebrovascular complications cannot be deployed in an economic argument favoring CEA over CAS. Initially, stenting resulted in a shortened hospital stay with most patients being discharged within 24 h. However, based on our experience and that of others, that complications associated with endarterectomy occur within 6 h, a growing tendency toward shorter hospitalization after CEA has evolved (48–50). Most patients undergoing CEA are discharged within 24 h. Although, the theoretical advantage of "early" hospital discharge supposed through percutaneous technology has yet to be determined, hospital stay subsequent to CAS may be lessened in the future through miniaturization of technology and routine use of arterial closure devices.

As expected, hospitalization is prolonged by procedural complications. Cranial or peripheral nerve injury or neck hematomas that are rapidly recognized and appropriately treated do not influence hospital stay (1,16); however, the occurrence of clinically significant retroperitoneal hemorrhage does prolong hospitalization (36). Although anticoagulation is necessary, the paradigm used in stenting probably can be lessened because most cerebral ischemic events are associated with post-stent dilation, at which time atheromatous material may be released from the arterial wall rather than hematologic emboli (51). Routine use of distal protection devices in conjunction with less anticoagulation may reduce the risk of both excessive retroperitoneal and intraprocedural ischemic events. However, the addition of distal protection devices designed to prevent cerebral embolization of atheromatous material actually may increase cost/charges.

The evaluation of pain and return to full activity also judges the economic efficiency of a procedure. The frequent bias that "open" surgical techniques are less well tolerated in terms of pain and discomfort than percutaneous approaches is not supported by this trial. Both procedures seem equally well tolerated in terms of pain and discomfort. Moreover, return to full activity was achieved in about two weeks regardless of the procedure. However, return to full activity was delayed by complications particularly after CAS. Pain associated with groin complications is more limiting than those involving incisions in the neck in terms of active daily living.

Whereas, this study shows that the effectiveness of CAS is equivalent to CEA in terms of the ability to correct symptomatic carotid stenosis without increased risk for major or minor stroke, fiscal considerations tend to favor CEA (52). Although pharmacy and "routine" hospital costs and charges may be similar, expenditures associated specifically with cardiac catheterization laboratories compared with standard operating rooms are higher. Stents, angioplasty balloons, catheters, guiding wires, sheaths and the use of temporary pacemakers are costly and nonreusable. If the use of a distal protection device becomes a "standard of care," the costs will escalate further. These data suggest that, from a perspective of an economic evaluation, the potential

effect gained through percutaneous carotid stenting may be lessened by increased incremental cost/charges.

Study limitations. This trial is limited to a single institution, and a select "team" with experience in cerebral vascular disease and endovascular techniques, thus, cannot advocate that CAS replace CEA as a primary revascularization procedure in patients with symptomatic carotid stenosis. However, it is the first randomized prospective study to demonstrate that carotid angioplasty and stenting is equivalent to endarterectomy for the treatment of symptomatic carotid stenosis without added risk for major or minor stroke. If the economic constraints of incremental costs associated with stenting can be overcome, this trial indicates that CAS has reached clinical equipoise with CEA.

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In-stent recurrent stenosis after carotid artery stenting: Life table analysis and clinical relevance

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Objectives: **Carotid artery stenting has been proposed as an alternative to carotid endarterectomy in cerebral revascularization. Although early results from several centers have been encouraging, concerns remain regarding long-term durability of carotid artery stenting. We report the incidence, characteristics, and management of in-stent recurrent stenosis after long-term follow-up of carotid artery stenting.**

Methods: **Carotid artery stenting (n = 122) was performed in 118 patients between September 1996 and March 2003. Indications included recurrent stenosis after previous carotid endarterectomy (66%), primary lesions in patients at high-risk (29%), and previous ipsilateral cervical radiation therapy (5%). Fifty-five percent of patients had asymptomatic stenosis; 45% had symptomatic lesions. Each patient was followed up with serial duplex ultrasound scanning. Selective angiography and repeat intervention were performed when duplex ultrasound scans demonstrated 80% or greater in-stent recurrent stenosis. Data were prospectively recorded, and were statistically analyzed with the Kaplan-Meier method and log-rank test.**

Results: **Carotid artery stenting was performed successfully in all cases, with the WallStent or Acculink carotid stent. Thirty-day stroke and death rate was 3.3%, attributable to retinal infarction (n = 1), hemispheric stroke (n = 1), and death (n = 2). Over follow-up of 1 to 74 months (mean, 18.8 months), 22 patients had in-stent recurrent stenosis (40%-59%, n = 11; 60%-79%, n = 6; ≥80%, n = 5), which occurred within 18 months of carotid artery stenting in 13 patients (60%). None of the patients with in-stent recurrent stenosis exhibited neurologic symptoms. Life table analysis and Kaplan-Meier curves predicted cumulative in-stent recurrent stenosis 80% or greater in 6.4% of patients at 60 months. Three of five in-stent recurrent stenoses occurred within 15 months of carotid artery stenting, and one each occurred at 20 and 47 months, respectively. Repeat angioplasty was performed once in 3 patients and three times in 1 patient, and repeat stenting in 1 patient, without complications. One of these patients demonstrated asymptomatic internal carotid artery occlusion 1 year after repeat intervention.**

Conclusions: Carotid artery stenting can be performed with a low incidence of periprocedural complications. The cumulative incidence of clinically significant in-stent recurrent stenosis (≥80%) over 5 years is low (6.4%). In-stent restenosis was not associated with neurologic symptoms in the 5 patients noted in this cohort. Most instances of in-stent recurrent stenosis occur early after carotid artery stenting, and can be managed successfully with endovascular techniques. (J Vasc Surg 2003;38:1162-9.)

Carotid artery stenting (CAS) has emerged as an alternative to repeat operation in the management of recurrent stenosis after previous carotid endarterectomy (CEA).[1,2] This approach has also been suggested for management of other subgroups, including patients with significant medical comorbid conditions, anatomically inaccessible lesions above C2, and radiation-induced stenosis.[3] Endovascular management of these high-risk subsets has been recommended on the basis of acceptable immediate postprocedural complications, and results of short-term follow-up from single-institution[1,2] and industry-sponsored trials[4] (M. H. Wholey, 2003, personal communication).

However, concerns remain regarding long-term durability of carotid artery stenting. The incidence of postprocedural in-stent restenosis ranges from 1% to 50% in published reports.[5-9] The reported rate of in-stent recurrent stenosis (ISR) depends on the definition of recurrent stenosis, duration of follow-up, and methods of diagnosis and calculation used. Most studies have had relatively short follow-up periods (≤12 months),[8-10] and report absolute recurrence rates weighting each procedure equally, regardless of duration of follow-up. This may result in underreporting of ISR stenosis rates. The current study was undertaken to prospectively determine the incidence, characteristics, and significance of ISR after long-term follow-up of carotid artery stenting. Rates of ISR to any degree were determined with life-table analysis to more accurately reflect recurrence relative to the population at risk at each interval of observation.

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METHODS

Patients. Carotid artery stenting (n = 122) was performed in 118 consecutive patients between September 1996 and March 2003 in an endovascular suite. These procedures were performed as part of an institutional review board–approved program in CAS. Patients with symptomatic carotid stenosis 50% or greater and asymptomatic carotid stenosis 80% or greater were considered for this protocol. Eligibility was further determined on the basis of criteria established at a consensus conference,[3] including recurrent stenosis after previous CEA; primary lesions in patients with significant medical comorbid conditions, such as coronary artery disease requiring angioplasty or bypass grafting that has not or cannot be revascularized, history of congestive heart failure, current ejection fraction 30% or less, steroid-dependent chronic obstructive pulmonary disease, or measured 1-second forced expiratory volume 30% or less; primary lesions anatomically inaccessible at surgery; and primary lesions with previous ipsilateral cervical radiation therapy.

Clinical protocol and follow-up. Patients were referred to the program after findings at history, physical examination, and duplex ultrasound (US) scanning confirmed eligibility for participation. Clinical, angiographic, and procedural data were prospectively collected. Angiographic stenosis was determined with criteria of the North Atlantic Symptomatic Carotid Endarterectomy Trial.[11] In-stent least luminal diameter was compared with the distal nontapering portion of the internal carotid artery serving as the reference segment. Postprocedure clinical examination and duplex US scanning were performed before discharge, to confirm stent patency and position and to establish a baseline. Each patient was subsequently followed up with serial and clinical evaluation at 6-month intervals. Technical failure was defined as inability to access or treat the lesion, or residual stenosis 20% or greater after CAS. Patients were assessed for neurologic complications at each visit, including amaurosis fugax (focal retinal deficit resolved in 4 hours), transient ischemic attack (TIA; focal hemispheric deficit resolved in <24 hours), and stroke (focal hemispheric deficit lasting ≥24 hours).

All duplex US scanning was performed at the same Intersocietal Commission on Accreditation of Vascular Laboratories (ICAVL)–approved vascular laboratory. Velocity criteria used to identify individual categories of stenosis have been validated in our laboratory and are based on a modification of the University of Washington criteria[12]: peak systolic velocity (PSV) less than 130 cm/s, 0% to 39%; PSV 130 to 210 cm/s, 40% to 59%; PSV 210 to 300 cm/s with end-diastolic velocity less than 120 cm/s, 60% to 79%; PSV greater than 300 cm/s and end-diastolic velocity greater than 120 cm/s, or internal carotid to common carotid artery systolic velocity ratio greater than 3.2, 80% to 99%. Clinically significant recurrent stenosis was defined as any ISR of 80% or greater. These recurrent stenostic lesions were further evaluated with selective angiography, and repeat intervention was performed when ISR was confirmed to be 80% or greater. Endovascular repeat intervention was offered to all patients with ISR 80% or greater. The procedure followed the same protocol as the primary intervention. However, angioplasty alone was preferred, with additional stenting performed if results were suboptimal (residual in-stent recurrent stenosis ≥20%). Patients were followed up at 3-month intervals for the first year, and every 6 months thereafter.

Carotid artery stenting protocol. The protocol used for performing CAS has been described in detail by our group.[1,5,13] In brief, all patients received aspirin, 325 mg once a day, and clopidogrel, 75 mg twice a day, for 2 days before the procedure. The procedure was performed with the patient under local anesthesia without sedation. Heparin was administered to achieve an activated clotting time of 250 to 300 seconds. Access was achieved through the common femoral artery, and the left brachial artery in one procedure. Digital angiography was performed to verify the severity of stenosis. Intracerebral views were obtained to establish baseline cerebrovascular anatomy. Self-expandable stents were used in all but four procedures, in which short balloon-expandable stents were used early in our experience. Stenoses were crossed with 0.018-inch Roadrunner extra-support guide wires (Cook Inc, Bloomington, Ind) for the WallStents (Meditech/Boston Scientific, Minneapolis, Minn), and 0.014-inch guide wires (Hi-Torque Floppy; Guidant, Menlo Park, Calif) for the Acculink carotid stents (Guidant). An antiembolic filter device (Accunet; Guidant) was used in all cases in which the Acculink stent was delivered. On completion, ipsilateral cervical and intracranial carotid angiography was performed to assess technical success and to exclude distal cerebral embolization. Post-procedure, patients were monitored in an intermediate care facility overnight, and were discharged the next morning. Clopidogrel was continued for 4 weeks, and aspirin indefinitely.

Statistical analysis. Data are expressed as mean ± SD. Thirty-day stroke and death rates and minor neurologic complication rates after CAS in patients with post-CEA recurrent stenosis versus primary lesions were compared with the Fisher exact test. Time to ISR was analyzed with life-table methods and Kaplan-Meier curves. Differences in ISR rates between symptomatic versus asymptomatic lesions, post-CEA recurrent stenosis versus primary lesions, and WallStents versus Acculink stents were assessed with log-rank statistics.

RESULTS

Patient characteristics. Carotid artery stenting procedures (n = 122) were performed in 118 patients between September 1996 and March 2003 in a dedicated endovascular suite. Fifty-five percent of patients had asymptomatic stenosis; 45% had symptomatic lesions. Indications for carotid artery stenting included recurrent stenosis after previous CEA (66%), primary lesions in high-risk patients (29%), and previous ipsilateral cervical radiation therapy (5%). Clinical characteristics are presented in Table I.

Table I. Patient characteristics

	n	%
Total patients	118	
Total procedures	122	
Age (y) (mean ± SD)	70 ± 9	
Female gender	52	43
Type of lesion		
Asymptomatic carotid stenosis	67	55
Symptomatic carotid stenosis	55	45
Amaurosis fugax	4	3
Transient ischemic attack	27	22
Stroke	24	20
Severity of stenosis (%) (mean ± SD)	86 ± 8	
Indication for carotid artery stenting		
Post-CEA recurrent stenosis	80	66
Previous ipsilateral cervical radiation	6	5
CAD that has not or cannot be revascularized	30	25
CHF or EF ≤ 30%	8	7
Steroid-dependent COPD or FEV_1 ≤ 30% of predicted	4	3
Comorbidity		
CAD	88	72
Hypercholesterolemia	78	64
Hypertension	106	87
Diabetes	44	36
Current or past smoker	45	37

CEA, Carotid endarterectomy; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *EF,* left ventricular ejection fraction; *COPD,* chronic obstructive pulmonary disease; *FEV,* forced exhaled volume in 1 second.

Thirty-day outcome of carotid artery stenting. The lesion was accessed and the procedure performed successfully in all cases, for a technical success rate of 100%. Mean stenosis treated was 86% ± 8%, and post-treatment mean residual stenosis was 9% ± 4%. WallStents were deployed in 72 procedures (59%), Acculink stents in 46 procedures (38%), and balloon-expandable stents in 4 procedures (3%) early in our experience. All Acculink stent deployments were performed with an antiembolic device (Accunet). No subintimal dissection, contrast material extravasation, arterial disruption, or conversion to open surgery were encountered. Overall 30-day stroke and death rate was 3.3%, and included one retinal infarction, one hemispheric stroke, and two deaths. One death occurred from a myocardial infarction 10 days after discharge, and the other from an intracranial hemorrhage. Minor neurologic events were noted in 7 patients, including TIA in 6 patients and amaurosis fugax in 1 patient, for a minor neurologic complication rate of 5.7%. Post-event computed tomography (CT) scans demonstrated no acute stroke, and duplex US scans demonstrated no carotid dissections or thromboses in patients with minor neurologic events. There were no significant differences between patients treated for post-CEA recurrent stenosis versus primary lesions in the 30-day stroke and death rates (n = 2 each; P = .61), incidence of minor neurologic events (n = 3 and n = 4, respectively; P = .23), or a combination of both (P = .19). Mean in-hospital length of stay was 1.7 ± 1 day.

Long-term follow-up. Over follow-up of 1 to 74 months (mean, 18.8 ± 10 months), 22 patients demonstrated ISR 40% or greater. None of these 22 patients had symptoms at presentation, and ISR was diagnosed at duplex US scanning during routine follow-up. Although recurrent stenotic lesions ranged from 40% to 99%, only 5 patients demonstrated clinically significant ISR (≥80%); of the remaining patients, ISR was 40% to 59% in 11 patients and 60% to 79% in 6 patients. The distribution of various ranges of ISR in the cohort at the end of follow-up are shown in Fig 1. Most recurrent stenosis 40% or greater occurred within 18 months of intervention (13 of 22, 60%), and most clinically significant recurrent stenosis 80% or greater occurred within 15 months (3 of 5, 60%; Fig 2).

On the basis of serial duplex US scans obtained after 122 procedures, 22 arteries had evidence of recurrent stenosis at the date of last follow-up; stenosis was clinically insignificant in 17 of these arteries, and clinically significant in 5, yielding absolute recurrence rates of 18.0%, 13.9%, and 4.1%, respectively (Fig 1). However, with cumulative

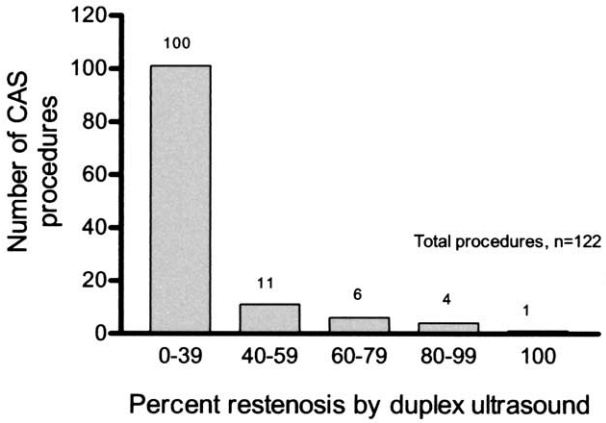

Fig 1. Distribution of various ranges of in-stent recurrent stenosis in the cohort at end of follow-up.

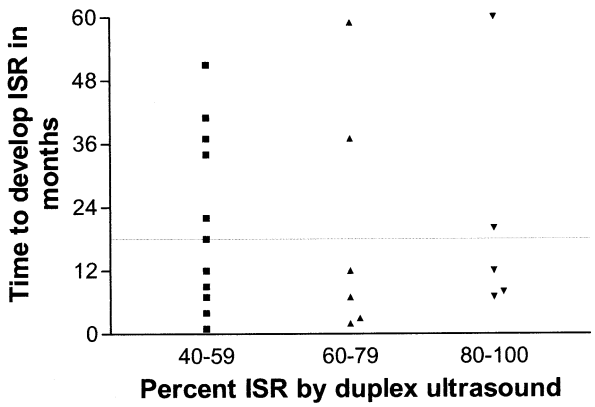

Fig 2. Time to development of in-stent recurrent stenosis. Most recurrent stenosis 40% or greater occurred within 18 months of intervention (13 of 22, 60%), and most clinically significant recurrent stenosis 80% or greater occurred within 15 months (3 of 5, 60%).

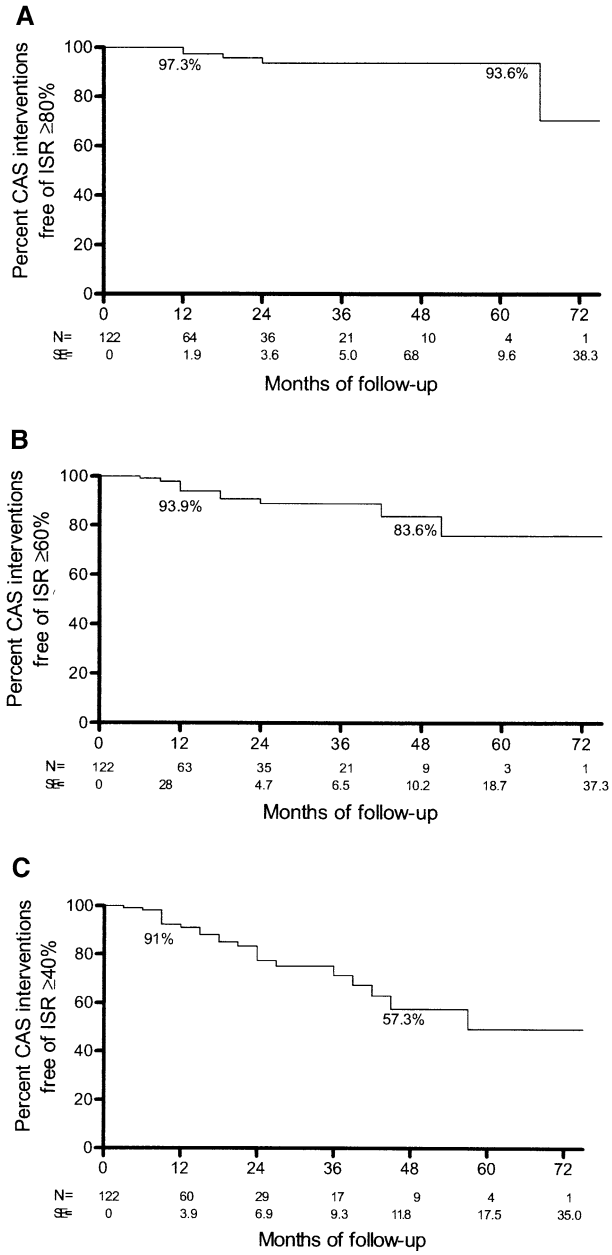

Fig 3. Cumulative life table analysis. **A,** Projected recurrence rates for 1 and 5 years were 2.7% and 6.4%, respectively, for clinically significant disease (in-stent recurrent stenosis ≥80%. Cumulative rates of in-stent recurrent stenosis 60% or greater at 1 and 4 years were 6.2% and 16.4%, respectively **(B)**, and of in-stent recurrent stenosis 40% or greater were 9.0% and 42.7%, respectively **(C)**.

life table analysis, projected recurrence rates for 1 and 5 years were 2.7% and 6.4%, respectively, for clinically significant disease (in-stent recurrent stenosis ≥80%; Fig 3, *A*; Table II, online only). Cumulative rates of in-stent recurrent stenosis 60% or greater at 1 and 4 years were 6.2% and 16.4%, respectively (Fig 3, *B*; Table III, online only), and of in-stent recurrent stenosis 40% or greater were 9.0% and 42.7%, respectively (Fig 3, *C*; Table IV, online only). Standard error was 10 or less for all results reported.

Log-rank statistics demonstrated no significant differences at 42 months in cumulative ISR (≥40%)–free rates between WallStents and Acculink stents (68.1% vs 72.3%; $P = .77$), presence or absence of preoperative neurologic symptoms (66.6% vs 75.9%; $P = .67$), and recurrent stenosis or primary carotid stenosis (71.8% vs 77.2%; $P = .93$). Similarly, log-rank statistics in this small cohort demonstrated that ISR rates were no different between male versus female patients, smokers versus nonsmokers, and patients with or without diabetes.

Management of in-stent restenosis. Patients with moderate ISR (40%-79%) were followed up with serial clinical evaluation and duplex US scanning at 3-month to 6-month intervals. The 5 patients with hemodynamically significant ISR (≥80%) underwent diagnostic angiography, which confirmed 80% or greater reduction in lesion diameter. Recurrences were located within or at the proximal or distal edge of the stent in all 5 instances. Patients were preferentially offered endovascular repeat intervention. Four lesions were successfully treated with repeat angioplasty, whereas one demonstrated a suboptimal response. A Palmaz stent (Cordis, Miami Lakes, Fla) was placed across this lesion to obtain a satisfactory result (<20% residual ISR). During follow-up 1 year later this patient had asymptomatic internal carotid artery occlusion. Three patients who underwent angioplasty alone have remained recurrence-free. One patient required two additional balloon angioplasty procedures over follow-up of 3 years, and is currently symptom-free, with duplex US scan–confirmed ISR of 40% to 59% that has been stable for 13 months. None of the patients have undergone surgical stent removal since initiation of our program in 1996.

DISCUSSION

The long-term outcome after CEA has been well-documented in several studies[14,15]; however, despite several thousand CAS procedures reported in the literature,[8] the long-term incidence of ISR remains ill-defined. In addition, the high incidence of recurrent stenosis after coronary stenting[16] and iliac angioplasty with stenting[17] has prompted several clinicians to question the durability of the CAS procedure. In-stent recurrent stenosis after carotid artery stenting has been reported as a relatively infrequent complication by some authors. Wholey et al[8] reported a rate of only 3.5%, Diethrich et al[18] defined a recurrent stenosis rate of 4.5%, Yadav et al[9] reported 4.9%, and Theron reported 4%.[10] In a previous report, we noted an incidence of 8%.[5] However, all of these reports were based on short follow-up.

With longer follow-up, and now with the use of life table analysis, we are able to report more informative data on ISR after carotid artery stenting. The life table method represents recurrences reported relative to the patient population at risk during a given interval of observation. These data therefore demonstrate all accumulated information

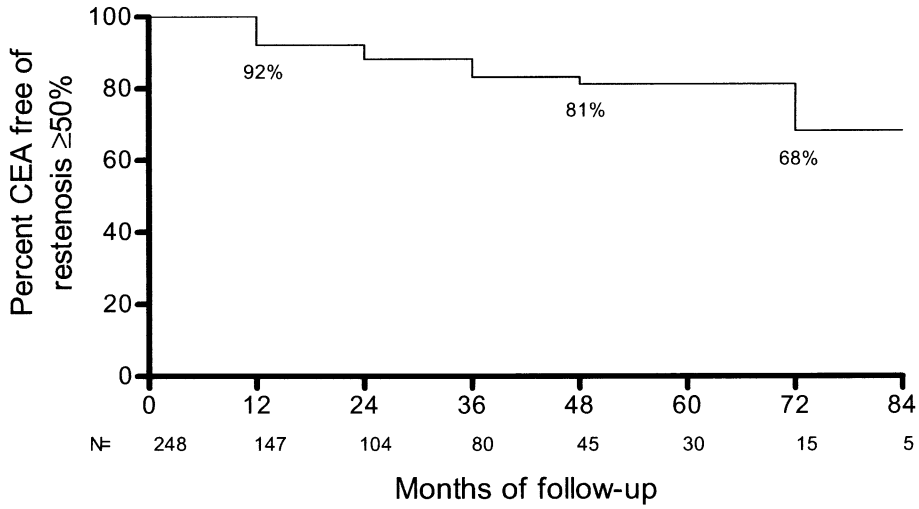

Fig 4. Life table incidence of recurrent stenosis 50% or greater was 19% at 48 months.

weighting the data in relationship to the duration of follow-up. Emphasis is placed on data at 60-month follow-up, when the incidence of arteries free of 80% or greater in-stent recurrent stenosis was 6.4% (Fig 3). Therefore the incidence of hemodynamically significant ISR is higher than the figures published in the literature, which were based on the short-term studies quoted above.

In addition, we demonstrate development of moderate degrees of ISR in several patients from this cohort. The incidence of ISR 40% or greater and 60% or greater was 42.7% and 16.4%, respectively, at 48-month follow-up. Our previously reported data on CEA (Fig 4) noted a life table incidence of recurrent stenosis 50% or greater to be 19% at 48 months.[14] Similar data regarding durability of CEA have been published by other groups.[15] Admittedly, historical data for CEA using duplex US scanning criteria for greater than 50% stenosis are not directly comparable with the current CAS follow-up data in which ICAVL-approved duplex US scanning criteria for stenosis 40% or greater and 60% or greater were used. However, it is clear that in a significant number of patients moderate in-stent recurrent stenosis will develop after carotid artery stenting, some of which will progress to high-grade stenosis. Information regarding this subgroup of moderate stenosis has not been emphasized in the literature. These data show the importance of life table assessment, and demonstrate that ISR is an on-going process that requires long-term follow-up. Our mean follow-up of 18.8 months (range, 1-74 months) is significantly longer than previously reported in the literature, and our current analysis enables a more realistic appraisal of ISR across ranges of 40% to 59%, 60% to 79%, and 80% to 99%. Our data provide reassurance that on life table analysis hemodynamically significant (≥80%) ISR after CAS was 6.4% at 5 years. While encouraging, this observation must be confirmed with a randomized comparison of the two procedures, such as is being conducted under the auspices of the National Institutes of Health (Carotid Revascularization and Endarterectomy vs Stent Trial [CREST]).[19] At our institution we have not used angiography to evaluate asymptomatic stenosis less than 80% by our ICAVL-approved vascular laboratory. Therefore patients with in-stent recurrent stenosis less than 80% did not undergo angiography. On the basis of these observations, we recommend close and frequent long-term duplex US scanning of all patients undergoing carotid artery stenting. Our own protocol includes clinical examination and duplex US scanning at 6-month intervals.

Of interest, ISR after carotid artery stenting was not associated with neurologic events. Recurrent stenosis after CEA also was associated with low rates of neurologic symptoms in several studies.[14,15] The absence of significant neurologic complications indicates that these are primarily myointimal hyperplastic lesions. While our analysis demonstrates that most of these lesions occur within the first 36 months of follow-up (Fig 2), some recurrent stenoses have been documented after longer follow-up and suggest the possibility of recurrent atherosclerotic plaque as a possible cause. In the absence of pathologic material, this assumption of myointimal hyperplasia occurring in the first 36 months, and atherosclerotic plaque thereafter, is based on previous reports.[20]

Patients with hemodynamically significant in-stent recurrent stenosis were treated successfully with further endovascular interventions, namely, angioplasty alone or in combination with stenting. Four of five lesions responded well to angioplasty alone, whereas one lesion required an additional stent. Embolic neurologic complications have been reported in some instances after endovascular treatment of ISR.[21] No periprocedural complications were noted in our series; however, one patient did have asymptomatic occlusion after 1 year. Surgical removal of a stent has not been required in this series; however, anecdotal reports in the literature suggest that this and other surgical procedures may be required in rare instances.[22,23] One

patient has required three balloon dilations to maintain arterial patency over 3 years. Notwithstanding the recommendations for conservative management of these asymptomatic lesions by some groups,[24] we suggest management of these high-grade stenoses with catheter-based techniques to prevent occlusion of the artery and possible neurologic complications.

There has been some speculation that CAS of recurrent stenotic lesions may be associated with higher rates of ISR secondary to stimulation of an already activated intimal hyperplastic lesion. In addition, stent material and physical properties have been hypothesized to influence recurrence rates.[16] The correlation of the degree of stent-induced injury to the vessel wall, with the extent of intimal hyperplasia, has been shown in experimental models.[16] Log-rank analysis of Kaplan-Meier curves for symptomatic versus asymptomatic lesions in this series did not demonstrate any significant differences in proportion of recurrence-free arteries. Similarly, there were no differences in recurrence-free survival observed between patients who received Wall-Stents versus Acculink stents, both of which are self-expanding stents. Balloon-mounted stents were deployed in too few instances in this series to compare them with self-expanding stents. No difference was noted in the proportion of recurrence-free arteries between patients treated for recurrent stenotic disease after CEA versus primary atherosclerosis. These results must be interpreted with caution, because a larger cohort may be required to unmask minor differences in long-term durability. Of interest, two separate industry- sponsored trials using two different stents (Acculink and Precise) have reported similar short-term complication rates of 30-day stroke, death, or myocardial infarction for both (7.8 vs 5.8%, respectively)[4] (M.H. Wholey, 2003, personal communication). Data for follow-up longer than 6 months and ISR rates are not available.

The ultimate value of CAS compared with CEA will be based on randomized clinical trials in North America (CREST[19]) and Europe (Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy [SPACE][25]). Within the next 2 to 3 years data will be available on the efficacy of these two procedures in treating primary extracranial carotid occlusive disease. Our study, comprising 66% post-CEA restenosis lesions, indicates that at long-term follow-up with life table analysis, the incidence of ISR after CAS is higher than that reported in the literature. We also demonstrate development of moderate degrees of ISR (40%-79%) in a significant number of patients. Both types of lesions tend to occur early in the course of follow-up, and may not be associated with neurologic complications. These findings suggest continuing use of carotid artery stenting under careful institutional review board supervision or in well-designed, well-controlled randomized studies in selected patients at high-risk.[3] They also emphasize the importance of regular duplex US scanning and clinical follow-up to monitor long-term complications.

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Additional material for this article may be found online at www.Mosby.com/jvs.

DISCUSSION

Dr Daniel Clair (New York, NY). I'd like to congratulate Dr Lal on an excellent presentation and the authors on a well-written paper addressing a topic that I believe most surgeons think has receive limited attention by nonsurgeons performing this procedure. I'd also like to thank the authors for supplying me with a copy of their manuscript for review.

I have several questions for the authors regarding their study. In terms of classification of the lesions, degree of stenosis with duplex ultrasound, are there any changes in specific duplex criteria that were utilized in patients evaluated with ultrasound in the poststenting situation?

It is clear that data generated from duplex evaluations have been confirmed in patients with primary carotid stenosis; however, the stents clearly alter the hemodynamics of the bifurcation and may affect classification of duplex ultrasound data in terms of the degree of stenosis. Were there any other evaluations done of these patients to confirm the degree of stenosis on the poststenting duplex evaluations?

Another question I have relates to standard errors (SEs) that were missing from the life table analysis at the 60-month time point. It was difficult with a mean follow-up of 18 months to get a sense of how meaningful the data at 60 months would be for this patient population without some form of SE bars on the life table analysis graphs.

Another question I have relates to information gained from this study in terms of the technique of carotid artery stenting. There are a limited number of patients who went on to have reintervention, and I'm sure those patients have had review of their initial angiographic data. Since the occurrences usually occurred at the stent end points, were there any abnormalities at the stent end points at initial stent placement? Specifically, were there problems with the stent-to-arterial wall coapctation in these regions, increased tortuosity, especially at the distal end points, or any other issues which may have altered the authors' techniques of carotid stenting in these patients?

Dr Brajesh K. Lal. In terms of changes in duplex ultrasound diagnostic criteria, the patients were scanned using the same criteria in our ICAVAL-approved laboratory. We have noticed changes in velocities in some of our patients and, in fact, are going to report a detailed analysis of this at the upcoming national meeting (Vascular 2003). We are revising our velocity criteria; however, our follow-up protocol also incorporates detailed B-mode scans in any patient identified as having restenosis on the basis of velocity criteria. Only then is the patient categorized as having a significant in-stent restenosis.

All the graphs clearly indicate the standard errors at the bottom. All the data reported at 60 months for 80% in-stent restenosis and at 48 months for the 60% and 40% in-stent restenoses are with standard errors less than 10. So they're all significant in that respect.

As far as the technique for reintervention is concerned, I agree with you: little has been written about it because very few of the physicians who have published on carotid stenting in large numbers have analyzed their incidence of in-stent restenosis, using life table analysis.

We chose to report our in-stent restenoses and discuss the technique and approach that we have used to try and open up a discussion on this fact. One of our patients, as we have described, went on to occlude after restenting. Another required 3 subsequent interventions to maintain arterial patency and is currently at 40% to 59% in-stent restenosis. So when do we call a halt and operate on these patients? These are issue that still need to be studied, reported, and debated.

Dr Ali F. AbuRahma (Charleston, WV). I'd like to emphasize a point, which I hope the author includes in the paper prior to submitting it to the *Journal of Vascular Surgery*, since the study will be quoted by many of our nonsurgical colleagues in North America. As the author indicated, a significant number of his patients have stenoses of >80%; as a matter of fact, you have a total of 14 patients with stenoses of 40% to 60% and 60% to 80% in this group. Can you imagine if the follow-up were longer? Some of these patients could have progressed to ≥80%. Therefore, perhaps the paper should emphasize the fact that even though the numbers of patients with stenoses of ≥80% was somewhat low at 18 months, this number could increase if the follow-up was longer.

Dr Lal. We agree on the importance of long-term follow-up. We have emphasized that there are several patients with in-stent restenosis who have not approached the hemodynamically significant (80%) limit That is why this study incorporated reporting on the 60% and the 40% in-stent restenosis rates. These patients do require longer follow-up and there's more to the story that may evolve later. Most of the publications on in-stent restenosis after CAS are on short-term follow-ups, with reporting of 80% restenosis. The current study identifies the entire range of restenoses.

Dr Bruce Perler (Baltimore, Md). My question relates to the obvious dramatic improvement in outcome in your center. As I recall Dr Hobson's earlier report, which you cited, at 1 year the rate of >80% restenosis was 8%. And now you're telling us that at 5 years the rate of 80% restenosis is about 6.5%. So I wonder whether that initial cohort of 50 patients was included in this series of 100+ cases. And whether it was or wasn't, might you speculate on why the long-term durability has gotten so much better? I could see periprocedural morbidity improving with experience, but I'm not sure I understand why the durability would improve. Is there a change in your selection of stent, change in technique, or some other cause?

I ask because, as the other speakers have said, there clearly are other series reporting much more dramatic rates of restenosis, such as CAVATAS, where at 1 year a severe restenosis or occlusion occurred in, I believe, 23% of patients, and other series support that. So why are your results becoming so much more durable? How have you changed what you're doing?

Dr Lal. To answer your last question first, in CAVATAS the majority of patients were treated with angioplasty alone, and carotid stenting was a rescue procedure that occurred in only 25% of the patients. That may explain the high restenosis rates in that study. After the four restenoses noted in our first 50 patients, there

Carotid artery stenting: Analysis of data for 105 patients at high risk

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Objectives: **Carotid artery stenting (CAS) has been recommended as an alternative to carotid endarterectomy (CEA) by some clinicians. However, recently published clinical trials have reported 30-day stroke and death rates of 10% to 12%. This prompted review of our experience with CAS in patients at high risk, to document our results and guide further use of CAS.**

Methods: **From September 1996 to the present, we performed 114 consecutive CAS procedures in 105 patients. Sixty-three patients were men (60%) and 42 patients were women (40%), with mean age of 70 years (range, 45-93 years). Indications for CAS included recurrent stenosis after previous CEA in 74 patients (65%), primary lesions in 32 patients at high risk (28%), and carotid stenosis with previous ipsilateral radiation therapy in 8 patients (7%). Asymptomatic stenosis (>80%) was managed in 70 patients (61%), and symptomatic lesions (>50%) were treated in 44 patients (39%).**

Results: **CAS was technically successful in all patients. Mean severity of stenosis before CAS was 87% ± 6%, compared with 9% ± 4% after CAS. Two patients (1.9%) died, 1 of reperfusion–intracerebral hemorrhage and 1 of myocardial infarction 10 days after discharge; and 1 patient (0.95%) had a stroke (retinal infarction), for a 30-day stroke and death rate of 2.85%. Two patients (1.9%) had transient neurologic events. No cranial nerve deficits were noted. No neurologic complications have been noted in the last 27 patients (26%).**

Conclusions: **A 30-day stroke and death rate of 2.85% in our experience demonstrates acceptability of CAS as an alternative to repeat operation or primary CEA in patients at high risk or in patients with radiation-induced stenosis. We recommend further clinical investigation of CAS and participation in clinical trials by vascular surgeons. (J Vasc Surg 2003;37: 1234-9.)**

Carotid endarterectomy (CEA) is the currently recommended standard for management of symptomatic[1-3] and asymptomatic[4,5] high-grade extracranial carotid stenosis. Carotid artery stenting (CAS) has emerged as a useful and potentially less invasive alternative to CEA.[6-11] Recently published consensus statements[12,13] have suggested that CAS may be preferred in specific subgroups of stenotic lesions, including carotid recurrent stenosis after previous CEA, stenosis in patients at high risk with significant medical comorbidity, anatomically inaccessible lesions above C_2, and radiation-induced stenosis. However, recent clinical trial reports[14,15] have documented 30-day stroke and death rates of 10% to 12%, raising significant issues and concerns regarding the safety of this new technique. To address these reports, we reviewed our experience with CAS in a cohort of patients at high risk, to document short-term and long-term results and guide further treatment with CAS.

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Competition of interest: none.

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METHODS

Patient population. From September 1996 to May 2002, 105 consecutive patients underwent 114 CAS procedures as part of an Institutional Review Board–approved program. Informed consent was obtained, and information was prospectively collected regarding symptomatic status, degree of stenosis, characteristics of previous operations, and presence of medical comorbidity.

Patients included in the program had symptomatic (>50% diameter) or asymptomatic (>80%) carotid recurrent stenosis after previous CEA; symptomatic (>50%) or asymptomatic (>80%) primary carotid stenosis with a history of radiation to the ipsilateral neck; and symptomatic (>50%) or asymptomatic (>80%) primary carotid stenosis with one or more medical comorbidity, including coronary artery disease requiring angioplasty or bypass grafting within the 6 months before carotid intervention, history of congestive heart failure (CHF), current ejection fraction less than 30%, steroid-dependent chronic obstructive pulmonary disease, or measured forced expiratory volume in 1 second less than 30% of predicted.

CAS protocol. Patients were referred after history, findings at physical examination, and results of duplex ultrasound scanning confirmed eligibility for participation. Pretreatment in all patients included aspirin, 325 mg/d, and clopidogrel, 75 mg twice a day, for 2 days before the procedure. Local anesthetic (1% lidocaine) was infiltrated at

Fig 1. Selective lateral carotid angiogram shows high-grade stenosis in proximal internal carotid artery.

Fig 2. Selective angiogram shows results after placement of a self-expandable nitinol stent. An antiembolic device (ACCUNET) was used during the procedure.

the access site. No sedation was given before or during the procedure. Intra-arterial blood pressure and oxygen saturation were monitored continuously, and neurologic status was assessed at regular intervals. Weight-adjusted heparin was administered (70 U/kg), and activated clotting time was maintained at 250 to 300 seconds.

A description of our endovascular technique has been published.[10,11] Standard retrograde access was achieved through the common femoral artery, or the left brachial artery in 1 patient, with a 6F vascular sheath. A 0.035 inch guide wire (Wholey modified J, 175 cm; Mallinkrodt, St Louis, Mo) in a 5F cerebral diagnostic catheter (Vitek; Cook, Bloomington, Ind) was introduced for selective cannulation of the common carotid artery. Digital angiography was performed in the lateral, anteroposterior, and oblique planes to clarify severity of stenosis (Fig 1). Intracerebral views were obtained to assess baseline cerebrovascular anatomy. Subsequently, the diagnostic catheter was exchanged over a 0.035 inch exchange-length (260 cm) Amplatz Super Stiff guide wire (Meditech/Boston Scientific, Natick, Mass) for an 8F or 6F 100 cm long sheath, which was passed into the common carotid artery. Self-expandable stents were used in all patients but 5, in whom short balloon expandable stents were used early in our experience. Stenoses were crossed with 0.018 inch Roadrunner extra-support guide wires (Cook) in patients in whom the WallStent (Meditech/Boston Scientific, Minneapolis, Minn) was used, and 0.014 inch guide wires were used in patients in whom the ACCULINK (Hi-Torque Floppy; Guidant, Menlo Park, Calif) was used. In the last 26 patients, an anti-embolic distal filter device (ACCUNET; Guidant) was used (Fig 2).[16] Pre-stent dilation was performed in about 20% of cases with low-profile 3× to 4× 30-mm balloon catheters inflated to 8 atm, followed by stent deployment. Post-stent dilation was performed with 5 or 6 mm high-pressure balloons inflated to 8 atm in all cases. On completion of the procedure, ipsilateral cervical (Fig 3) and intracranial carotid angiography was performed to assess technical success and to exclude distal cerebral embolization.

Patients were transferred to a monitored intermediate care facility and were discharged the next morning. A post-procedure clinical examination and duplex ultrasound scanning was performed before discharge to assess stent patency and position. Clopidogrel was continued at 75 mg/d for 4 weeks, and aspirin was continued indefinitely. Patients were followed up at 6-month intervals with clinical examination and duplex ultrasound scanning. Technical failure was defined as inability to access the lesion or post-stenting residual stenosis 15% or greater. Transient ischemic attack (TIA) was defined as a focal hemispheric deficit that resolved within 24 hours, whereas a similar deficit lasting more than 24 hours was defined as a stroke. Amaurosis fugax was defined as focal retinal deficit lasting less than 24 hours. Clinically significant in-stent recurrent stenosis was defined as more than 80% reduction in diameter as identified at duplex ultrasound scanning and confirmed at angiography. A significant arterial access site complication was defined as any dissection, hematoma, pseudoaneurysm, arteriovenous fistula, or infection requiring blood transfusion, intravenous antibiotic therapy, or surgical or endovascular intervention.

RESULTS

Patient characteristics. Patient mean age was 70 years (range, 45-93 years). Sixty percent of patients were men (n = 63), and 40% were women (n = 42). Thirty-nine percent of procedures were performed to treat symptomatic primary carotid stenosis or carotid recurrent stenosis after previous CEA (stroke, n = 12; TIA, n = 27; amaurosis fugax, n = 5), and 61% were performed for management of

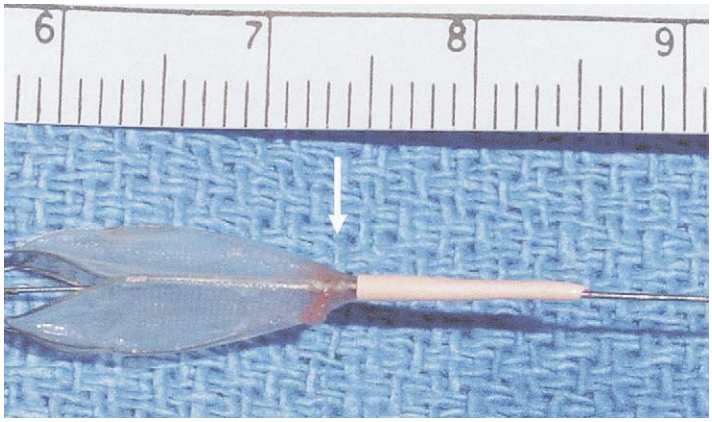

Fig 3. Post-procedure photograph of the anti-embolic device (ACCUNET) used in the patient in Fig 2. Note debris *(arrow)* trapped within the device.

Table I. Indications for carotid angioplasty stenting in a consecutive series of 105 patients

Indication	*No.*	*%*
Carotid recurrent stenosis after previous carotid endarterectomy	74	64.9
Primary carotid stenosis in patients with severe medical comorbidity	32	28.1
Carotid stenosis with previous ipsilateral cervical radiation therapy	8	7

Table II. Medical comorbidity in a consecutive series of patients undergoing carotid artery stenting

Medical Comorbidity	*No.*	*%*
CAD	74	64.9
CAD with coronary intervention within 6 months before CAS	26	22.8
History of CHF or EF ≤30%	4	3.5
Steroid-dependent COPD or FEV_1 ≤30% of predicted	2	1.8
Hypercholesterolemia	68	59.6
Hypertension	97	85.8
Diabetes	44	38.6
Smoking	44	38.6

CAD, Coronary artery disease; *CAS*, carotid angioplasty stenting; *CHF*, congestive heart failure; *EF*, left ventricular ejection fraction; *COPD*, chronic obstructive pulmonary disease; FEV_1, forced exhaled volume at 1 second.

asymptomatic disease (no neurologic symptoms, n = 62; nonlateralizing "global" symptoms, eg, lightheadedness or headache, n = 8). Mean severity of stenosis treated was 87% ± 6% (SD). Indications for CAS are presented in Table I, and medical comorbidity are summarized in Table II.

RESULTS

All CAS procedures were accomplished successfully. Self-expanding WallStents (8 × 20 mm and 10 × 20 mm) were used in 81 CAS procedures (71%); self-expanding ACCULINK stents (nickel-titanium, 8 to 6 mm or 10 to 7 mm tapered by 20 or 30 mm) were used in 28 instances (24.6%); and 5 balloon-expandable stents were used during the early part of our experience (4.4%).

No contrast extravasation, arterial disruption, or subintimal dissections were observed. Residual stenosis after CAS did not exceed 15% in any case; mean residual stenosis was 9% ± 4% (SD). Arterial access site hematoma or pseudo-aneurysm requiring blood transfusion or operative intervention was observed in 5 patients (4.7%).

Overall 30-day stroke and death rate was 2.85%. Two deaths occurred (1.9%), 1 from myocardial infarction 10 days after discharge in a patient with symptomatic stenosis with medical comorbidity (1 of 32 [3.1%]) and 1 from intracranial hemorrhage 1 day after CAS in a patient with asymptomatic recurrent stenosis after CEA. Stroke, a retinal infarction with partial field of vision loss, occurred in 1 patient (0.95%) with asymptomatic recurrent stenosis (2 of 74 [2.7%]). No complications occurred in symptomatic or asymptomatic patients who had undergone radiation therapy (0 of 8 [0%]). Minor neurologic events (TIA) occurred in 2 patients (1.9%). Mean in-hospital stay was 1.6 days (range, 1-7 days) for the entire series; and 72% of patients were discharged the morning after the procedure.

All patients were followed up at 6-month intervals (mean follow-up, 25.9 months; median follow-up, 22.4 months; range, 3.1-69 months). During this period, high-grade in-stent recurrent stenosis with 80% or greater diameter reduction developed in 4 patients (3.8%). Although these patients had no symptoms, repeat intervention was recommended because of severity of the recurrent stenosis. In 3 of these patients treatment with angioplasty alone was successful, whereas in 1 patient angioplasty with additional stenting was required. Mean time to recurrent stenosis was 13 months (range, 6.8-21 months). All 4 patients have remained asymptomatic without recurrent stenosis during further follow-up.

DISCUSSION

Results from two randomized clinical trials comparing CAS with CEA have reported 30-day stroke and death rates in the 10% to 12% range. In a trial that was stopped early by the sponsor, Alberts[14] presented data comparing CEA with CAS in 219 patients with symptomatic carotid stenosis in the range of 60% to 99%. No risk stratification was attempted, and the cohort comprised a mix of patients eligible and ineligible for the North American Symptomatic Carotid Endarterectomy Trial (NASCET). All patients in the CAS group received a WallStent endoprosthesis, as well as aspirin and ticlopidine periprocedurally. The 30-day periprocedural stroke and death rate was 12.1% for CAS and 4.5% for CEA ($P = .049$). The 1-year ipsilateral stroke rate was 3.6% in the operative group, compared with 12.2% in the stent group ($P = .022$). The reliability of results in this study was limited by the observations that complications were clustered around inexperienced operators and that the number of patients was small.

The recently published Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) multicenter trial[15] randomized 504 patients with carotid artery stenosis, of which most had symptoms (96%), to undergo either balloon angioplasty or CEA. Patients were not stratified according to medical comorbidity or cause of stenosis; therefore this cohort also contained patients with minimal or absent medical comorbidity and those who would have been considered eligible for NASCET. Of note, stenting was performed in only 26% of the 251 patients randomized to the endovascular treatment arm. The authors of CAVATAS acknowledged that the results of balloon angioplasty would be out of date when their study was published, because carotid stent placement has emerged in the past few years as the preferred method. The 30-day disabling stroke and death rate was 6.4% for endovascular management and 5.9% for CEA, compared with 10.0% and 9.9% for overall stroke and death. Cranial nerve palsy occurred in 8.7% of surgical patients, but in none in the endovascular treatment group. While endovascular and surgical management resulted in comparable complication rates, the complication rate reported for the endovascular group was higher than previously reported.[6-11]

This prompted review of our own data for a carefully selected group of patients with carotid stenosis or recurrent stenosis who would be considered at higher risk for perioperative neurologic or cardiac morbidity and mortality. In this group of 105 patients, we performed 114 carotid interventions, with a combined 30-day stroke and death rate of 2.85%. This complication rate compares favorably with the 30-day stroke and death rates noted after CEA by our group[10] and subsequently by randomized multicenter trials.[1-5] Our results are also similar to the 30-day stroke and death rates for CAS in studies with a larger number of patients that did not limit the procedure to high-risk groups.[9,17]

We accomplished carotid revascularization in 114 consecutive procedures, with a technical success rate of 100%. Mean residual stenosis immediately post-procedure was 9% ± 4% (SD). This indicates technical feasibility of CAS once appropriate training and experience with necessary catheter and guide wire skills are obtained. Our mean follow-up was 25.9 months (median, 22.4 months), with the longest follow-up more than 5 years. An in-stent recurrent stenosis rate of 3.8% over this long follow-up confirms that the procedure is durable. The recurrence rate was low even when most patients (67%) reviewed had post-CEA intimal hyperplastic recurrent stenotic disease. Initial concerns were raised that CAS may produce the high recurrence rates of 16% to 59% observed in the coronary interventional experience.[19-21] A report of 8 CAS procedures performed because of recurrent stenosis after CEA suggested a similarly high in-stent recurrent stenosis rate.[18] However, significantly larger clinical series, including the present study and others,[22,23] confirmed in-stent recurrent stenosis rates after CAS of less than 5%.

Seven percent of patients in this series had previously received cervical radiation. These stenoses are frequently long, multiple, or located in surgically less accessible locations. CEA through irradiated tissue historically has been associated with increased perioperative morbidity and mortality, including cranial nerve palsy.[13] Radiation-induced carotid stenosis has been identified as a high-risk group at the Montefiore Consensus conference.[13] CAS was recommended as an appropriate alternative to CEA at that meeting. We have used CAS preferentially to treat radiation-induced carotid stenosis at our institution.

Carotid recurrent stenosis after CEA is uncommon and is attributed to myointimal hyperplasia during the early postoperative period (within 36 months) or recurrent atherosclerosis thereafter. Hill et al[24] reported absence of operative morbidity and mortality in a series of 40 operations to treat recurrent stenosis after CEA. O'Donnell et al[25] reported a 4.2% 30-day stroke and death rate after operative intervention in 48 patients with recurrent stenosis after CEA. Transient cranial nerve palsy was observed in 18.9%, and 7.5% of the medically treated group experienced a de novo stroke while being followed up medically because of recurrent stenosis after CEA. The authors' meta-analysis of six other clinical series demonstrated an overall 30-day stroke and death of 5.2%. While the operative complication rate in the series of O'Donnell and colleagues was not significantly greater than that for primary CEA, others report that repeat operation is associated with increased risk for perioperative complications. In general, the rate for neurologic events ranges from 4.3% to 19.5%, and for cranial nerve palsy ranges from 9.2% to 19.8%.[26-28] Because of these issues, several authors regard patients with recurrent carotid stenosis as at high risk for repeat operation, as compared with primary CEA, and recommend CAS as an alternative to operative management.[6,10,11,29,30] Most patients (67%) in the current series underwent CAS to treat recurrent stenosis after CEA. No cranial nerve palsies were noted, and the overall periprocedural stroke and death rate (2.85%) compares favorably with published data on operative complications.

Several authors have attempted to define higher risk for primary carotid endarterectomy. McCrory et al[31] analyzed data for 1160 CEAs performed at 12 academic medical centers and identified predictors of heightened risk. Overall 30-day stroke and death rate was 4.8%; however, predictors of heightened risk included age older than 75 years, symptomatic status (hemispheric TIA, non-disabling stroke), diastolic blood pressure greater than 110 mm Hg, CEA before planned aortocoronary bypass with history of angina, evidence of intra-arterial thrombus, and stenosis near the siphon (lesion above C_2). Presence of two or more predictors suggested a twofold increase in risk, which would then approach 10%. Goldstein et al[32] more recently reviewed the same database and noted higher postoperative stroke and death rates for women (5.6% vs 1.6%; $P = .02$), for age older than 75 years (7.7% vs 1.8%; $P = .01$), and for history of CHF (8.1% vs 2.3%; $P = .03$). Recently, Ouriel et al[33] identified a subset of patients at high-risk whose composite end point of stroke, myocardial infarction, and death was 7.4%, whereas the corresponding rate in a subset of patients at low risk was 2.9% ($P < .005$). The subgroup at high risk was identified by presence of coronary artery disease, history of CHF, chronic obstructive lung disease, or renal insufficiency. Finally, Rothwell et al[34] analyzed data for 1729 patients from the European Carotid Surgery Trial who underwent CEA. They noted that risk for perioperative complications was higher in women, in cerebral as opposed to ocular ischemia, in patients older than 75 years, in systolic hypertension, and in the presence of peripheral vascular disease. On the basis of these published data, we identified a high-risk subset of patients with primary carotid stenosis with severe cardiac or pulmonary disease. These patients formed a small subset of our overall experience (28%) and were preferentially offered CAS.

Our results demonstrate that CAS can be performed successfully once sufficient technical expertise is acquired. Contrary to published reports,[14,15] periprocedural complications were low and results were durable. Each institution must make decisions regarding continued use of CAS on the basis of their individual experience. However, for our group, continued use of the technique in subsets of patients considered at higher risk seems appropriate until data are generated from larger randomized clinical trials and registries over the next 2 or 3 years.[16]

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Safety and durability of redo carotid operation: An 11-year experience

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Purpose: **With the recent emergence of carotid stenting in the management of carotid disease, the role of surgery has been challenged, particularly for recurrent carotid stenosis. This study was undertaken to determine the safety and durability of redo carotid operation (RCO) for recurrent stenosis.**

Methods: **A retrospective review identified 64 consecutive patients who underwent 66 RCOs between 1990 and 2000. There were 33 males (52%) and 31 females, with a mean age of 68.2 years (range, 38-84 years). The mean interval from the primary carotid surgery to RCO was 77.5 months (range, 1-292 months). Operative indications were severe asymptomatic stenosis in 33 cases (50%), transient ischemic attacks (TIA) or amaurosis fugax in 25 (38%), recent stroke in 6 (9%), and nonhemispheric symptoms in 1. Two operations were tertiary carotid reconstructions. A total of 56 (85%) patch angioplasties were performed, 49 with vein and 6 with synthetic material. Primary closure was performed in three cases (5%), whereas interposition grafts were required in eight (12%). Complete follow-up was available in 59 patients (92%) and averaged 4.3 years (range, 0.2-12.9 years); 97% of patients underwent follow-up duplex scanning.**

Results: **There were no operative deaths and only two operative strokes (3.1%). Permanent cranial nerve deficit occurred in one patient (1.5%). Late stroke occurred in five patients: four ipsilateral and one contralateral. Kaplan-Meier estimates for 5- and 10-year stroke-free survival were 92% and 74%, and for overall survival were 72% and 50%. Duplex scanning detected significant recurrent carotid stenosis (>80%) or occlusion in six cases (9%) at a mean follow-up of 4.1 years. Kaplan-Meier estimates for freedom from recurrent stenosis of >80% were 94% and 86% at 5 and 10 years.**

Conclusions: **RCO for recurrent carotid stenosis can be performed safely with excellent protection from stroke and long-term durability. These data provide a standard against which the results of carotid stenting can be compared. (J Vasc Surg 2004;39:155-61.)**

No surgical procedure has endured more intense scrutiny than carotid endarterectomy (CEA). Through multiple randomized trials for symptomatic[1-3] and asymptomatic[4-6] carotid stenosis, CEA has been proven to be an effective and durable procedure to reduce the risk of stroke. With the recent emergence of carotid angioplasty and stenting (CAS) as a safe alternative to CEA[7-12] clinical equipoise between CAS and CEA now exists among different specialists. As a result, the role of CEA is again being challenged, in particular for high-risk patients or for those with recurrent carotid stenosis (RCS). Long-term results after CAS are scarce and, when available, will need to be compared with those of CEA to help resolve uncertainty about its role. Although the literature is replete with papers on RCS, long-term outcome after redo carotid operation (RCO) with objective documentation of carotid artery patency is relatively scarce.[13-16] This study was undertaken to review a contemporary series of patients undergoing RCOs to define the safety and durability of such procedures.

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METHODS

From a computerized vascular surgery registry and institutional operative logs, all patients who underwent CEA on the vascular surgery service at the Henry Ford Hospital between January 1990 and December 2000 were identified. Of the 1127 consecutive CEAs performed during this period, 66 RCOs were carried out in 64 patients, representing 6% of the total. Two of these patients, who had had a secondary RCO performed elsewhere, underwent a tertiary carotid reconstruction. Individual RCOs were counted separately so that patients undergoing staged, bilateral procedures were recorded and evaluated as two entries. Specifically excluded were patients who underwent re-exploration in the immediate postoperative period for lesions related to technical problems, such as clamp injuries, intimal flaps, or kinks.

The specific end points analyzed were 30-day death, stroke, and other procedure-related complications and the occurrence of late stroke, death, and secondary restenosis. Stroke was defined as any focal neurologic deficit of abrupt onset persisting for more than 24 hours. Incidence rates for late death, stroke, and carotid artery secondary restenosis were studied. Perioperative morbidity and mortality, as well as 5-year stroke-free survival and 5-year survival rates, were compared with those of primary CEAs performed during the same period.[17] Follow-up data were obtained through review of medical records and clinic notes or by direct contact with the patient or family. Records of carotid duplex scans were retrieved from a computerized vascular

Table I. Comorbidities

	No. of patients (%)
HTN	49 (75)
Smoking	41 (63)
Hyperlipidemia	36 (55)
Heart disease	35 (54)
DM	16 (25)
Renal insufficiency	5 (8)

HTN, Hypertension; *DM,* diabetes mellitus.

Table II. Complications

	Number of patients (%)
Stroke	2 (3)
TIA	2 (3)
Cardiac	3 (5)
CN injury	
Partial transection of CN XII	1 (1.5)
Permanent vocal cord paralysis	1 (1.5)
Transient CN X palsy	1 (1.5)
Transient CN XI palsy	1 (1.5)
Transient mandibular nerve palsy	2 (3)
Brachial artery thrombosis	1 (1.5)
Hematoma requiring evacuation	2 (3)

A patient may have more than one complication.
TIA, Transient ischemic attacks; *CN,* cranial nerve.

Table III. Comparison of perioperative complications between RCO and primary CEA

	RCO (%)	*1° CEA (%)*	P
Stroke	3	3	.99
Death	0	0.9	.5
TIA	3	0.5	.02
CN injury	6	2.5	.08
Cervical hematoma	3	1.7	.6
MI	3	1.1	.2
Death, stroke, TIA	6	4	.5
Death, stroke, TIA, MI	9	5	.2
TIA, CN injury, cervical hematoma	12	5	.01
All combined	18	10	.03

RCO, Redo carotid operation; *1° CEA,* primary carotid endarterectomy; *TIA,* transient ischemic attack; *CN,* cranial nerve; *MI,* myocardial infarction.

laboratory registry. Our noninvasive vascular laboratory grades the degree of carotid stenosis on the basis of the classic categories defined by the University of Washington vascular laboratory in the early 1980s and updated in the 1990s.[18] The following categories were used: 0%-15%, 16%-49%, 50%-59%, 60%-79%, 80%-99%, and occlusion.

Because secondary restenosis is likely to occur before its detection, the time of secondary restenosis was chosen to be the midpoint between the last normal examination (<50% stenosis) and its detection.

Sociodemographic data and risk factors associated with perioperative morbidity and mortality were evaluated by using χ^2 and the Student *t*-test as appropriate. Cox proportional hazard model was used for relative risk determination for data with variable follow-up. Actuarial survival analysis was performed by using Kaplan-Meier life tables. A *P* value of <0.05 (log-rank) was considered significant for all statistical analyses.

RESULTS

The study population included 33 males (52%) and 31 females, with a mean age of 68.2 years (range, 38-84 years). Comorbidities are listed in Table I. No differences were noted in the distribution of risk factors between symptom-free patients and those with symptoms. When compared with 1045 primary CEAs performed at the Henry Ford Hospital from January 1990 to December 1999,[17] no significant differences were detected in the incidence of risk factors.

Operative indications were severe asymptomatic stenosis detected on routine follow-up duplex examinations in 34 cases (52%), TIAs or amaurosis fugax in 25 cases (38%), recent stroke in 6 cases (9%), and nonhemispheric symptoms in 1 case. Among the symptom-free patients, 31 (91%) were found to have a stenosis of greater than 80% on duplex imaging. The remaining three patients with less than 80% recurrent stenosis underwent RCO for 60%-79% stenosis with either an ulcerated lesion (two patients) or kinking of the internal carotid artery (one patient). The mean interval from the primary carotid surgery to RCO was 6.6 years (range, 0.2-24.7 years). Thirty-five percent of patients underwent RCO within 18 months of their primary CEA.

All RCOs were performed under general anesthesia, with continuous electroencephalographic (EEG) monitoring in 94% of the patients. Intraoperative shunting was used in 27% of the cases (17 of 62), on the basis of EEG changes. Arteriotomies were closed predominantly with patch angioplasty in 55 cases (85%): 49 with vein and 6 with Dacron. Primary closure was performed in 3 cases (5%), whereas interposition grafts were required in 8 cases (12%): 7 with vein and 1 with expanded polytetrafluoroethylene.

Mandibular subluxation was employed in 11 cases (17%), with resection of the styloid process to expose a high, distal lesion in one patient. The contralateral ICA was occluded in eight patients (12%) and the ipsilateral ICA was occluded in two patients (3%), one of whom underwent endarterectomy of external carotid artery for amaurosis fugax, and the other for an upper extremity weakness. The pathology of recurrent stenosis was available in 55 cases (83%). RCOs were performed for neointimal hyperplasia in 18 patients at a mean of 1.3 years (range, 0.3-4.1 years) after the primary CEAs and for recurrent atherosclerosis in 33 patients at a mean of 7.8 years (range, 0.8-24.8 years). Four patients were found to have combined atherosclerotic and neointimal hyperplastic changes on gross examination of plaques at a mean of 1.9 years (range, 0.2-6.8 years). Of those with neointimal hyperplasia, four patients (25%) had symptoms at the time of RCO; 61% of those with recurrent atherosclerosis were symptom-free. The neointimal hyperplasia was treated by redo endarterectomy and patch angio-

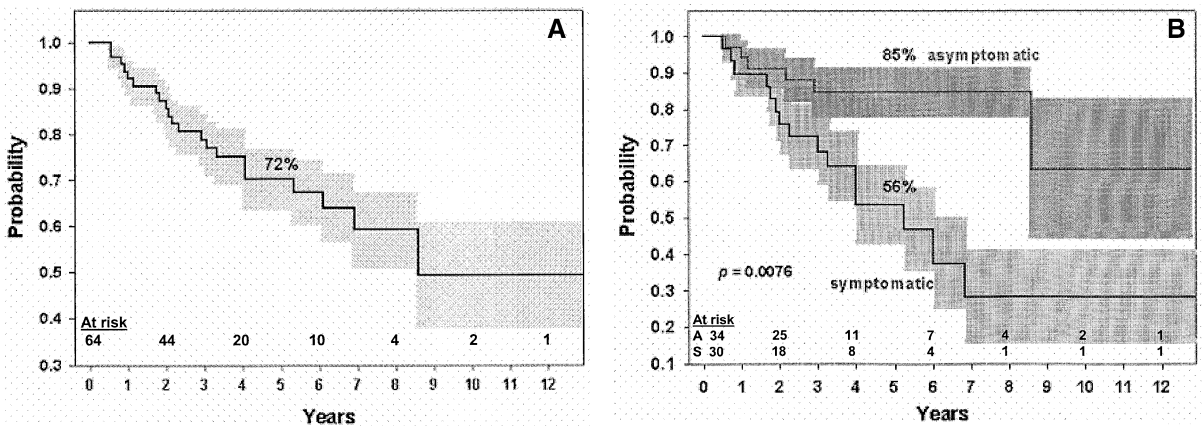

Fig 1. Kaplan-Meier estimates for overall survival (**A**) and survival stratified by symptom status (**B**) at the time of redo carotid operation. Shaded areas in curves represent SE.

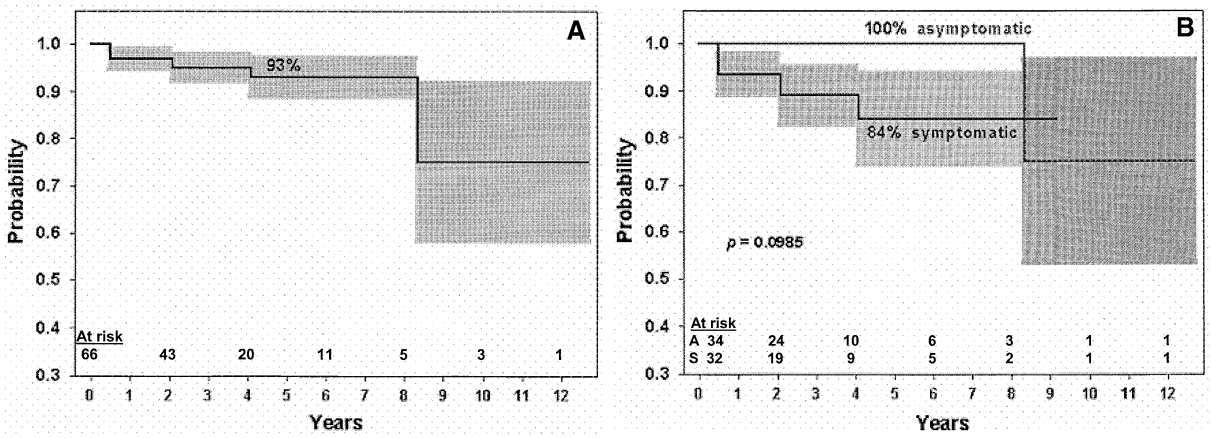

Fig 2. Kaplan-Meier estimates for ipsilateral stroke-free survival (**A**) stratified by symptom status (**B**) at the time of redo carotid operation. Shaded areas in curves represent SE.

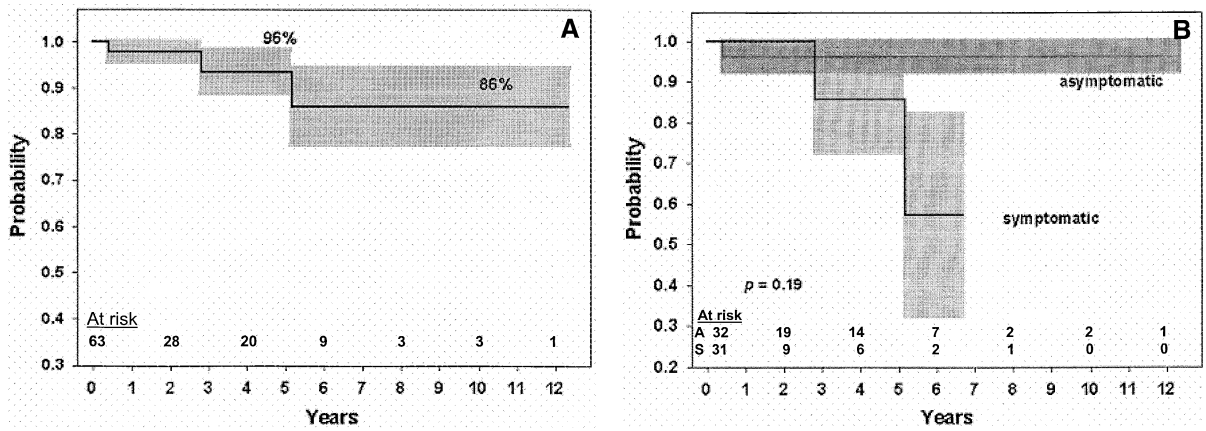

Fig 3. Kaplan-Meier estimates for freedom from recurrent stenosis of >80% (**A**) stratified by symptom status (**B**) at the time of redo carotid operation. Shaded areas in curves represent SE.

Table IV. Summary of reports on management of recurrent carotid stenosis

Author	*Study period*	*No. pts/no. arteries*	*Indications*	*Stroke*	*TIA*	*Death*
Ballinger[44]	1/84-8/95	67/74	Sx 65% Asx 35%	1.4%	NA	1.4%
Rockman[13]	1/80-12/96	74/83	Sx 41.5% Asx 35.3%	3.7%	NA	0
Archie[14]	1/81-12/99	66/69	Sx 48% Asx 52%	1.4%	1.4%	0
AbuRahma[15]	10/91-10/98	124/124	Sx 78% Asx 22%	4.8%	4%	0
O'Hara[16]	1/89-12/99	199/206	Sx 43% Asx 57%	3.4%	NA	1.0%
Hill[19]	9/93-3/98	40/40	Sx 50% Asx 50%	0%	0%	0
Mansour[25]	8/76-8/96	69/82	Sx 66% Asx 34%	4.8%	1%	0
Current series	1/90-12/2000	64/66	Sx 48% Asx 52%	3%	3%	0

TIA, Transient ischemic attack; *MI,* myocardial infarction; *Sx,* symptomatic; *Asx,* asymptomatic; *NA*, not available; *MI*, myocardial infarction.

plasty in all but four patients, who underwent interposition grafting.

There were no operative deaths and two operative strokes (3%): one ipsilateral and one contralateral. Overall, 16 complications occurred in 13 patients (Table II). Perioperative TIAs were noted in two patients. Myocardial infarction occurred in two patients (3%), requiring coronary artery bypass grafting in one patient. Major cranial nerve injuries occurred in four patients (6%), in two of whom mandibular subluxation was employed for distal exposure. A partial severance of the hypoglossal nerve was recognized and repaired intraoperatively in one patient; he did not manifest any clinical deficit postoperatively. One patient suffered a permanent vocal fold paralysis. A transient spinal accessory nerve palsy occurred in one patient, who required mandibular subluxation and resection of the styloid process for access to a high, distal lesion; her symptoms resolved after 5 months. A recurrent laryngeal nerve palsy occurred in another patient with mandibular subluxation; she regained full mobility of her vocal folds after 8 months. Two patients had transient marginal mandibular branch nerve palsy. Cervical wound hematoma requiring operative drainage developed in two patients (3%). One patient required a brachial artery thrombectomy for problems related to an arterial line. The overall perioperative complication rate was higher when compared with those for primary CEA (Table III), primarily because of an increased incidence of cranial nerve injury and TIA.

Comparison of comorbidity analysis for RCO with the authors' experience for primary CEA[17] failed to demonstrate any traditional risk factor that was associated with RCO; smoking was the only factor that showed a trend towards statistical significance ($P = .06$).

Follow-up data were available on 59 patients (89%) and ranged from 0.2 to 12.9 years, with a mean of 4.3 years. During follow-up, 20 late deaths occurred at a median of 2.0 years (range, 0.5-8.3 years). Causes of death were cardiac in 8 patients, malignancy in 5 patients, pulmonary in 2 patients, stroke in 1 patient, and gangrene-induced sepsis in 1 patient. In three patients, the cause was undetermined. Kaplan-Meier estimates for the probability of overall survival were 72% at 5 years and 50% at 10 years (Fig 1). The symptom status at the time of RCO had differential effects on survival: symptom-free patients had 5- and 10-year survival rates of 85% and 64%, compared with 56% and 29%, respectively, for patients with symptoms ($P = .008$; Fig 1, *B*).

Late stroke occurred in five patients (8%): four ipsilateral and one contralateral. One patient developed a fatal ipsilateral stroke 4 years after her RCO. Another patient developed an ipsilateral stroke 6 weeks after a saphenous vein interposition grafting and was found to have severe stenosis of the saphenous graft. To avoid the partial mandibulectomy that would have been required to gain access to the lesion, a superficial temporal-to-middle cerebral artery bypass grafting was performed without complication. One patient developed an ipsilateral stroke 8.2 years after RCO in the immediate postoperative period following coronary artery bypass grafting. The duplex scan performed at the time of the stroke revealed a secondary recurrent 60% to 80% ICA stenosis. Follow-up duplex imaging performed 4 years later showed regression to <50%. One contralateral stroke occurred in a patient who underwent prophylactic aortoinnominate bypass grafting 4 months after the RCO. The probability of freedom from any stroke at 5 years was 92%, and 74% at 10 years (Fig 2, *A*). Again, symptom-free patients at the time of RCO appeared to enjoy better stroke-free survival than those who had symptoms (100% vs 84% at 5 years; $P = .1$). The probability of freedom from ipsilateral stroke was 93% at 5 years and 75% at 10 years (Fig 2, *A* and *B*). Univariate analysis of comorbidities and symptom status at the time of RCO revealed renal insufficiency ($P = .03$) and symptomatic presentation ($P = .04$) to be significant predictors of postoperative stroke. How-

Table IV. Continued

30-day stroke and death	*MI*	*Cranial nerve injury*	*Mean follow-up*	*Stroke-free survival*	*Freedom from restenosis (>80%)*
2.8%	NA	2.7%	48.2 mos	93.6% at 5 yrs (ipsilateral)	NA
3.7%	0%	1.2%	35 mos	83.5% with veins; 93.9% with prosthetics at 3 yrs	NA
2.9%	0%	4.3%	50 mos	90% at 5 yrs (cumulative) 86% at 10 yrs	88.2% at 5 yrs (>50%)
4.8%	0	17%	49 mos	82% at 5 yrs (cumulative)	95% at 5 yrs (>50%)
5.3%	1.0%	1.0%	47 mos	92% at 5 yrs	89% at 5 yrs
0%	2.5%	10%	14 mos	NA	NA
4.8%	2%	7.3%	NA	92.3% at 5 yrs	92.3% at 5 yrs
3%	5%	6%	52 mos	93% at 5 yrs (ipsilateral)	96% at 5 yrs

ever, on multivariate analysis, none of these proved to be of significance.

Postoperative duplex imaging was available in 97% of cases, of which 53% had carotid imaging beyond 18 postoperative months (range, 1 month– to 12.1 years). Of 31 cases with carotid duplex imaging follow-up in <18 months, 16 patients died. Greater than 50% secondary restenosis was detected in five patients (8%) at a mean of 27 months (range, 4-61 months). Of these, three patients developed >80% secondary restenosis at a mean time of 33 months, including one patient who had an asymptomatic internal carotid artery occlusion 4 months after RCO. No patient had symptoms develop. Kaplan-Meier estimates for freedom from >80% secondary restenosis were 96% at 5 years and 86%, at 10 years (Fig 3, *A* and *B*). The patients' symptom status at the time of RCO did not influence the outcome.

DISCUSSION

This study illustrates that RCO can be performed safely and effectively with long-term durability in the modern era. There was no 30-day operative mortality, and the operative stroke rate was only 3%. This is comparable to the findings of other series (Table IV), as well as to those of the authors' combined stroke and death rate of 3.9% for 1045 primary CEAs performed between 1990 and 1999.[17]

Half of the redo carotid operations performed in this series were in symptom-free patients. The operative indications in this series did not differ from those reported by others.[14,16,19,20] With respect to risk factors, none of the traditional risk factors emerged to affect the incidence of RCO; smoking was the only factor that showed a trend toward statistical significance ($P = .06$). Other studies have observed that smoking was associated with RCS.[21-24]

Neointimal hyperplasia accounted for the vast majority of early (<18 months) recurrences, whereas atherosclerosis was the cause for most late (>18 months) recurrences, relatively evenly distributed along the time line. Consistent with previous reports,[19,25] plaques with mixed atherosclerotic and hyperplastic changes were also noted in both early and late recurrent lesions in this series. It is also of interest to note that a quarter of those with neointimal hyperplasia had symptomatic presentation, which is higher than that reported by Das et al.[26] Although histologic examination of plaques was not performed, these findings lend support to the notion that early and late recurrent lesions are one and the same, just observed at different time points along a continuum.[27]

The cumulative survival rate at 5 years after RCO was 72% and was favorably influenced by the lack of preoperative symptoms. This was comparable to our 75% 5-year survival rate following primary CEA.[17] The overall ipsilateral stroke-free survival was 93% at 5 years and 75% at 10 years, consistent with the findings of others (Table IV) and with our results for primary CEA (94% at 5 years). When stratified by symptom status, the results of RCO for symptom-free patients are comparable to those for primary CEA[17] and to those reported by the Asymptomatic Carotid Atherosclerotic Study.[6] Similarly, for patients with symptoms, the 5- and 9-year estimates for ipsilateral stroke-free survival were both 84%, comparable to our primary CEA results[17] and to North American Symptomatic Carotid Endarterectomy Trial data.[1] Although statistical significance was not achieved, symptom-free patients appeared to enjoy a higher degree of ipsilateral stroke prevention than did patients with symptoms. This series shows that RCO is as effective as primary CEA is in stroke prevention.

An evaluation of the durability of RCO showed that the probability of freedom from >80% secondary restenosis was 96% at 5 years. These results are consistent with the experience of other investigators (Table IV). The ACAS and other prospective surveillance programs have reported late recurrence rates ranging from 4.9%[28] to 21% at 7 years.[29-31] In the current series, only one patient developed

an ipsilateral stroke that was specifically the result of a secondary carotid stenosis. These findings reaffirm that RCO is a durable means of stroke prevention with comparable efficacy to that of primary CEA.

An increased rate of perioperative complication was noted in this series compared with the authors' series of primary CEA. Although several series have documented that RCO can be performed with morbidity and mortality rates similar to those of primary CEA,[16,19,20] the complication rates for RCO are generally considered higher than those for primary CEA.[15,26,32,33] Cranial nerve injuries account for the majority of these complications and have been reported in up to 48% of cases.[14,15,22,25,32,34-36] These injuries result from the fibrotic tissue reaction that obscures the normal plane of dissection.[25,32] Even though most cranial nerve injuries are transient,[15,22,25,32] they do result in disability and may take a prolonged period of time, often exceeding many months, for full recovery. In this series, two of four patients with major cranial nerve injuries required mandibular subluxation, including one patient who had resection of the styloid process. Mandibular subluxation was employed in 17% of cases when the recurrent lesion, on preoperative arteriography, was found to be extending beyond the second vertebral body. This relatively high incidence of utilization of mandibular subluxation probably reflects the referral pattern to our institution. Distal lesion requiring mandibular subluxation may be a marker for potential cranial nerve injury. It is this group of patients in whom CAS may prove most beneficial.

Early results for CAS in high-risk patients have improved significantly since its introduction.[7,11,37,38] Some early trials comparing the efficacy of CEA with CAS were terminated early because of the high incidence of adverse events and poor short-term results in the endovascular group.[39,40] In 2000, New et al[41] reported, in a retrospective review of multicenter registry on CAS performed for recurrent stenosis in 338 patients (358 arteries), a 3.7% periprocedural stroke and death rate.[41] More recently, the Carotid and Vertebral Artery Transluminal Angioplasty Study trial was completed, and its results were released in 2001.[42] This study showed no difference in the 30-day combined death and stroke rates between CAS (10%) and CEA (9.9%), whereas cranial nerve injury (9%), myocardial infarction (1%), pulmonary embolism (1%), and respiratory failure (1%) occurred only in the surgical arm.

Carotid stenting has been further supported by the improved results seen with the use of a distal protection device as in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. In this first US prospective randomized multicenter trial comparing CAS with distal protection against CEA in high-risk patients, 307 patients were randomized to either CAS or CEA at 22 sites. The preliminary results presented at the American Heart Association meeting in November of 2002 documented that the 30-day combined death and stroke rate did not differ between the two groups: 4.5% for CAS and 6.6% for CEA. However, when myocardial infarction was included in the calculation of major adverse outcome rates, the complication rate was significantly lower in the CAS group (5.8%) than the CEA group (12.6%). Furthermore, cranial nerve injury occurred only in the CEA group (5.3%).

Carotid stenting has been criticized because of a high recurrent stenosis rate. Although New et al[41] have reported a 96% probability of freedom from stroke at 3 years, subsequent studies have shown higher recurrence rates. In the CAVATAS trial,[42] severe ipsilateral RCS was present more frequently in the endovascular group (14%) than in the surgical group (4%) at 1-year follow-up. However, this difference did not translate into a difference in the rates of death or disabling stroke at 3 years (endovascular and CEA, 14.3% and 14.2%, respectively). Roubin and colleagues[43] reported an 88% probability of freedom from any stroke at 3 years in their follow-up of 604 CASs performed on 528 patients. It is noteworthy that a large proportion of the patients in this trial were high-risk patients who would have been ineligible for NASCET.

These early results, although limited, look promising and success rates will likely continue to improve with advances in technology. The long-term outcome data from prospective randomized trials will provide definitive answers for both low-risk and high-risk patients. Until then, the surgical results from modern series will serve as a benchmark against which the efficacy and durability of these newer modalities will be measured.

There are several limitations with this study. It has the usual shortcoming of any retrospective study. Follow-up was not complete in all patients—five patients were lost to follow-up. Late neurologic events occurring outside of our institution may have been missed. The incidence of perioperative neurologic adverse events might have been underestimated. Referral and selection bias might have affected the outcomes.

Nonetheless, this study clearly demonstrates that RCO can be performed with acceptable stroke and death rates and that it is an effective means of stroke prevention in patients with RCS. That the perioperative complications rates for RCO are higher than those for primary CEA should not detract from its long-term benefits. Redo carotid operation is a durable procedure with excellent long-term patency. Careful patient selection, preoperative planning, and meticulous operative technique, including use of bipolar cautery and nerve stimulator, should be emphasized to minimize cardiac neurologic and other complications. Extra caution should be taken to avoid cranial nerve injury when mandibular subluxation is required for distal exposure. Until long-term results of CAS are available, redo carotid operation should remain the standard of treatment for recurrent carotid stenosis.

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Early Outcome of Carotid Angioplasty and Stenting With and Without Cerebral Protection Devices

A Systematic Review of the Literature

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Background—Carotid angioplasty and stenting (CAS) is increasingly being used for treatment of symptomatic and asymptomatic carotid artery disease (CAD). To evaluate the efficacy of cerebral protection devices in preventing thromboembolic complications during CAS, we conducted a systematic review of studies reporting on the incidence of minor stroke, major stroke, or death within 30 days after CAS.

Summary of Review—We searched for studies published between January 1990 and June 2002 by means of a PubMed search and a cumulative review of reference lists of all relevant publications. In 2357 patients a total of 2537 CAS procedures had been performed without protection devices, and in 839 patients 896 CAS procedures had been performed with protection devices. Both groups were similar with respect to age, sex distribution, cerebrovascular risk factors, and indications for CAS. In many studies the periprocedural complication rates had not been presented separately for patients with symptomatic and asymptomatic CAD. The combined stroke and death rate within 30 days in both symptomatic and asymptomatic patients was 1.8% in patients treated with cerebral protection devices compared with 5.5% in patients treated without cerebral protection devices ($\chi^2=19.7$, $P<0.001$). This effect was mainly due to a decrease in the occurrence of minor strokes (3.7% without cerebral protection versus 0.5% with cerebral protection; $\chi^2=22.4$, $P<0.001$) and major strokes (1.1% without cerebral protection versus 0.3% with cerebral protection; $\chi^2=4.3$, $P<0.05$), whereas death rates were almost identical ($\approx$0.8%; $\chi^2=0.3$, $P=0.6$).

Conclusions—On the basis of this early analysis of single-center studies, the use of cerebral protection devices appears to reduce thromboembolic complications during CAS. These technical aspects should be taken into account before the initiation of further randomized trials comparing CAS with carotid endarterectomy. **(*Stroke*. 2003;34:813-819.)**

Key Words: angioplasty ■ carotid arteries ■ protective devices ■ stenosis ■ stents

Carotid endarterectomy (CEA) is one of the most commonly performed peripheral vascular procedures and is currently considered the most effective treatment for stroke prevention in patients with high-grade symptomatic or asymptomatic carotid artery disease (CAD).[1–3]

However, in the past few years, evidence has accumulated that carotid angioplasty and stenting (CAS) might become an alternative to CEA for the treatment of these disorders. Despite an increasing enthusiasm for the application of CAS in CAD, only a single completed, prospective, multicenter trial comparing endovascular versus surgical treatment for CAD has been reported to date: the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS).[4] This study reported a similar major risk and effectiveness for CAS compared with CEA.[4] In contrast, a recent systematic comparison of the 30-day outcome of CAS and CEA for symptomatic CAD in single-center studies performed during 1990–1999 revealed a significantly higher risk of stroke or death for CAS than for CEA.[5] Both this survey and CAVATAS elucidate the great challenges associated with the performance of trials comparing CEA with CAS. The field of endovascular therapy is subject to rapid technological advances. Therefore, the current state of the art may be outdated before completion of randomized trials. In CAVATAS, for instance, most of the CAS patients were treated with angioplasty alone, and only 55 of a total of 240 patients underwent carotid angioplasty in combination with stenting. No procedure was performed with cerebral protection devices. Similarly, the survey of Golledge et al[5] included many case series in which angioplasty had been performed without stenting and only 2 case series, with a total of 82 patients, in which cerebral protection devices had been used.

Fear of distal embolization of plaque fragments to the brain has generated great concern regarding the safety of CAS.[6]

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Recent technical refinements therefore have led to the widespread use of CAS with cerebral protection devices. With accumulating experience and technical improvements aiming to reduce procedure-related embolic complications, it is likely that the results of the early CAS studies might not reflect current complication rates. Additionally, insurance companies and governments are increasingly demanding cost-effective healthcare. This raises the question of whether the widespread introduction of costly cerebral protection devices really improves the quality of care.

Therefore, the goal of this study was to search systematically for reports on CAS with and without cerebral protection devices to critically appraise the data and to determine the occurrence of minor and major strokes and death within 30 days according to the criteria set forth by the large CEA trials.[1–3]

Materials and Methods

Search Strategy

An extensive search of the literature from January 1990 to June 2002 was performed with PubMed with the advanced search option. We used the key words *carotid artery*, *stenosis*, *angioplasty*, *stent*, and *protection* in different permutations. We examined the reference lists of all included articles for other relevant references. Additionally, we performed a hand search of relevant general medical, neurological, radiological, surgical, and neurosurgical journals. Contact with other authors of the field was made to identify additional studies. The abstract of each article was carefully studied, and if there was any suggestion of relevant data, the full text was retrieved. All studies were independently assessed by 2 reviewers (A.K. and K.G.) and then cross-checked; disagreements were resolved by consensus.

Eligibility Studies

Studies were included if the following criteria were fulfilled: (1) the study comprised a total of at least 10 stent procedures; (2) the number of peri-interventional complications rates (ie, minor stroke, major stroke, or death) within 30 days was reported for patients with high-grade symptomatic or asymptomatic CAD; and (3) the number of peri-interventional complications rates (ie, minor stroke, major stroke, or death) within 30 days was reported separately for stent procedures with and without cerebral protection devices. Articles were excluded if only angioplasty without stent placement had been performed. Further exclusion criteria were editorials, letters, and reviews. In case of multiple publications on the same study population, we used the most recent publication. All articles that did not clearly meet our inclusion criteria were excluded at this stage. Six articles[7–12] were excluded because the case series included <10 patients.

Data Extraction and Analysis

For each study the following data were extracted: (1) general: year of publication, number of patients, institutions; (2) patient characteristics: sex, age, risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, hypertension, coronary artery disease; (3) initial diagnosis of high-grade CAD: carotid duplex ultrasound, cerebral invasive/noninvasive angiography; (4) indications for angioplasty and stent: asymptomatic, transient hemispheric ischemic attack, amaurosis fugax, minor stroke, and major stroke; (5) stent procedure: procedural technique, types of stents, types of cerebral protection devices; (6) number of patients and number of arteries treated; (7) periprocedural complications within 30 days: minor stroke, major stroke, and death.

In most studies peri-interventional complication rates within 30 days had been defined according to the criteria set forth by the large CEA trials.[1–3] A minor stroke was defined as a persisting new neurological deficit that increased the National Institutes of Health Stroke Scale score by <3 points and a major stroke as a persisting new neurological deficit that increased the National Institutes of Health Stroke Scale score by >3 points.

For statistical analysis, χ^2 tests were used, and a value of $P<0.05$ was considered statistically significant.

Results

Our literature search resulted in 40 studies of CAS without cerebral protection[13–52] and 14 studies of CAS with cerebral protection[17,30,53–64] that met the inclusion criteria. Of these, several articles were excluded because they reported on patients already used in other publications from the same institutions: Theron et al[65] was excluded in favor of Guimaraens et al[58]; several studies of the group of Roubin et al[36–42] were excluded in favor of Roubin et al[32]; Jordan et al[43] and Jordan et al[44] were excluded in favor of Jordan et al[22]; Chakhtoura et al[45] was excluded in favor of Hobson et al[20]; Henry et al[66] was excluded in favor of Henry et al[59]; Jaeger et al[46] was excluded in favor of Jaeger et al[21]; Macdonald et al[61] was excluded in favor of Al-Mubarak et al[55]; and Angelini et al[56] was excluded in favor of Reimers et al.[62]

One recent study[49] evaluating the efficacy of abciximab in patients undergoing CAS was also excluded. Another small case series of 22 patients[50] had included patients with carotid dissections after gunshot wounds and was therefore also excluded. One small case series with 33 patients published in the *South African Medical Journal* was not accessible in any library in Germany.[51]

The main characteristics of the remaining studies are summarized in Tables 1 and 2. The number of patients in the studies of stenting with cerebral protection devices totaled 839, and the number of patients in the studies without cerebral protection totaled 2357. Because most cerebral protection devices are currently being tested, 21 patients (ie, 0.8% of all patients without protection) had been stented with protection in 4 studies mainly reporting on the results of CAS without protection[15,20,29,48](Table 1). Although the peri-interventional complications rates were not reported separately for stent procedures with and without cerebral protection devices in these studies, they were still considered for this analysis.

In both groups there was a similar age and sex distribution (69±3 years in the group without cerebral protection versus 68±2 years in the group with cerebral protection [P=NS]; 69% male, 31% female in the group without cerebral protection versus 73% male, 27% female in the group with cerebral protection [P=NS]). Additionally, the number of asymptomatic or symptomatic patients presenting with amaurosis fugax, hemispheric transient ischemic attacks, or minor stroke before stenting was comparable in the groups with and without cerebral protection (64% symptomatic patients and 36% asymptomatic patients in the group with protection versus 59% symptomatic patients and 41% asymptomatic patients in the group without protection [P=NS]).

In both groups arterial hypertension and hyperlipidemia were the most frequent vascular risk factors, followed by cigarette smoking and diabetes mellitus (Table 3).

In all studies the majority of patients had been treated for atherosclerotic CAD, and in some case series a few patients

TABLE 1. Carotid Angioplasty and Stent Without Cerebral Protection: Study Characteristics and 30-Day Outcomes

Author	Year	No. of Patients	Male/Female	Mean Age, y	Symp/Asymp	No. of Treated Arteries	Minor Stroke	Major Stroke	Death
AbuRahma[14]	2001	23	11/12	71	18/7	25	1	2	1
Bonaldi[15]*	2002	68	41/27	68	68/0	71	3	1	...
Brooks[47]	2001	53	NG	66	53/0	53	...	...	...
Cremonesi[48]	2000	119	93/26	70	29/90	119	3	...	...
Criado[16]	2002	132	86/46	68	53/79	135	2	1	...
Dangas[13]	2000	133	93/40	71	NG	140	8	1	1
D'Audiffret[17]	2001	42	NG	68	NG	42	1	...	...
Diethrich[18]	1996	110	79/31	72	31/79	129	10	2	1
Gupta[19]	2000	100	76/24	76	85/15	100	...	1	...
Hobson[20]**	2002	54	28/26	69	19/35	54	1	...	...
Jaeger[21]	2002	67	47/20	67	NG	70	...	1	...
Jordan[22]	1998	268	184/84	69	72/196	312	20	4	3
Kastrup[52]	2003	100	75/25	70	63/37	100	2	2	1
Kaul[23]	2000	14	12/2	61	14/0	15	2	...	...
Kirsch[24]	2001	53	38/15	71	36/17	57	3	1	...
Lanzino[25]	1999	18	12/6	69	9/9	18	...	...	...
Malek[26]	2000	28	18/10	71	18/0	18	...	1	...
Mericle[27]	1999	21	13/8	64	12/9	21	...	...	...
Paniagua[28]	2001	62	NG	67	52/10	69	2	2	1
Pappada[29]***	2001	27	NG	NG	25/2	27	...	...	...
Parodi[30]	2000	21	20/1	70	6/15	21	1	...	...
Qureshi[31]	2002	71	43/28	71	27/46	73	...	1	1
Roubin[32]	2001	528	356/172	69	241/287	604	29	6	8
Shawl[33]	2000	170	100/70	73	104/66	192	4	1	...
Vozzi[34]	1997	22	16/6	68	12/10	19	1	1	...
Waigand[35]	1998	53	42/8	NG	14/36	53	1	...	1
Total		2357				2537	94	28	18

*10 patients stented with cerebral protection devices.
**2 patients treated with cerebral protection devices.
***3 patients treated with protection devices.

had been treated for radiation-induced or inflammatory carotid artery stenoses.

In both groups the most commonly used stents were self-expandable Easy Wallstents (Boston Scientific–Schneider Corp), SMART stents (Cordis), and Palmaz biliary stents (Johnson and Johnson Interventional Systems Co). In most recent studies the periprocedural protocol was similar, and the patients had received either ticlopidine (250 mg twice daily) or clopidogrel (75 mg daily) as well as aspirin (100 mg daily) for at least 48 hours before the procedure and for at least 2

TABLE 2. Carotid Angioplasty and Stent With Cerebral Protection: Study Characteristics and 30-Day Outcomes

Author	Year	No. of Patients	Male/Female	Mean Age, y	Symp/Asymp	No. of Treated Arteries	Minor Stroke	Major Stroke	Death
Adami[53]	2002	30	22/8	72	15/15	30	...	...	...
Al-Mubarak[55]	2002	162	128/34	68	77/85	164	2	...	2
D'Audiffret[17]	2001	15	NG	NG	NG	15	...	...	...
Dietz[57]	2001	43	30/13	67	43/0	43	...	...	1
Guimaraens[58]	2002	164	128/36	63	146/18	194	2	...	3
Henry[66]	1999	167	129/38	70	74/93	184	...	2	1
Jaeger[60]	2001	20	12/8	67	13/7	20	...	...	...
Parodi[30]	2000	25	15/10	69	12/13	25	...	...	...
Reimers[62]	2001	84	63/21	69	30/54	88	1	...	1
Tübler[63]	2001	54	46/8	69	NG	58	...	1	...
Whitlow[64]	2002	75	54/21	67	75/0	75	...	...	...
Total		839				896	5	3	8

TABLE 3. Risk Factor Distribution Separated by Groups According to the Use of Cerebral Protection Devices

Risk Factors	CAS Without Protection	CAS With Protection	*P*
Hypertension	79%	73%	NS
Hyperlipidemia	57%	66%	NS
Tobacco use	53%	43%	NS
Diabetes	32%	34%	NS
Coronary artery disease	51%	43%	NS
Previous CEA	16%	10%	NS
Contralateral ICA/CCA occlusion	9%	7%	NS

CAS indicates carotid angioplasty and stenting; ICA, internal carotid artery; CCA, common carotid artery.

weeks after the procedure. Notably, in the early study of Diethrich et al,[18] the patients had only received aspirin.

Although higher complication rates of CEA or CAS procedures in symptomatic patients have been reported in the past,[67] the periprocedural and 30-day complication rates were not presented separately for patients with symptomatic or asymptomatic CAD in most studies.

Table 4 summarizes the overall complications within 30 days in patients treated with and without cerebral protection in patients with symptomatic and asymptomatic CAD. The combined stroke and death rate within 30 days was 1.8% in patients treated with cerebral protection devices compared with 5.5% in patients treated without cerebral protection devices ($\chi^2=19.7$, $P<0.001$). This effect was mainly due to a decrease in the occurrence of minor strokes (3.7% without cerebral protection versus 0.5% with cerebral protection; $\chi^2=22.4$, $P<0.001$) and major strokes (1.1% without cerebral protection versus 0.3% with cerebral protection; $\chi^2=4.3$, $P<0.05$), whereas the death rate was nearly identical ($\approx$0.8%; $\chi^2=0.3$, $P=0.6$).

When these numbers were used to calculate odds ratios, there was a 3-fold increased risk of any stroke or death and a >6-fold increase of minor stroke within 30 days of CAS without protection compared with protection.

When we analyzed those studies without protection that differentiated between symptomatic and asymptomatic CAD, the combined stroke and death rate within 30 days was significantly higher in symptomatic than in asymptomatic patients (6.4% versus 1%; $P<0.01$).

In both groups there was no clear relationship between the year of publication and the reported complications. However, the high combined stroke and death rate of 12% in the study of Diethrich et al[18] is likely due to the sole use of aspirin before and after stenting. Nonetheless, even after this study was excluded from the analysis, the combined stroke and death rate within 30 days was still significantly lower in those patients treated with cerebral protection devices than in those patients treated without protection (1.8% versus 5.2%; $P<0.01$).

TABLE 4. Comparison of Overall Minor, Major Stroke or Death Within 30 days of Carotid Angioplasty and Stenting With and Without Cerebral Protection

	Events per Procedure	
	Without Cerebral Protection	With Cerebral Protection
Minor stroke	94/2537	5/896
Major stroke	28/2537	3/896
Death	18/2537	8/896
Any stroke or death	140/2537	16/896

Discussion

Since 1990 many single-center studies on CAS have been published, reflecting the increased enthusiasm for the application of CAS in the treatment of CAD. However, before widespread application of these new techniques, they must be evaluated critically by properly performed prospective, randomized trials. While only 1 prospective multicenter trial comparing endovascular versus surgical treatment for CAD has been reported to date,[4] 3 state-of-the-art large-scale clinical trials have clearly established the value of CEA to reduce the risk of stroke in patients with symptomatic or asymptomatic high-grade CAD.[1–3]

To validate CAS as an alternative treatment strategy, case series and uncontrolled trials are generally considered to be of low scientific value. Nevertheless, the collective information from these observational studies is useful for informing patients and as a source of decision making in everyday clinical practice until the results of further multicenter trials are available. Additionally, the collective information from observational studies is pivotal in planning further randomized trials.

On the basis of a total of 2537 stented arteries, the overall stroke and death rate within 30 days of 5.5% in patients treated with CAS without cerebral protection is similar to the results of an unmonitored worldwide survey of 5210 CAS procedures (30-day procedure-related mortality rate of 0.86%, major stroke rate of 1.49%, and minor stroke rate of 2.7%).[68] This figure is also comparable to the results of the large CEA trials, in which the overall stroke and death rates within 30 days were 5.8%,[1] 7.5% for symptomatic patients,[3] and 2.3% for asymptomatic patients.[2] With the use of the data of those CAS studies that differentiated between symptomatic and asymptomatic CAD, the combined stroke and death rate within 30 days was 6.4% in symptomatic and 1% in asymptomatic patients. The combined stroke and death rate within 30 days of 6.4% in symptomatic patients is in the range of 7.8% found in a recent survey of the literature, in which most symptomatic patients had been treated with angioplasty alone.[5] Although a comparison between these 2 reviews should be made with caution because of the wide heterogeneity in patients and study designs, the similar complication rates indicate that the additional stent deployment does not increase clinically relevant thromboembolic complications. While this might appear self-evident, the insertion of a stent is associated with an increased occurrence of microembolic signal as detected by transcranial Doppler,[54] which could lead to more thromboembolic complications.

The increasing enthusiasm for nonsurgical endovascular procedures and the favorable comparison of the early outcome of CAS without protection with CEA in this analysis

should not hide the fact that on average almost 6% of all patients had experienced a minor or major stroke or died within 30 days of the CAS procedure. In an attempt to reduce periprocedural complication rates during CAS, cerebral protection devices were developed in the past few years. These are based either on a temporary distal balloon occlusion with subsequent aspiration of embolic particles, such as the PercuSurge system, or on intravascular filter devices such as the NeuroShield system (MedNova Ltd). From a theoretical point of view, the maintenance of antegrade blood flow might be an advantage of intravascular filter devices, whereas balloon protection systems have a favorable low-crossing profile.

The findings of our review suggest that the use of cerebral protection devices during CAS in general can significantly reduce thromboembolic complication rates, namely, the occurrence of minor and major strokes. Accordingly, a recent study has demonstrated a significant reduction of the frequency of microembolic signals during protected versus unprotected CAS.[54] While the type of cerebral protection devices that offer the best results needs to be established in randomized trials, there was no significant difference in the overall stroke and death rate within 30 days in patients treated with balloon or intravascular filter protection devices. The missing difference in fatal outcomes within 30 days in comparison to CAS procedures without cerebral protection is likely attributable to the inclusion of all cardiac deaths in both groups.

Despite these encouraging preliminary results, there are several points of concern, some of which are also applicable to the CAS data without protection. In general, our systematic review of the literature is clearly limited by the retrospective analysis of the reported case series and small studies, some of which showed severe methodological weaknesses. There was a wide heterogeneity in the study designs, material, and patient populations. Furthermore, differential complication rates for CEA in symptomatic and asymptomatic patients are well known.[67] However, only a minority of CAS studies presented the early complication rates separately for patients with symptomatic or asymptomatic CAD. As in any field of medical sciences, publication biases likely exist toward selective submission and acceptance of studies with good results over studies with poor results. Finally, this review concerned a newly developed treatment. Increasing expertise within single institutions might influence the complication rates. While the data were not sufficient to analyze the effect of learning on current complication rates, Roubin et al[32] demonstrated a significant reduction of the overall 30-day minor stroke rate during CAS without protection with increasing experience in the largest single-center study reported to date. This possible effect on outcome must be taken into account when the favorable results of CAS procedures with cerebral protection are interpreted, particularly when one considers that these new therapeutic devices were tested primarily in very experienced centers.

To validate the effectiveness of CAS as an alternative to CEA, neither the results of CAS without protection nor the favorable results of CAS with protection of this systematic review can replace properly performed randomized trials. On the other hand, our results suggest that the use of cerebral protection devices can significantly reduce thromboembolic complications during CAS. Therefore, future randomized trials comparing CEA with CAS will have to take into account the rapid technological improvements in the field of endovascular therapy.

Irrespective of the results of large trials, it should be stressed that the usefulness of any revascularization procedure for stroke prevention is principally dependent on a low complication rate within each institution. To achieve a beneficial effect of CEA versus medical therapy alone, the combined mortality and morbidity rate should be $<3\%$ for asymptomatic patients and $<6\%$ to 7% for symptomatic patients.[69] Although the heterogeneity of patient populations and different risk profiles might hamper the comparability of data across various institutions, the combined stroke and death rate was $>8\%$ in 3 CAS series without cerebral protection, indicating that CAS might not have been an efficient therapy in some institutions.[14,18,22] The large variability of the early complication rates, ranging from 0% to 17%, (or at least those that are reported and published) stresses the need for ongoing evaluations of all complication rates during CAS within single institutions.[52] Since the low complications rates of large multicenter CEA trials cannot be generalized to everyday clinical practice without reservation,[70,71] this call for continuing evaluations should also include all surgical procedures within single institutions.

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Carotid Artery Stenting in Patients With High-Risk Anatomy for Carotid Endarterectomy

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Purpose: To report the results of carotid artery stenting (CAS) in patients considered to have high-risk anatomical characteristics for carotid endarterectomy.
Methods: CAS was performed in 39 carotid arteries of 37 consecutive patients (26 men; mean age 72 ± 8 years, range 56–88) who met the criteria for high-risk surgical anatomy: previous ipsilateral carotid endarterectomy (20/39, 51.3%), common carotid bifurcation above the mandibular angle (5/39, 12.8%), contralateral carotid artery occlusion (15/39, 38.5%), or previous radiation therapy to the neck (1/39, 2.6%). Palmaz, Integra, or Wallstents were deployed via a percutaneous femoral artery access. Independent neurological evaluation was performed at specified time points, and a dedicated committee adjudicated all clinical events.
Results: Procedural success was 100%, with no major in-hospital complications. Neurological events were rare. Only 1 (2.6%) transient ischemic attack occurred prior to discharge; at 30 days, 1 (2.6%) additional minor stroke had been observed, giving a 2.6% cumulative 30-day "death plus any stroke" rate. Over a mean 11 ± 6-month follow-up, 2 (5.4%) patients died of nonneurological causes, but there were no strokes.
Conclusions: CAS is a viable endovascular revascularization technique that can be performed safely and effectively in patients with high-risk anatomy for carotid endarterectomy.

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Key words: angioplasty, stroke, carotid artery, occlusive disease, Palmaz, Wallstent, Integra

Carotid endarterectomy (CE) is considered to be of high risk in several patient subsets that have been largely excluded from the CE randomized trials.[1–3] One group consists of patients with recurrent disease after CE. Surgical repair of restenotic lesions has a 3% perioperative mortality and a perioperative stroke rate up to 12%.[4,5] Neck irradiation is another factor that appears to increase operative risk (7% perioperative stroke rate),[6] as is the presence of an occluded contralateral carotid artery. Subset analysis of the NASCET (North

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American Symptomatic Carotid Endarterectomy Trial) trial indicated that patients with contralateral carotid occlusion had significantly greater risk for CE complications (14.3%) compared to patients with a patent contralateral carotid artery (5.1%).[1,7] Last, a common carotid bifurcation above the level of the second cervical vertebral body hinders surgical access to the internal carotid artery (ICA) distal to the lesion.[8]

The term "high-risk surgical anatomy" does not imply that CE is "absolutely contraindicated" in these patients. In fact, several recent registries have reported low complications after CE in some of these patient subsets.[9–13] On the other hand, these results, from experienced high-volume centers, likely do not reflect the average surgical risk for lesions with any of the above characteristics.[3,14] Nonetheless, they underline the effort to optimize the surgical results in these selected patients with high-risk surgical anatomy.

Carotid artery stenting (CAS) is an investigational revascularization technique that we have studied in patients meeting any of the above 4 criteria for high-risk surgical anatomy.

METHODS

Thirty-seven patients (26 men; mean age 72 ± 8 years, range 56–88) with high-risk anatomy for CE underwent CAS in 39 carotid arteries between October 1995 and August 1998. No patient was excluded from CAS because of clinical comorbidity, and most patients were referred for the minimally invasive alternative after a vascular surgeon refused CE. The prevalences of the high-risk criteria were: 20 (51.3%) of the 39 arteries had undergone CE, 5 (12.8%) lesions were above the mandibular angle, 15 (38.5%) target arteries were associated with a contralateral occlusion, and 1 (2.6%) artery was in a patient who had undergone radiation therapy to the neck. Patients were considered symptomatic at the time of CAS if they had had an ipsilateral neurological event within the previous 4 months. Lesion severity criteria matched the NASCET recommendations of ≥60% stenosis in asymptomatic patients and ≥70% for symptomatic lesions.[1–3]

TABLE 1
Baseline Characteristics of 37 Patients Undergoing 39 CAS Procedures

Clinical characteristics	
Age, y (mean ± SD)	72 ± 8
Male sex	26 (70.3%)
Myocardial infarction	18 (48.6%)
Coronary artery bypass surgery	20 (54.1%)
Diabetes	8 (21.6%)
Hypertension	32 (86.5%)
Chronic renal insufficiency	9 (24.3%)
Peripheral vascular disease	27 (73.0%)
Neurological characteristics	
Transient ischemic attack	18 (48.6%)
Minor stroke	15 (40.5%)
Major stroke	4 (10.8%)
Contralateral carotid occlusion	15 (38.5%)*
Contralateral carotid stenosis	18 (46.2%)*
Previous carotid endarterectomy	25 (63.0%)*
Ipsilateral	20 (54.1%)*
Bilateral	12 (30.8%)*

* Rates are per artery.

Severe cardiovascular and medical comorbidity characterized this population (Table 1). Half the patients (51.4%) had histories of ipsilateral stroke and transient ischemic attacks (TIA, 48.6%). However, only 9 (24.3%) patients had the event within 4 months of hospital admission and were thus considered symptomatic.

The lesion was located in the internal and common carotid in 2 (5.4%) patients and in the left ICA in 24 (64.9%); the remaining lesions were located in the right ICA. Twenty (51.3%) lesions had angiographically documented calcification, and at least a moderate degree was observed in 11 (28.2%). Ulceration was seen in 16 (41.0%) and likely thrombus in 3 (7.7%). Tortuosity at the lesion level was 34° ± 28° (range 0–100°) and 31° ± 19° (range 10–70°) at the bulb level.

An interdisciplinary team of interventional cardiologists, neuroradiologists, and neurologists was involved in patient care, according to a protocol approved by the hospital's Institutional Review Board. Neurological evaluation was scheduled at specified intervals: pretreatment and before discharge; at 1, 6, and 12 months; and yearly thereafter. The cerebral circulation was routinely investigated angiographically before and after CAS; computed

TABLE 2
Angiographic Results in 39 Carotid Arteries

Variable*	
Lesion length, mm	21.3 ± 9.1
Number of lesions >20 mm	20 (51.3%)
Carotid bulb diameter, mm	8.0 ± 2.0
Distal reference diameter, mm	4.5 ± 1.0
Prestent minimal lumen diameter, mm	1.4 ± 1.0
Final minimal lumen diameter, mm	4.4 ± 1.0
Prestent percent diameter stenosis	74 ± 5
Final percent diameter stenosis	1.0 ± 0.1

* All values mean ± SD unless otherwise indicated.

tomography or magnetic resonance imaging of the brain and carotid duplex scanning were recommended pre- and posttreatment.

Percutaneous CAS was performed via a 9-F femoral arterial sheath. Temporary pacemaker insertion and pretreatment with atropine were routine. Heparin was administered as a single 5000-unit bolus after sheath insertion. Predilation with a 4.0-mm noncompliant balloon was followed by implantation of any of 3 stent models: Palmaz (Cordis Endovascular, Warren, NJ, USA), Wallstent (Boston Scientific, Natick, MA, USA), or Integra (Boston Scientific). Stent selection was based on availability, operator preference, and the acquired knowledge on hemodynamic complications after CAS (currently, self-expanding stents are used routinely[15]). Stents were dilated after deployment with a balloon matched to the size of the distal ICA reference diameter. Ticlopidine therapy was typically initiated within 24 hours prior to the procedure, using an initial 500-mg dose; the antiplatelet agent was continued for 4 weeks (250 mg bid) in combination with aspirin (325 mg daily).

An independent core angiographic laboratory performed qualitative analysis, using standard methods and quantitative analysis with digital calipers; reference vessel and lesion site measurements were made using NASCET methodology.[1–3] Angiographic success was defined as a final diameter stenosis <30%; procedural success was angiographic success and the absence of major procedural complications.

Clinical follow-up was obtained through contacts with patients and referring physicians by a Data Coordinating Center. All events were source documented and adjudicated by a dedicated committee. Major complications included death, myocardial infarction, urgent CE, or major permanent stroke. TIA was a cerebrovascular event that resolved completely within 24 hours. A minor stroke was a new neurological deficit that increased the National Institutes of Health (NIH) Stroke Scale score by ≤4.[16] A major stroke was a new neurological deficit that increased the NIH Stroke Scale by >4. Cerebral infarctions were categorized as major and minor stroke. Embolization in the distribution of the ophthalmic artery was considered a neurological event and was incorporated in the above criteria.[15]

RESULTS

Angiographic (Table 2) and procedural success was achieved in 100% of patients. The length of hospital stay was 2.2 ± 2.4 days, including 0.2 ± 0.8 days in the intensive care unit. There were no major in-hospital complications (Table 3), and all patients had patent carotid arteries at the predischarge duplex ul-

TABLE 3
Clinical Events Associated With Carotid Stenting of 39 Lesions in 37 Patients

	In-Hospital	30-Day	Follow-up*
Death			
Transient ischemic attack			
Minor stroke		1/39 .6%)	
Major stroke			
Q-wave myocardial infarction			
Carotid endarterectomy			0

* Mean 11 ± 6 months.

trasound study. There was only 1 (2.7%) in-hospital neurological event (TIA). Four (10.8%) patients developed prolonged (>1 hour) transient (<24 hours) postprocedural hypotension, which was treated with isotonic fluid administration. Three (8.1%) patients experienced postprocedural bradycardia, which was treated with atropine. All hypotensive and bradycardic episodes were clinically attributed to vagal stimulation, without evidence of hemorrhagic volume depletion (negative abdominal CT scans for retroperitoneal bleeding). There was only 1 (2.7%) vascular complication necessitating surgery for a femoral artery pseudoaneurysm at the access site.

All patients completed 6-month follow-up (mean 11 ± 6 months), and 68% were examined at 1 year. Two (5.4%) patients died at 3 and 13 months from a cardiac event. The only neurological event (2.6%) was a minor ipsilateral stroke that occurred within 30 days of discharge in a patient who already had a long-standing ipsilateral neurological deficit. Thus, the 30-day cumulative rates were: 5.1% "death plus any neurological event" (n = 2), 2.6% "death plus any stroke" (n = 2), and 0% "death plus any major/disabling stroke."

DISCUSSION

According to published reports,[17–22] CAS appears to be safe, feasible, and efficacious, even in patients with postsurgical restenosis and contralateral carotid occlusion.[20] Moreover, CAS appears to have low incidences of periprocedural complications and 6-month angiographic restenosis and target vessel revascularization (<5%).[17–19] However, these studies focused mainly on the high comorbid profile of the treated patients. A careful evaluation of both vascularization methods in certain lesion subsets may amplify the merits and minimize the drawbacks of each technique.

We investigated the results of CAS in a patient group with high-risk anatomy for CE, which incorporated patient groups that have typically been excluded from CE trials because of the potential for increased complications, regardless of medical comorbidity.[4–8] This cohort represented 28% of our CAS cases during the study period.[15]

In our patient series, all the arteries were successfully stented, with few neurological sequelae. At the well-accepted safety window of 30 days,[3] no deaths or disabling strokes had been observed, and only isolated incidences of TIA and minor stroke were seen (2.6% overall "all cause death plus any stroke" rate). Thus, the endovascular approach appears to be specifically helpful in the treatment of carotid stenoses with anatomical features predisposing to a higher surgical risk. Although randomized trials will be needed to determine the superior carotid revascularization method in routine cases, we believe that results from CAS series such as this one will strengthen the ultimate impact of the results of the major randomized studies.

This study was an analysis of consecutive patients; there were no surgical or medical control groups. In addition, the sample size was relatively small and the follow-up time limited. Thus, no firm conclusions comparing CE with CAS can be drawn solely from these data. Our main purpose was to observe the procedure-related complication rates after CAS, particularly the 30-day outcome, which is considered to be the most important safety parameter for the evaluation of carotid revascularization procedures.[3] In this regard, CAS appears to have a low complication rate in patients with high-risk anatomical characteristics for CE. These specific anatomical features may indicate a differential efficacy and safety profile for CE and CAS.

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Cerebral Protection During Carotid Artery Stenting

Collection and Histopathologic Analysis of Embolized Debris

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Background and Purpose—Histopathologic analysis was performed to better understand quantity, particle size, and composition of embolized debris collected in protection filters during carotid artery stent implantation.

Methods—Elective carotid stent implantation with the use of a distal filter protection was attempted in 38 consecutive lesions (36 patients) of the internal carotid artery presenting >70% diameter stenosis (mean, 82.1±11.1%). Mean age of the patients was 70.7±7.7 years; 75% were men, and 50% of patients had previous neurological symptoms.

Results—In 37 lesions (97.4%) it was possible to position the filter device, and in all lesions a stent was successfully implanted. The only complication occurring in the hospital and during the 30-day follow-up was 1 death due to acute myocardial infarction. Neurological sequelae did not occur. Histomorphometric analysis was performed on the filters. Presence of debris was detected in 83.7% of filters. The mean surface area of the polyurethane membrane filter covered with material was 53.2±19.8%. Particle size ranged from 1.08 to 5043.5 μm (mean, 289.5±512 μm) in the major axis and 0.7 to 1175.3 μm (mean, 119.7±186.7 μm) in the minor axis. Collected debris consisted predominantly of thrombotic material, foam cells, and cholesterol clefts.

Conclusions—By the use of distal protection filters during carotid artery stenting, it was possible to collect particulate debris potentially leading to distal vessel occlusion in a high percentage of cases. Qualitative analysis of embolized material showed debris dislocated during the percutaneous intervention from atheromatous plaques. **(*Stroke*. 2002;33: 456-461.)**

Key Words: angioplasty ■ carotid arteries ■ embolism ■ pathology ■ stents

Stent placement for extracranial carotid artery disease has emerged as a potential alternative to carotid endarterectomy, the current gold standard treatment for carotid artery stenosis.[1–3] However, compared with the surgical approach, percutaneous carotid stenting is accomplished with an increased incidence of microemboli, as shown by transcranial Doppler monitoring.[4] These emboli are associated with a higher neurological complication rate[5] and are also recognized as a potential cause of periprocedural stroke during endarterectomy.[6–9]

Only a few studies give a detailed morphological evaluation of the material retrieved during percutaneous intravascular procedures.[10–15] From these studies it appears that most of the embolic dissemination occurs during iatrogenic manipulation of the atheromatous plaque.

Protection devices have the potential to reduce the incidence of intracranial debris embolization and render percutaneous carotid artery revascularization safer.[12–19] In light of novel observations made by Reimers et al[18] suggesting the safety and feasibility of filter devices for carotid artery stenting, the present prospective study was designed to analyze histopathologically debris collected during intravascular percutaneous carotid artery stent implantation with the use of a recently available protection device.

Subjects and Methods

Patient and Lesion Characteristics

Between September 2000 and February 2001, elective carotid artery stent implantation with the use of a distal protection filter was attempted in 38 lesions in 36 consecutive patients. These were the most recently treated patients and represent 38% of all lesions treated in our center to date. Eighteen patients (50%) had previous symptoms of transient ischemic attack and/or stroke. All 37 lesions produced a >70% diameter stenosis (mean, 82.1±11.1%) of the internal carotid artery. Thirty-seven lesions were de novo lesions, and 1 was restenosis occurring after endarterectomy. The clinical and angiographic characteristics are listed in Table 1.

Angiographic Evaluation

Baseline and postprocedural quantitative angiography was performed online with the use of the automated analysis system coordinated with the angiographic equipment (Intergris 3000, Phil-

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TABLE 1. Clinical and Angiographic Characteristics

	Patients (n=36)/ Lesions (n=38)
Mean age, y	70.7±7.7
Male sex	27 (75%)
De novo lesions	37 (97.4%)
Previous endarterectomy	1 (2.6%)
Previous stroke/TIA	18 (50%)
Angiographic evaluation	
Mean % diameter stenosis	82.1±11.1
Irregular lesion	28 (73.7%)
Ulcerated lesion	15 (39.5%)
Lesion calcification	15 (39.5%)
Bilateral significant (>70%) carotid disease	12 (31.6%)

TIA indicates transient ischemic attack.

ips, Medical Instruments). The angiographic diameter stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria with the distal, nontapering portion of the internal carotid artery used as the reference segment.[20] Qualitative angiographic evaluation was performed offline by 2 independent operators according to the criteria described by Mathur et al.[21]

Drug Regimen

All patients were taking aspirin (100 to 325 mg). Ticlopidine (500 mg) was started at least 48 hours before the procedure. Heparin 70 to 100 U/kg was given intra-arterially to achieve an activated clotting time of >250 seconds. In case of inadequate anticoagulation, additional boluses of 2000 U of heparin were given until the target value was achieved. Atropine 1 mg was administered only when required to treat bradycardia during balloon inflation. Arterial blood pressure was monitored during the procedure and, if needed, was modulated with nitrates or dopamine. After the procedure, patients received aspirin indefinitely and ticlopidine for 1 month. Glycoprotein IIb/IIIa inhibitors were not used.

Carotid Stenting Procedure

Percutaneous access was gained through the femoral or brachial (1 lesion) artery. Long sheaths (6F or 7F) or coronary guiding catheters (8F) were advanced into the common carotid artery on long 0.035-inch support wires previously placed in the external carotid artery with the use of 4F or 5F diagnostic catheters. Angiography of the carotid artery and the intracranial circulation was performed in angulated views (Figure 1). Stenoses were crossed with the filter protection device. After filter opening, predilatation with 3.5- to 4.0-mm-diameter coronary angioplasty balloons was performed in 60.5% of the lesions at medium-low pressure (6 to 10 atm) until complete expansion of the balloon was seen. Appropriately sized self-expandable stents (Carotid Wallstent, Boston Scientific–Schneider; Smart 0.018 inch, J&J Cordis) were implanted, covering the carotid bifurcation in all cases. All stents were postdilated with the use of 5.5- to 7.0-mm (mean, 6.06±0.62 mm) balloons at medium-high pressures (8 to 12 atm; mean, 11.0±0.1). The arterial sheaths were removed on the same day. After the procedure, patients were transferred to the cardiology ward with continuous ECG monitoring for the following 12 hours, and noninvasive blood pressure measurements were taken every 2 hours for at least 12 hours.

Filter Device

The first-generation filter device (Angioguard, J&J Cordis) consists of an olive-shaped nitinol skeleton covered at its distal portion by a polyurethane membrane with pores of 100 μm in diameter. The filters used had diameters of 6, 7, and, in 1 case, 8 mm. The device is connected to a proximal, floppy wire tip and a distal 0.014-inch wire shaft 300 cm in length used as guidewire for the interventional procedure.

The closed filter, contained in a delivery sheath (diameter of 0.061 to 0.065 inch) with a maximum profile of 4F to 4.5F, was advanced through the lesion. The filter was opened in the internal carotid artery distal to the lesion by removal of the delivery sheath. A filter 0.5 to 1.0 mm larger than the visually estimated distal vessel diameter was chosen. This was to ensure complete apposition of the filter to the vessel wall. At the end of the procedure, a retrieval sheath was advanced, and the filter was closed and removed from the artery. Visual inspection of the filter was performed by the interventional cardiologist at the end of each procedure to evaluate the macroscopic presence of material.

Neurological Evaluation

A board-certified neurologist performed a complete neurological examination, including the National Institutes of Health Stroke Scale, before and after stent implantation.

Follow-Up

Clinical follow-up was performed 30 days after the procedure in all patients.

Histopathologic Evaluation

After removal, the filters were immediately fixed in 10% neutral, buffered formalin. Photographs of the device in its integrity and after removal of the metallic wire were taken under a stereo microscope. These images were used for the computerized morphometric analysis with Image-Pro Plus software (Media Cybernetics). The total area of the filter membrane and the area covered by particulate material were quantified. The percentage of membrane occupied by debris was expressed as percentage of covered surface area. According to the extension of the covered area, patients were divided into 4 groups: group 1 had a covered area of ≤25%, group 2 >25% and ≤50%, group 3 >50% and ≤75%, and group 4 >75%. If particles were entrapped in the scaffolding metallic wires, they were carefully removed and separately photographed. Particulate floating in the formalin was filtered and processed for histological characterization.

Particles identifiable as such were outlined by an experienced pathologist. The particles were subsequently counted and measured by the computer software. The 2 longest perpendicular diameters of

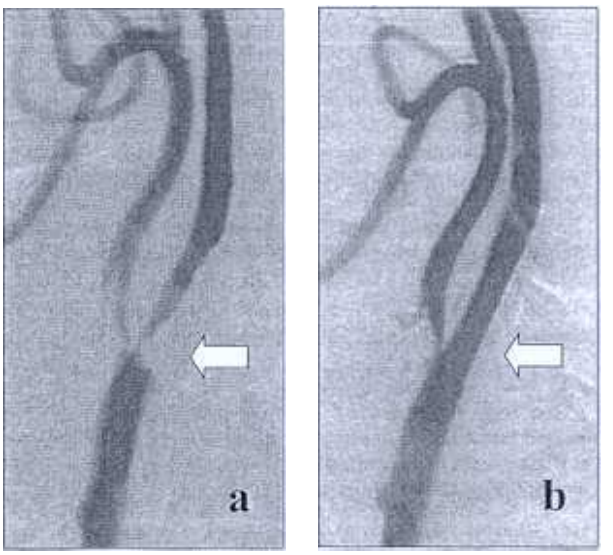

Figure 1. a, Severe (>90%) ostial stenosis of both the internal (arrow) and the external carotid artery is shown. b, The internal carotid artery (arrow) is shown after successful stent implantation performed with distal filter protection. The external carotid artery appears open with persistent significant ostial stenosis.

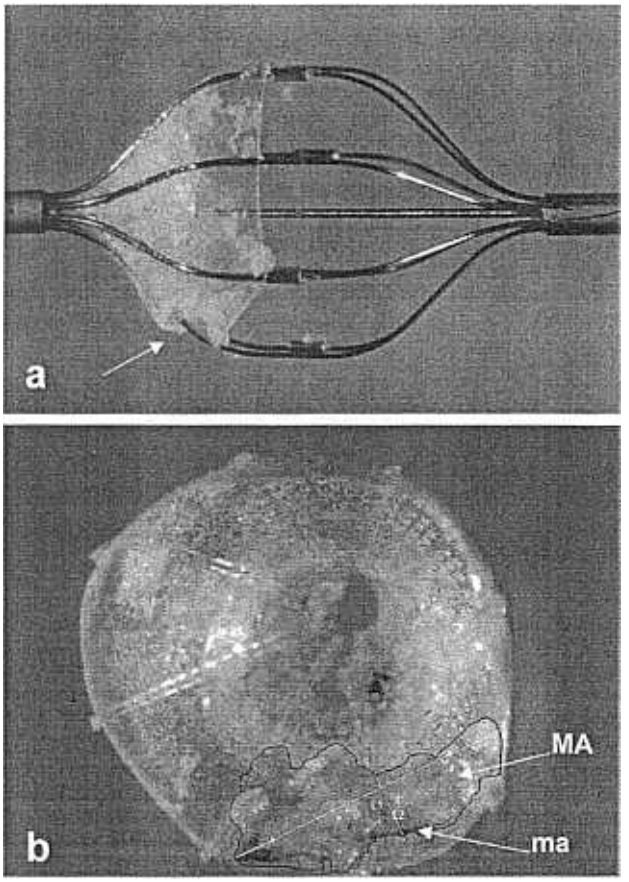

Figure 2. a, The filter device used during the procedures. Note the fold in the plastic membrane (arrow) that occurred during the retrieval of the device. b, The polyurethane plastic filter membrane after removal of the metallic wire containing embolic material. The inside of the filter membrane is shown, with morphometric measurements of a large particle (major axis [MA], 3492.2 μm; minor axis [ma], 1035.2 μm).

the largest particles were recorded (Figure 2). All measurements were made at least twice.

For histology and tissue characterization, the material was removed from the filter, dehydrated, and embedded in paraffin, and the sections (5 μm thick) were stained with hematoxylin-eosin and Heidenhain trichrome.

Scanning electron microscopy was performed on the internal surface of the polyurethane membrane after it had been flattened. After removal from the 10% buffered formalin, the material was washed first in normal saline solution and then in distilled water. Subsequently it was dehydrated in crescent series of alcohol, with a final incubation in amyl acetate, and processed for the CO_2 critical dry point and gold sputtering. The specimens were observed under a scanning electron microscope (Philips XL 30).

Statistical Analysis

The data were computerized and analyzed with the use of the GraphPad Prism Software package. Mean, SD, and lower and upper 95% CIs were calculated for all parameters. Results are expressed as mean±SD. $P<0.05$ was considered significant.

Results

Procedural and Follow-Up Results

In all patients it was possible to position a stent at the lesion site (Figure 1). In 1 case (2.6%) the filter could not be positioned, and an occlusive balloon protection was adopted (Guardwire, Percusurge Inc). In 5 cases (13.5%) the filter device crossed the lesion only after predilatation with the use of 2.0-mm-diameter coronary balloons. Distal vessel spasm, which resolved after intra-arterial nitrate administration, was observed during 3 procedures (8.1%). In 6 cases (16.2%) slow flow and in 2 cases (5.4%) no flow in the internal carotid artery occurred. The flow impairment resolved completely after filter removal in all 8 cases. Mean postprocedural diameter stenosis was 12.8±9.2%. Procedural data and results are shown in Table 2.

TABLE 2. Procedural Data and Results

	Lesions (n=38)
Successful stent procedure	
Filter successfully positioned	
Filter positioned only after predilatation (2.0-mm balloon)	
Filter did not cross lesion*	
Predilatation	
Vessel spasm resolved with intra-arterial nitrates	
Flow impairment resolving after filter removal	
Slow flow	
No flow	
Postdilatation	
Mean balloon diameter, mm	
Mean pressure, atm	
Mean % diameter stenosis, baseline	
Mean % diameter stenosis, postprocedural	
30-day mortality rate	

*Crossover to occlusive balloon protection, filter crossing after predilatation not attempted.

Careful neurological examination, including the National Institutes of Health Stroke Scale, performed after the procedure, at discharge, and during the follow-up visit at 30 days did not reveal the occurrence of any neurological complications. Two patients required prolonged intravenous dopamine infusion for persistent hypotension. The 30-day mortality rate was 2.8% (1 patient). This patient with unstable coronary disease suffered massive anterior myocardial infarction 4 days after the procedure and died 3 days later.

Histopathological Results

Microscopic evaluation revealed that particles could be detected in 31 of 37 filters (83.7%) and that they were adherent mostly to the filter device (Figure 2). The mean number of particles in these filters was 33.7±5.6 (range, 24 to 46). In 13 of 37 filters (35%), additional material was entangled in the scaffolding metallic wire. Only a small number of immersed particles were retrieved from the fixative. The average covered area on the plastic filter was 53.2±19.8%. Mean particle size ranged from 1.08 to 5043.5 μm (mean, 289.5±512 μm) in the major axis and from 0.7 to 1175.3 μm (mean, 119.7±186.7) in the minor axis (Figure 2b). The distribution of the size of the particles is shown in Figure 3, and results of the histopathological analysis are shown in Table 3. Scanning electron microscopy was performed, and mean particulate

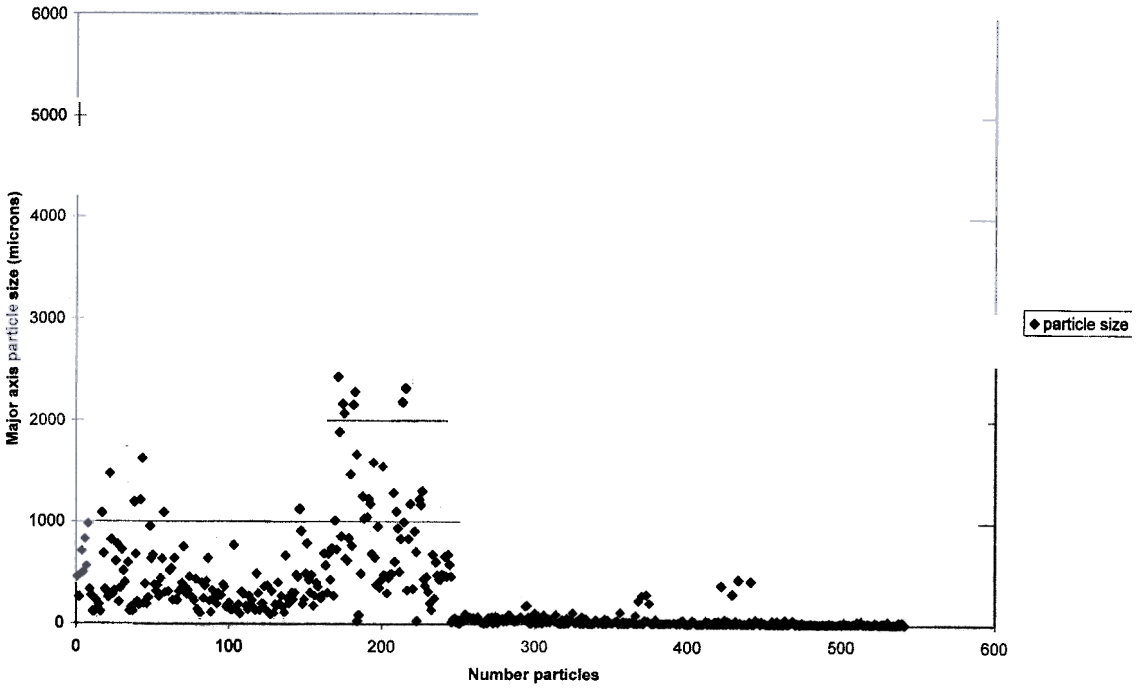

Figure 3. Distribution of size (major axis) and number of embolic particles captured during carotid artery stenting.

size of 311.6±251.5 μm in the major axis and 257.76±247.9 μm in the minor axis was observed (Figure 4). In all 8 filters of patients in which slow flow or no flow was observed, embolic material was detected, with an average covered area of 53.2±14.8%. Moreover, no relations could be detected between particle size and average covered area occupied by the material on the filters (*P*=NS).

Qualitative analysis with light microscopy revealed that the particles consisted primarily of soft acellular and amorphous material characterized by lipid-rich macrophages and cholesterol clefts. To a minor degree, calcium particulates and platelets entrapped in fibrin strands were found (Figure 5).

TABLE 3. Pathological Data

	Filters (n=37)
Macroscopic presence of debris	
Presence of particulate material at microscopic evaluation	
Mean % covered area on filter	
Mean % covered area on filter per group	
Group 1: covered area ≤25% (3.4±6.1)	8* (21.6%)
Group 2: covered area >25–≤50% (37.8±7.9)	10 (27.0%)
Group 3: covered area >50–≤75% (63.6±4.5)	15 (40.5%)
Group 4: covered area >75% (79.2±3.9)	4 (10.8%)
Mean particle size, μm	
Major axis	289.5±512
Minor axis	119.7±186.7
Mean no. of particles per filter	33.7±5.6
Filters with particles >300 μm, major axis	31/31 (100%)
Filters with particles >1000 μm, major axis	16/31 (51.6%)

*Including 6 filters without particulates.

All detected material is typically identifiable in an atheromatous plaque whether complicated or uncomplicated. The single case treated with distal occlusive balloon protection showed similar findings.

Discussion

Filter protection during carotid artery stenting has been recently reported by our group to be feasible and safe in a small cohort of patients with a low incidence of neurological complications.[18]

The present study shows that embolic particulates that are commonly released during carotid artery stent implantation[3,4] can be captured by distal filter protection devices. This is the clinical confirmation of the experience with filter protection in the ex vivo model reported by Ohki et al.[13] Debris was captured in 83.7% of procedures compared with 81%[12] and 100%[14,15] in previously published studies in which occlusive balloons were used for protection. The size of the particles detected in the present study (289.5±512 μm in diameter in the major axis; range, 1.08 to 5043.5 μm) was greater compared with the ex vivo filter evaluation (226±130 μm)[13] and 1 of the distal occlusive balloon studies (54.4 mm crystal and 110.67 mm lipoid mass)[5] and smaller compared with another distal balloon protection study (800 μm).[14] In our experience, as well as in all previous observations, particles >300 μm were found in all filters with debris.[12–15,18] The microcirculation encompasses vessels with diameter <300 μm.[22] The arterial network arborizes from the aorta to arteries up to 400 to 300 μm, small arteries with diameter between 300 and 100 μm, arterioles with diameter between 100 and 12 μm, and capillaries with diameter of approximately 12 μm. In the present study 100% of filters with materials presented particles >300 μm, and 52% of filters presented particles

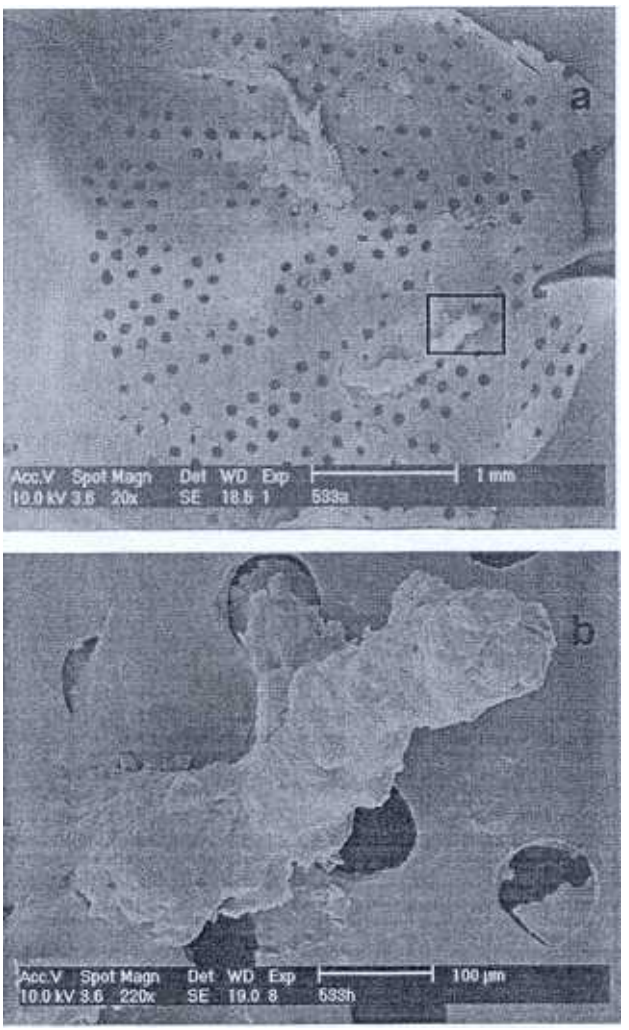

Figure 4. a, Scanning electron micrograph image of the luminal surface of polyurethane plastic filter membrane containing captured particles. b, The same filter at higher magnification of boxed area, showing captured particulates.

>1000 μm. It cannot be excluded that some of the retrieved thrombotic material could have been locally produced inside the filter, explaining the relatively high incidence (21.1%) of flow impairment and the high filter surface coverage of >50%, which was not correlated to the size of particles. As for the amorphous material, we cannot see any source other than the amorphous material dislocated from the atheromatous core of the plaque. All cases of transient flow impairment due to pore occlusion occurred immediately after postdilatation of the stent. Therefore, it appears that most emboli are released during this part of the procedure. Possible emboli release may occur during the passage of the closed filter device through the stenosis, and in the absence of intracranial Doppler we cannot exclude it. Protection systems such as low-profile distal occlusion balloons or proximal occlusion systems, which do not require any lesion crossing without protection, have the potential to reduce embolization during this procedural step.

It is, however, assumable that not all captured particles would have had acute clinical sequelae. The significance of

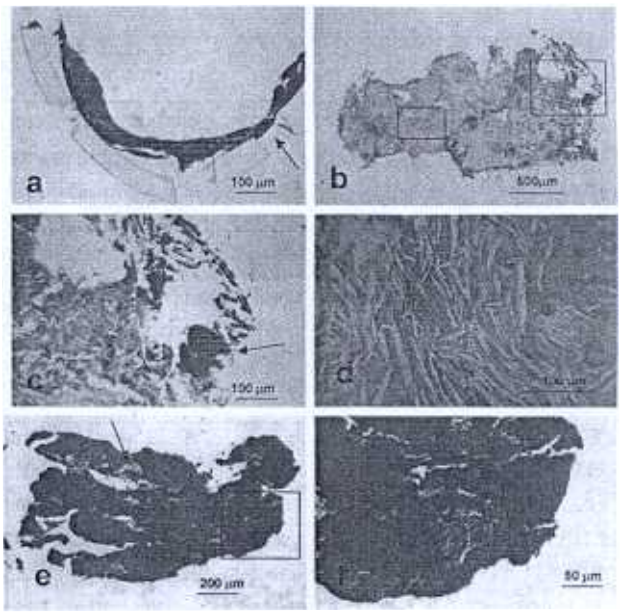

Figure 5. a, Heidenhain trichrome staining cross section of polyurethane filter membrane. Note thrombotic materials adherent to the inside of the membrane and the pores in the membrane (arrow) (magnification ×50). b, Hematoxylin-eosin staining of a particle removed from the filter (magnification ×10). c, A higher magnification of panel b (right boxed area): necrotic material, cholesterol clefts, and calcium precipitates can be observed (arrow). (magnification ×40). d, A higher magnification of panel b (left boxed area) showing amorphous, acellular material rich in cholesterol clefts (magnification ×62). e, Heidenhain trichrome staining of thrombotic material including fibrotic tissue fragments (arrow) (magnification ×20). f, A higher magnification of panel e (boxed area) with evidence of platelets (magnification ×80).

clinically silent embolization during carotid artery interventions has not yet been established, and possibly microvascular obstructions are difficult to recognize.[23,24] According to recent observations,[22] emboli can potentially trigger platelet aggregation and may amplify microvascular obstructions. A shower of small particulate matter could cause microvascular obstruction. Furthermore, particles of vasoactive substances contained within plaque or thrombus could cause intense, prolonged vasospasm and subsequent cerebral infarction.[25]

The histopathologic analysis showed that retrieved material consists of dislocated debris featuring atheroembolism as a consequence of atheromatous plaque squeezing and rupture occurring during carotid stent implantation. This result confirms the data of previously reported studies evaluating different emboli protection devices during percutaneous intravascular interventions.[11–15]

Our study confirms that this method of cerebral protection[18,25] is feasible and safe and that it limits intracranial debris embolization. Therefore, it strongly supports the use of protection devices during percutaneous carotid stenting. However, we could not exclude the development of a stroke even in the setting of distal protection.[25] In a recently published article, Roubin et al[2] reported the important reduction of periprocedural complication rate over 5 years of experience from 9.3% in the first year to 4.3% in the fifth year. This was probably due to refinement of stenting techniques and newly developed equipment. We cannot rule out, as suggested by Qureshi et al,[26] that the cardiac death

occurring in our study within the 30-day window may be in some way related to the hemodynamic instability after carotid stenting. To achieve the target of ≤3% periprocedural complication rate recommended by the American Heart Association/Society of Vascular Surgery guidelines[27] for the treatment of asymptomatic patients, cerebral protection may well be essential.

Limitations of the Study

Because of the absence of intracranial Doppler monitoring during the stent procedure, this study does not exclude the presence of emboli not captured by the filter. In a recent ex vivo study, the filter device captured 88% of embolized particles.[13] Moreover, the small study size does not allow conclusions regarding the clinical efficacy of protection filters. Larger evaluations are warranted.

Conclusions

The present study demonstrates that protection filters collect debris of significant quantity and size during carotid artery stent implantation. Histopathological analysis showed that the collected material is dislocated from the atherosclerotic plaque during the intravascular procedure. Protection devices have the potential to further reduce neurological complications during the treatment of carotid artery stenosis.

Acknowledgments

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Multicenter Evaluation of Carotid Artery Stenting With a Filter Protection System

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OBJECTIVES The aim of this study was to evaluate the feasibility and safety of carotid artery stenting (CAS) with a filter protection system.

BACKGROUND Neurologic events linked to the embolization of particulate matter to the cerebral circulation may complicate CAS. Strategies designed to capture embolic particles during carotid intervention are being evaluated for their efficacy in reducing the risk of these events.

METHODS Between September 1999 and July 2001, a total of 162 patients (164 hemispheres) underwent CAS with filter protection (NeuroShield, MedNova Ltd., Galway, Ireland) according to prospective protocols evaluating the filter system at three institutions.

RESULTS Angiographic success was achieved in 162 of the procedures (99%) and filter placement was successful in 154 (94%) procedures. Carotid access was unsuccessful in two cases (1%) and filter placement in eight cases (5%). Of the latter, five procedures were completed with no protection and three were completed using alternative protection devices. On an intention-to-treat basis, the overall combined 30-day rate of all-stroke and death was 2% (four events: two minor strokes and two deaths). This includes one minor stroke in a patient with failed filter placement and CAS completed without protection. There was one cardiac arrhythmic death and one death from hyperperfusion-related intracerebral hemorrhage. There were no major embolic strokes.

CONCLUSIONS Carotid artery stenting with filter protection is technically feasible and safe. Early clinical outcomes appear to be favorable and need to be confirmed in a larger comparative study. (J Am Coll Cardiol 2002;39:841–6) © 2002 by the American College of Cardiology Foundation

The efficacy of carotid endarterectomy (CEA) in preventing stroke is dependent on the perioperative incidence of stroke and death (1). Accordingly, the American Heart Association has set guidelines for the performance of CEA. On the basis of these guidelines, CEA should only be performed if the combined rate of perioperative stroke and death can be kept ≤6% in symptomatic patients and ≤3% in asymptomatic patients with severe extracranial carotid stenoses (1). Extrapolating these guidelines to the performance of carotid artery stenting (CAS), experienced groups have reported outcomes that are consistent with these recommendations (2–4). However, despite advanced stenting techniques, neurologic events may still complicate CAS and remain an obstacle to its widespread acceptance. Obstructive carotid artery lesions are known to contain friable thrombotic and atherosclerotic components that have the potential to embolize during intervention and may be responsible for the majority of the neurologic events during CAS. This has been demonstrated in an ex vivo human carotid artery model by Ohki et al. (5), as well as by several transcranial Doppler (TCD) studies during CAS (6). A number of "distal protection" strategies, designed to capture embolic debris released during carotid intervention, are currently being evaluated for their efficacy in minimizing the risk of embolic neurologic events. One such strategy is the placement of a temporary intravascular filter that captures embolic matter in the distal internal carotid artery (ICA) during intervention (6). The aim of this study was to prospectively investigate CAS with a filter protection system.

MATERIALS AND METHODS

Between September 1999 and July 2001, a total of 162 patients (164 hemispheres, 164 procedures) underwent elective CAS with a filter protection system (NeuroShield, MedNova Ltd., Galway, Ireland) according to prospective protocols examining the feasibility and safety of the system during CAS at three institutions: New York, 64 cases (40%); Milan, 50 cases (30%); and Sheffield, 50 cases (30%). The enrollment criteria were identical and included patients with symptomatic or asymptomatic extracranial ICA stenosis of ≥50% and ≥70% (diameter obstruction) respectively, as determined by carotid angiography. Additionally, all enrolled patients satisfied the following criteria: 1) age ≥18 years; 2) ability to understand the procedure and sign a written consent; 3) a negative pregnancy test in women of childbearing age; 4) suitable lesion for treatment with angioplasty and stenting (based on the absence of significant calcification, thrombus and extremely tortuous anatomy); 5)

From the *Lenox Hill Heart and Vascular Institute, New York, New York; †Centro Cuore Colombus-Interventional Cardiology, Milan, Italy; and ‡Sheffield Vascular Institute, Sheffield, United Kingdom. Support for the study came from MedNova Ltd. (Galway, Ireland), who supplied the filter devices (all patients), in addition to grant support at two centers (Colombus Hospital [Milan, Italy] and Sheffield Vascular Institute [Sheffield, England]).

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JACC Vol. 39, No. 5, 2002
March 6, 2002:841–6

Abbreviations and Acronyms

CAS	= carotid artery stenting
CEA	= carotid endarterectomy
CREST	= Carotid Revascularization Endarterectomy vs. Stenting Trial
ECA	= external carotid artery
ICA	= internal carotid artery
NIHSS	= National Institutes of Health Stroke Score
TCD	= transcranial Doppler

sufficient space for filter placement distal to the lesion; and 6) ICA diameter ≥4 mm but ≤6 mm.

Exclusion criteria included: 1) breastfeeding women; 2) stroke within seven days before the procedure; 3) National Institute of Health Stroke Score (NIHSS) of ≥15 within seven days before the procedure or baseline major ipsilateral stroke that is likely to confound the determination of the study clinical end points; 4) more than one ipsilateral carotid lesion requiring treatment; 5) the presence of a cardiac source of embolus (such as atrial fibrillation); 6) the presence of known intracranial tumors or vascular malformation; 7) renal insufficiency (creatinine ≥2.5 mg/dl); and 8) comorbidity with a life expectancy of ≤1 year.

The primary end points included: 1) technical success (angiographic and device success) and 2) procedural and 30-day incidence of minor stroke, major stroke, myocardial infarction and death.

All procedures were performed according to the guidelines of the Institutional Review Board or the local medical ethics committee. All patients signed a written consent. All patients had a complete neurologic evaluation performed by a neurologist that included an assessment of the NIHSS before and within 24 h after the procedure. Additionally (at Lenox Hill), clinical events were adjudicated, based on patient chart review, by an independent clinical events committee that was selected to include a neuroradiologist, a neurologist and a surgeon.

Clinical and procedural data were documented by a dedicated research coordinator using a special case report form and were entered into a computerized database. Thirty-day follow-up that included queries regarding potential neurologic events was completed on each patient. Imaging studies were utilized in determining occurrences of end points whenever necessary.

Patients were premedicated with clopidogrel (Plavix, Pfizer Inc., New York, New York) 75 mg once a day and aspirin 100 to 325 mg twice a day for a minimum of seven days before the procedure. Clopidogrel was continued for 30 days after CAS (14 days in Sheffield) and aspirin was continued indefinitely. All carotid stenting procedures were performed using a standard technique as previously described (7). A 7F/90-cm long guiding sheath (Shuttle, Cook Inc., Indianapolis, Indiana) was used to access the carotid artery. A single bolus of intravenous heparin (5,000 U or 70 U/kg) was administered at the beginning of the procedure. The filter system was employed according to the manufacturer's instructions as described later. Glycoprotein IIb/IIIa antagonists were not utilized.

Device description. The Generation-II NeuroShield (MedNova Ltd.) is a temporary intravascular filtration system designed to capture atheromatous material released during the carotid interventional procedures (Fig. 1). The system is composed of three major components: 1) the filter guidewire, 2) a delivery catheter and 3) a retrieval catheter.

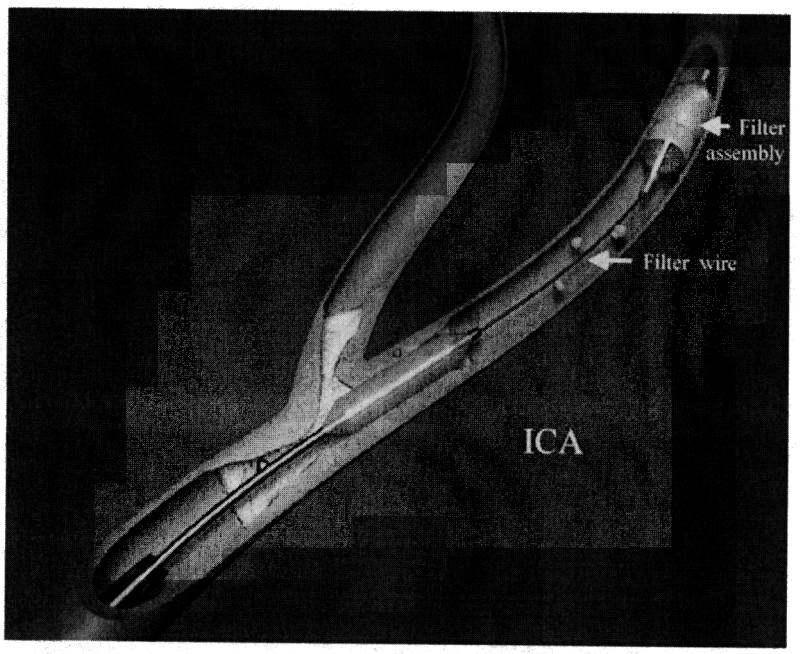

Figure 1. Application of the NeuroShield filter system during carotid artery stenting. The filter is mounted on a filter wire that is used to cross the lesion and deliver interventional balloon and stent catheters. ICA = internal carotid artery.

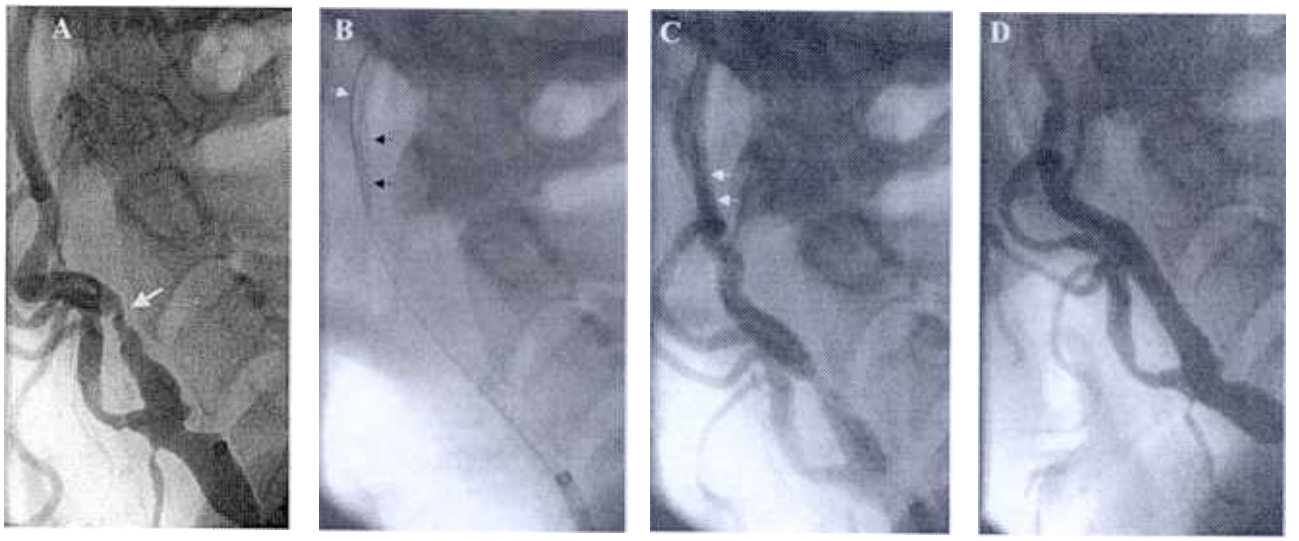

Figure 2. Carotid angiogram demonstrating flow preservation during carotid artery stenting with the filter protection system. **(A)** Preprocedural angiogram showing a high-grade stenosis of the internal carotid artery. **(B)** The filter **(the bottom two arrows)** is positioned distal to the lesion. In this case a "buddy wire" **(the white arrow)** was required to facilitate filter placement. **(C)** Carotid angiogram demonstrating flow through the filter **(arrows)**. **(D)** Final angiography: the stented site is widely patent.

The filter assembly is located at the distal end of 0.014-inch guidewire that is used to cross the lesion (Fig. 1). The filtration element, made of polyurethane, has four proximal entry ports and multiple distal perfusion pores (100 to 150 μm) that allow blood flow to the cerebral circulation (Fig. 2). The filter is available in diameters of 4 to 6 mm and is sized to the selected distal ICA segment (1:1). A preshaped Nitinol expansion system assists in filter deployment and apposition to the arterial wall.

Filter deployment and retrieval are performed using dedicated catheters. At the commencement of an interventional procedure, the filter system is loaded into the delivery catheter. The system is then advanced through the guiding sheath and across the target lesion into the distal ICA. The delivery catheter is withdrawn and, as it is withdrawn, the filter is deployed. After the delivery catheter is removed, an angiogram is obtained to document blood flow through the filter and document device placement distal to the target lesion (Fig. 2C). The filter guidewire is used to deliver the balloon and stent delivery catheters. Following the completion of the procedure, the filter assembly is recovered using the retrieval catheter. This is advanced over the guidewire and through the stented lesion, then further over the deployed filter assembly. As the retrieval catheter distal pod contacts the proximal edge of the filter assembly, the Nitinol expanders collapse and the filter assembly is rewrapped, fully contained within the retrieval catheter. The entire device is then removed from the patient with the captured emboli contained in the filtration element. In cases where the filter delivery catheter system is unable to cross the lesion on the initial attempt because of lesion severity or vessel tortuousity, a gentle predilation (using a 2-mm balloon) or a side-wire "buddy wire" was used to facilitate the system advancement (Fig. 2).

DEFINITIONS

Technical success. *Device success:* successful placement and retrieval of the NeuroShield filter device. *Angiographic success:* successful stent deployment resulting in ≤30% residual diameter stenosis.

Stroke. *Minor stroke:* an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit that persists for ≥24 h. In all cases, patients must be nondisabled. *Major stroke:* an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit (NIHSS ≥9) persisting for a minimum of 30 days.

Procedural event. A procedural event is the occurrence of any clinical event during the procedure, from the time femoral arterial access is obtained and until vascular access site hemostasis is successfully achieved.

30-day outcome. The 30-day outcome was the composite incidence of the clinical end points within the first 30 days.

Statistical analysis. The primary end points were analyzed on an intention-to-treat basis. All values were expressed in mean ± SD.

RESULTS

Table 1 summarizes the patient clinical and angiographic characteristics. The mean age of the patients was 68 ± 8 years (range 51 to 85 years, 11 patients (7%) were ≥80 years). Seventy-seven patients (48%) had symptoms attributable to the treated artery within the three months before the procedure. Of these, 61% had transient ischemic attacks, 23% had stroke and 16% had amaurosis fugax. One patient was treated using the filter system after he developed intolerance symptoms during CAS with the distal-balloon protection.

Immediate outcome. Angiographic success was achieved in 162 (99%) of the patients. Successful filter placement and

JACC Vol. 39, No. 5, 2002
March 6, 2002:841–6

Table 1. Clinical and Angiographic Characteristics

Age (yrs) (mean ± SD)	68 ± 8
Age ≥80 yrs	11 (7%)
Men (n, %)	28 (87%)
Symptomatic lesions	77 (48%)
Hypertension	31 (80%)
Diabetes	12 (31%)
Hyperlipidemia	26 (67%)
Coronary artery disease	21 (54%)
Prior ipsilateral CEA	13 (8%)
Stenosis severity (mean ± SD)	82 ± 9%
Lesion length (mm) (mean ± SD)	12 ± 6
Contralateral ICA stenosis of ≥50%	49 (30%)
Contralateral ICA occlusion (n, %)	18 (11%)

CEA = carotid endarterectomy; ICA = internal carotid artery.

retrieval was achieved in 154 (94%) of the procedures. An additional maneuver, such as a gentle predilation (using a 2-mm diameter balloon) and/or a "buddy wire" placement, was necessary in 12 (8%) of the cases to facilitate the filter placement. In these cases, high-grade lesions and/or severe distal vessel tortuousity made the initial attempt unsuccessful. Failure to place the filter occurred in eight cases (5%) because of inability of the device to cross-sever stenoses with tortuous distal anatomy despite additional maneuvers (buddy wire and predilation) in two cases. The procedure was completed with no protection in five patients and with an alternative protection system in three; distal balloon protection (GuardWire, Percusurge Inc., Sunnyville, California) in two patients, and a different filter protection device (Angioguard, Cordis Inc., Miami, Florida) was negotiated through the lesion in one patient after an additional balloon dilation. Preserved flow through the ICA was angiographically documented in all of the procedures where the filter was successfully placed. There was no device failure following deployment, and all filters were successfully retrieved in a completely collapsed condition. Macroscopically visible particles were retrieved in 54 (35%) of the filters. Pathohistologic analysis of the filter contents was performed in a subset of 11 consecutive patients. This revealed multiple debris (mean number of particles per filter was 12, range 0 to 41) that included fibrin, cholesterol clefts, organized thrombi and red and white blood cell aggregates.

Nonflow-limiting spasm that resolved after removal of the filter (with/without intravascular nitroglycerin) occurred in five cases (3%). Flow-limiting spasm at the filter site occurred in three patients (2%). This resolved completely with the filter removal in one patient, by advancing the filter few millimeters in one, and by intravascular nitroglycerin administration in the third patient. All three procedures were successfully completed with filter protection with no associated clinical sequelae. There were no vascular dissections.

There were two procedural minor strokes (1%). One patient developed blurred vision during a CAS procedure in which the filter placement was unsuccessful. The intervention was successfully completed without distal protection. The second patient, a known case of von Willebrand's disease whose aspirin had been withheld on the advice of the hematologist, developed dysphasia immediately following successful filter retrieval. Both patients recovered completely within 48 h. Of the 154 patients in whom the filter was successfully deployed, there was one embolic neurologic event (0.6%).

30-day outcome. On an intention-to-treat basis, the overall combined rate of all strokes and deaths at 30 days was 2% (four events). These include the two procedural minor strokes and two deaths. One patient suffered prolonged brady/tachyarrhythmia following a control arch aortogram, and a temporary transvenous pacer was placed before stenting and was removed following successful intervention. Subsequently, the patient developed an asystolic cardiac arrest and she could not be resuscitated. Autopsy demonstrated a perforated right ventricle with hemopericardium, and fatal arrhythmias were given as the cause of death. A second patient developed massive ipsilateral intraventricular/subarachnoidal hemorrhage four days following an uncomplicated CAS and died within 24 h from the onset. This constituted the only neurologic death and was thought to be due to reperfusion injury. All the remaining patients were asymptomatic, with no neurologic events or myocardial infarctions.

DISCUSSION

Carotid artery stenting without distal protection has been associated with embolic minor stroke rates of 2% to 5% and major stroke rates of 1% to 1.5% (2–4). In the largest report of CAS, a multicenter registry by Wholey et al. (8) that included 5,210 patients, the rates of minor and major embolic strokes were 2.7% and 1.5%, respectively. Distal protection has the potential to reduce the risk of embolization and enhance the safety of CAS. Preliminary results of a multicenter trial of CAS using the distal balloon protection have already shown a favorably low rate of embolic events (9). Moreover, the ability of the distal balloon protection to reduce the microembolic load has been demonstrated (10).

The present study demonstrates that the application of a filter protection system during CAS is feasible and safe. The risk of atheroembolic complications in patients who had successful filter placement appears to be favorably low and notable for the absence of major embolic events. This series represent the largest experience with a single-design filter system during CAS, and it confirms the results of two prior smaller series that evaluated various filter designs during CAS. Parodi et al. (11) reported the successful application of an umbrella-shaped filter system during CAS in six patients with no complications. In a recent report, Reimers et al. (12) reported no neurologic events during CAS using various filter designs in a series of 84 patients. The ability of the NeuroShield filter system to capture embolic particles during the carotid intervention has been demonstrated in an ex vivo human carotid artery model (13). In the current study, macroscopically visible particles were detected in 30%

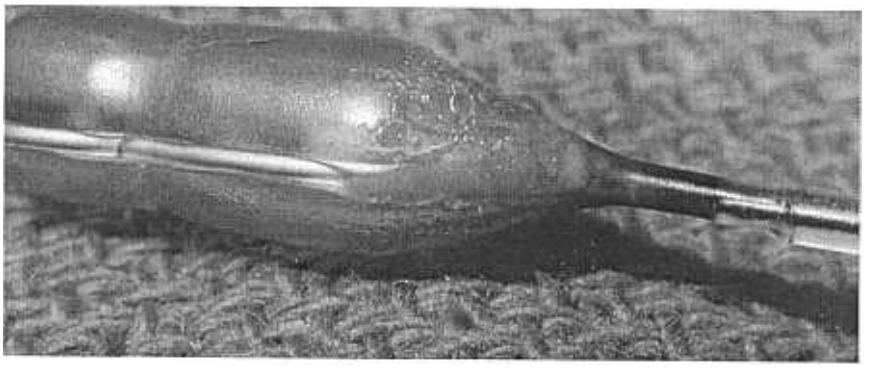

Figure 3. Retrieved filter showing macroscopically visible captured material.

of the filters (Fig. 3), clinically confirming the prior ex vivo observation. Moreover, the retrieval of these particles in the filters provides further clinical evidence of the particulate matter release during CAS.

Embolic profile during CAS. The majority of CAS-associated neurologic events occur during the procedure, less commonly within the immediate 2 to 4 h following the intervention, and rarely thereafter. Transcranial Doppler studies have shown that stent deployment, predilation and postdilation are the most emboligenic phases of the unprotected CAS procedure, and that the risk of embolization after CAS is completed is very low (10,14). Gensori et al. (14), using TCD, reported a very low emboligenic potential in a group of patients within the 24 h following CAS. Therefore, it is intuitive that the successful application of any protection strategy during balloon dilations and stent deployment will result in significant reduction in the risk of embolic neurologic events during CAS.

Distal protection strategies. Two additional approaches for distal protection during CAS are under evaluation (6). The first involves the use of a distal balloon that interrupts flow though the ICA during intervention. The proximal blood column, potentially containing embolic material, is then aspirated before re-establishing the blood flow. The second approach involves reversing the flow within the ICA. This is achieved by occluding the CCA, diverting the blood into the ECA or simultaneously occluding the ipsilateral CCA and the ECA and diverting the blood into the guiding catheter that is externally connected to the contralateral femoral vein. Preliminary experience has shown that all of these strategies are effective in capturing embolic matter. However, each of these strategies has its inherent advantages and limitations. The utility of any distal protection system in the individual patient depends on the lesion anatomy, the adequacy of collateral circulation, the ease of use and, most importantly, the efficacy in reducing the risk of embolic events. Although the filter protection offers the advantage of a constant cerebral perfusion during CAS, allowing more time for careful and precise intervention, microscopic particles smaller than the size of the filter pores ($\leq$100 μm) may not be captured. The clinical significance of these particles, however, is uncertain (15). On the other hand, although both balloon occlusion systems are more applicable in severe lesions and tortuous vessels, intolerance may occur rapidly in 5% to 10% of the patients who have poor collateral blood supply due to incomplete circle of Willis (4). Confirming the early observation, the current series demonstrates that following successful placement, the flow through the filter is preserved and that the filter system is well tolerated. The crossing profile of the Generation-II system used in this study made it difficult to cross high-grade obstruction and/or tortuous anatomy, resulting in 5% failed filter placements in this series. Recent experience with the new Generation-III (authors' personal experience) has shown that this is more applicable in the tortuous anatomy. Compared with Generation-II, the new system has a lower profile and over-the-wire design with a free (nonmounted) filter. Using this system, the lesion is first crossed using a bare 0.014 178 guidewire. The filter is then delivered and retrieved over the wire in a similar fashion to the older version.

Future directions. The introduction of distal protection into the CAS procedure has set the stage for a randomized comparison of CAS with the traditional surgical treatment of carotid obstructions, such as CEA (16). Several trials are being commenced (16). The largest is the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), a randomized controlled trial of CEA versus CAS with filter protection in the symptomatic patients with extracranial carotid internal carotid stenosis (16). A second study is the Carotid Revascularization with Endarterectomy or Stenting Systems, evaluating CAS with distal protection in asymptomatic patients as well as those patients excluded from CREST. These and other ongoing trials will further define the role of CAS in stroke prevention.

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Carotid Stenting for Radiation-Induced Stenoses
A Report of 7 Cases

Emmanuel Houdart, MD; Charbel Mounayer, MD; René Chapot, MD;
Jean-Pierre Saint-Maurice, MD; Jean-Jacques Merland, MD, PhD

Background and Purpose—Radiation-induced stenoses of the carotid artery are associated with fibrosis of the arterial layers and tissue planes that renders their surgical treatment difficult. We present our clinical experience in carotid angioplasty stenting (CAS) of patients harboring such stenoses.

Methods—Seven patients underwent transfemoral CAS of 10 radiation-induced stenoses located on either the common or the internal carotid artery. Six patients presented neurological symptoms. Four patients had undergone previous radical neck dissection, and 3 had permanent tracheostomies. Stenoses were primarily covered with a self-expandable stent before carotid dilation.

Results—All interventions were successful, with residual stenoses <20%. No permanent complication occurred. The mean follow-up was 8 months. Patients were symptom free at the last clinical examination, and Doppler control showed no evidence of restenosis.

Conclusions—Carotid stenting appears very attractive for such "hostile neck" patients and seems a safe and efficient treatment for radiation-induced stenoses. (***Stroke*. 2001;32:118-121.**)

Key Words: angioplasty ■ carotid artery diseases ■ stenosis ■ stents

Extracranial carotid stenosis is a known complication of head and neck external irradiation. These stenoses are usually challenging for the vascular surgeon. Indeed, even when the stenosis is due to an atherosclerotic process, it is associated with fibrosis of both the arterial wall and normal tissue planes, which makes endarterectomy more difficult than for usual cases.[1-3] In addition, many of these stenoses involve extensive segments of the carotid artery in the upper or lower part of the carotid bifurcation, which again renders their surgical approach more complicated. With the development of self-expandable stents, carotid angioplasty stenting (CAS) has become used more frequently.[4,5] This technique avoids cervical dissection and therefore seems quite appropriate for these "hostile neck" patients. We review our experience with 7 patients who were treated by CAS over a 2-year period for 10 radiation-induced carotid artery stenoses.

Subjects and Method

Between April 1998 and April 2000, 7 patients with 10 radiation-induced stenoses of the carotid arteries underwent CAS. Since the beginning of this period, surgery had no longer been performed for that specific indication in our institution. All patients gave written informed consent for both the intervention and materials used.

Imaging Protocol

Before intervention, all patients underwent cerebral MRI or CT scan and 4-vessel angiography, including cervical and intracranial views. Stenoses were measured before and after CAS on radiographic films. Only patients with stenosis >70% according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria were treated. Intervention was judged successful when the residual stenosis was <20% on the control angiography. We termed internal carotid artery (ICA) stenosis a stenosis located either exclusively on the ICA or at the carotid bifurcation, and we termed common carotid artery (CCA) stenosis a stenosis located exclusively below the bifurcation. To measure the exact diameter of the arteries and length of the stenoses, angiography was performed after placement of a coin on the neck in a plane orthogonal to the radiographic view. It was possible to calculate the size of the structures studied when the diameter of the coin was known.

Clinical Protocol

A neurological examination by an experienced neurologist was performed on all the patients before the procedure, after the intervention, and before discharge. Clinical follow-up and a cervical Doppler were performed at 1 month and every 6 months after CAS for all patients.

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Characteristics of Patients and Stenoses

Case No.	Age, y/Sex	Interval*/Initial Malignancy	Previous Associated Treatment	Neurological Symptoms	Stented Arteries/Length of Stenosis, mm	Associated Arterial Lesions
1	79/M	12 y /laryngeal carcinoma	Cervical Surgery	TIA	L ICA /35	Thrombosis R ICA
2	53/M	6 y /lymphoma	...	TIA	R ICA /10 L ICA /40 R VA /5	Thrombosis L SCA
3	56/M	4 y /laryngeal carcinoma	...	TIA	L ICA /20	...
4	78/M	5 y /laryngeal carcinoma	Cervical surgery, tracheotomy	TIA	R CCA /30 L CCA /30 L ICA /20	...
5	59/M	15 y /laryngeal carcinoma	...	TIA	L ICA /40	Stenosis R ICA
6	63/M	4 y /pharyngeal carcinoma	Cervical surgery	Minor stroke	L ICA /6	
7	60/M	10 y /laryngeal carcinoma	Cervical surgery, tracheotomy	None	L CCA /40	

TIA indicates transient ischemic attack; L, left; R, right; VA, vertebral artery; and SCA, subclavian artery.
*Interval from irradiation to neurological symptoms.

Antithrombotic Protocol

Antiplatelet therapy, with clopidogrel 75 mg and aspirin 100 mg, was started 5 days before CAS and continued for 1 month after the procedure, after which clopidogrel was interrupted and the aspirin continued for life. During the intervention, 5000 U of intravenous heparin was given once the femoral sheath was in place. One patient had a poststenotic thrombus seen on initial angiography and received an intravenous perfusion of abciximab (ReoPro, Lilly Inc). This treatment resulted in disappearance of the thrombus, which allowed the CAS procedure to be performed.

Balloon Angioplasty and Stenting Protocol

The interventions were performed by the femoral approach. An 8F guiding catheter was placed in the CCA. Primary stenting was performed with the use of a self-expandable stent in all cases. We used an Easy Wallstent in the first 3 patients and a Carotid Wallstent (Schneider-Boston Scientific Inc) in the other patients. The diameter of the prosthesis was adapted to the largest diameter of the artery that needed to be covered. The stenosis was passed with a wire, and the stent was deployed to cover the entire length of the stenosis. A balloon angioplasty catheter was then introduced into the stent and inflated to a maximum pressure of 10 atm. Atropine 1 mg was given before balloon inflation. In 2 cases of ICA stenosis, we used a cerebral protection device (Guardwire, Percusurge Inc) during stent deployment and balloon dilation. Control angiography, including cervical and intracranial views, was systematically performed. The femoral sheath was removed on the same day after normalization of the activated clotting time. In case of bilateral carotid stenoses, CAS was performed sequentially at a 15-day interval. After angioplasty, the patients were systematically observed for 24 hours in the intensive care unit.

Results

Patient and Stenosis Characteristics

The clinical characteristics of the patients and stenoses are shown in the Table. Six of the 7 patients were symptomatic. Five patients had presented either a motor deficit or aphasia, and 1 had presented retinal symptoms. The mean interval between radiation therapy and neurological symptoms onset was 8 years (range, 4 to 15 years). Four patients had undergone previous cancer surgery on the same side as the carotid stenosis, and 2 of them had permanent tracheostomies. Six of the 10 stenoses had a length ≥30 mm. Three of the 10 stenoses affected the CCA exclusively. Two patients had stenoses on >2 major cerebral arteries.

Clinical and Angiographic Results

Nine interventions were performed. Two patients had bilateral carotid stenoses that were treated in separate sessions.

Ten carotid arteries were stented: 7 ICA and 3 CCA. Additionally, in 1 patient a vertebral artery was stented during a CAS session. In the 2 stenoses treated under cerebral protection, analysis of the blood aspirated below the protecting balloon revealed cholesterol debris.

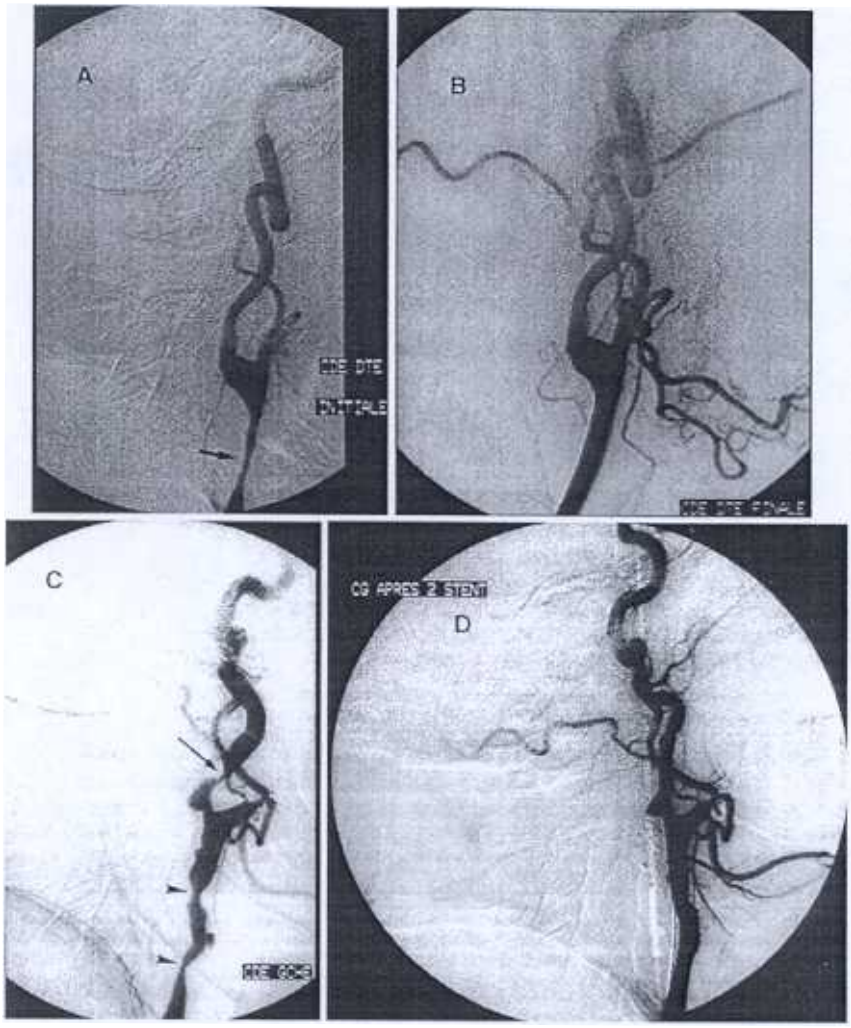
Interventions were successful for all stenoses. There was no permanent complication. One transient complication occurred in the patient presenting occlusion of the opposite ICA. Inflation of the balloon angioplasty led to a partial motor seizure that resolved immediately after the deflation of the balloon.

The hospitalization duration was 3 days for all patients.

The mean clinical and Doppler follow-up was 8 months (range, 3 to 24 months). All the patients were symptom free at the last clinical examination. All the stents were permeable on the last Doppler control.

Illustrative Case: Case 4

A 78-year-old right-handed man was seen in June 1999 after several episodes of visual flashes followed by blurred vision that occurred alternatively in both eyes. These symptoms occurred mainly during physical activity and were interpreted by our neurologist as transient bilateral retinal ischemia. The patient had undergone total laryngectomy with permanent tracheostomy followed by cervical irradiation for a laryngeal carcinoma in 1984. The neurological examination was nor-



Case 4. A, Initial angiography of the right carotid artery shows a long tight stenosis of the CCA (arrow). B, Angiography after CAS of the right CCA. C, Initial angiography of the left carotid artery shows very long stenoses of both CCA (arrowheads) and ICA (arrow). D, Angiography after CAS of both left CCA and ICA.

mal. Clinical examination found typical "hostile neck" signs. Cervical Doppler revealed tight stenoses of both carotid arteries. Transcranial Doppler showed decreased velocities in both middle cerebral arteries.

Angiography revealed a long, tight stenosis of the right CCA associated with a long stenosis of the left CCA and left ICA (Figure).

It was decided to perform sequential CAS of the right and left carotid arteries, beginning with the right CCA stenosis because this was the simplest lesion to treat. Indeed, the longest intervention was to be on the left side, and we wanted to improve the arterial blood flow to the brain through the right carotid artery before performing it. Follow-up after CAS of the right side was uneventful, and the patient was discharged on day 2. Treatment of the left carotid stenoses was undertaken 1 month later. Two stents were implanted, one at the CCA stenosis and the other at the ICA stenosis. The patient was discharged on day 2, neurologically intact. At 6-month follow-up, the visual symptoms had completely disappeared. The control cervical Doppler showed normal carotid diameters, and the transcranial Doppler showed normalization of the velocity in the middle cerebral artery.

Discussion

Three types of radiation damage to the carotid artery after neck irradiation have been described. Carotid rupture has been reported mainly when radiotherapy was associated with radical neck dissection. In the majority of the cases, the rupture occurred after a surgical complication such as postoperative necrosis of skin flaps, fistulas, or infection of the surgical wound.[6,7] Early arterial occlusion, occurring within months after radiotherapy, is the second reported complication.[8] The third and most frequent lesion is the late development of atherosclerosis in the arteries included in the radiation fields.[9,10] This complication has been reported to occur more frequently in patients with nasopharyngeal or laryngeal carcinomas.[11] Six of the 7 patients of our series had been treated for such carcinomas. In this type of lesion, neurological symptoms occur several years after irradiation. Although histology of the surgical specimens has shown atherosclerotic plaque with cholesterol crystals,[1,12] angiographic findings differ from the nonirradiated cases. The stenoses are unusually long and affect arteries infrequently involved by standard atherosclerosis, such as the CCA. The clinical and radiological findings in our series were concordant with those data.

Surgical treatment of such stenoses is more difficult than for usual cases. Indeed, cervical dissection is disturbed by the scar tissue caused by irradiation. These difficulties are further increased if the patient has undergone previous radical neck surgery on the same side because of the additional surgical scar. Such changes increase the risk of damage to the adjacent vessels or nerves. Endarterectomy of ICA stenoses is also more difficult because of vessel wall changes consisting of adhesion of the different layers, which complicates the removal of the plaque itself. When stenosis involves a proximal segment of CCA, the treatment sometimes requires a surgical bypass, implying a more aggressive dissection. In addition to the risks related to irradiation, some of these patients had undergone previous tracheostomy because of their initial malignancy, which carries an additional risk. Indeed, the proximity of the stoma to the operative field increases the risk of postoperative infection, especially if a synthetic material has been used for vascular reconstruction. There are few surgical reports of endarterectomy for radiation-induced stenoses. In a series of 10 patients, 1 postoperative stroke occurred, and 1 patient developed a pseudoaneurysm. Wound closure required dermal grafting in 2 other patients.[2] In the largest series including 24 patients, 6 had postoperative cranial nerves palsies, and 4 required dermal grafting.[3]

Because of the development of self-expandable stents, the number of patients treated by CAS is increasing rapidly. This technique has not been compared with endarterectomy and therefore cannot be proposed routinely for treatment of standard stenoses. However, for radiation-induced stenoses that have been excluded from the NASCET and European Carotid Surgery Trial studies, CAS is attractive for those patients with predictable difficulties in neck dissection. For CCA stenoses (whose surgical results have not been prospectively assessed), CAS seems much less invasive than surgical bypass. Since the development of self-expandable stents, radiation-induced stenoses have been treated exclusively by CAS at our institution. Indication for treatment was justified in 6 cases by neurological symptoms. In the asymptomatic patient, CAS was performed because of the tightness of the stenosis, which was associated with a decrease of velocity of the middle cerebral artery.

We applied our usual technique, which primarily involves covering of the stenosis with a self-expandable stent followed by its dilation. Balloons were not inflated to >10 atm because we were concerned about potential arterial rupture at higher pressure. Bilateral carotid stenoses were treated in sequential sessions. We established this policy to avoid ischemic complication in both hemispheres (with its catastrophic cognitive consequences), which could occur if the stenoses were treated at the same time.

We used a protective cerebral device in 2 cases of ICA stenoses when the device was available. Although the benefit of this technique has not been demonstrated, it is increasingly recommended to avoid possible embolic migration to the brain during CAS.[13] Because radiation-induced stenoses are actually accelerated atherosclerosis, cerebral protection is justified to the same degree as for standard patients. No consensus exists in the literature for use of cerebral protection. Our policy is to use it when treating long stenoses because embolic migration seems more likely to occur in that situation.[14]

With the exception of our series, only 1 article has been published regarding the use of CAS for radiation-induced stenoses.[15] The reported results in those 14 patients are similar to ours.

Because of the prolonged survival of patients treated by radiation, the frequency of this long-term side effect is expected to increase. In a prospective study, late stenosis of carotid artery was depicted in 11.7% of 240 patients who underwent cervical irradiation.[11] Some physicians are reluctant to consider surgical options for these high-surgical-risk patients. Accordingly, CAS is a potential alternative that seems both safe and effective. However, further studies with longer follow-up are required to confirm these initial results.

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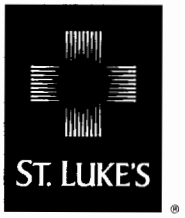
Comment #16:

Submitter: Zvonimir Krajcer, MD, Ali Mortazavi, MD, Neil Strickman, MD, Arup Achari, MD, and Emerson Perin, MD

Organization: The University of Texas Health Science Center, Kelsey-Seybold Clinic, and St. Luke's Episcopal Hospital

Date: July 13, 2004

Comment:



EPISCOPAL
HOSPITAL

Dr. Joe Chin, MD
And Dr. Carlos Cano, MD
Lead Medical Officers
Medicare Coverage

July 13, 2004

RE: Coverage Request-Carotid stenting with protection in patients at high risk for endarterectomy.

Dear Dr's.

Like other large peer-reviewed medical centers, St. Luke's Episcopal Hospital and the Texas Heart Institute have extensive experience with embolic protection during angioplasty and stenting of the carotid arteries in patients at high risk for endarterectomy. Over 350 IRB approved high-risk carotid artery stent procedures have been performed at our institution. We strictly adhere to eligibility criteria when enrolling patients into a carotid stent protocol and closely follow them with routine duplex ultrasound and neurological exams. A multi-disciplinary team consisting of an independent neurologist, radiologist, interventional cardiologist and a vascular surgeon are consulted for each potential carotid stent candidate. Patients undergo a complete and thorough neurological examination before and after carotid stenting and must have 4-vessel cerebral angiography prior to carotid stenting.

Patients are considered at high-risk for endarterectomy if they have multiple co-morbidities including symptomatic coronary artery disease, severe left ventricular dysfunction, chronic obstructive lung disease or those who have obstructions surgically inaccessible. Of the 350 carotid stent procedures performed at St. Luke's, 45% did not meet NASCET inclusion criteria, 19% were octogenarians, 28% had already undergone previous carotid endarterectomy and 13% had neck radiation and/or radical neck surgery to treat their cancer.

Currently at our institution only Principle Investigators and Co- Investigators of IRB approved clinical trials can perform carotid artery stenting. All of the investigators have extensive experience with peripheral and cerebral anatomy, arteriography and intervention, as well as, the use of distal embolic protection devices. All carotid stent procedures are monitored and followed by a designated peripheral vascular research coordinator.

A preceptor training program has been implemented at St. Luke's and coordinated by the carotid stent investigators. Those physicians wishing to obtain carotid stent privileges must adhere to the multi-disciplinary approach, including the neurological evaluation before and after the procedure. In addition each physician must satisfactorily perform 10 computer-simulated procedures, participate in 25 carotid stent procedures and perform an additional 10 proctored carotid stent procedures. All of the cases are subject to peer review.

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We would like to urge CMS to extend coverage beyond clinical trials to allow those patients at high risk for endarterectomy to undergo carotid artery stenting with protection.

If you have any further questions or comments or if we may be of further assistance please do not hesitate to contact us directly.

Sincerely,

Zvonimir Krajcer, MD
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Baylor College of Medicine
The University of Texas Health Science Center
Principle Investigator, MAVErIC II

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Comment #17:
Submitter: William H. Brooks, MD
Organization: Neurosurgical Associates, PSC
Date: July 15, 2004
Comment:

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TO: The Centers for Medicare and Medicaid Services (CMS)
1. Dr. Joe Chin
2. Dr. Carlos Cano
3. Rana Hogarth, MSH

FROM: William H. Brooks, M.D.

RE: Carotid Stenting Coverage Policy (CAG – 00085R)

I welcome an opportunity to comment and present my conditional support, yet significant and serious concerns regarding a proposed approval of reimbursement for carotid angioplasty and stenting (CAS). The issues surrounding CAS are numerous and require careful consideration before providing reimbursements to providers, in my opinion. How this can be clearly and reasonably addressed is anything but clear. Local credentialing committees are plagued by politics and "turf-wars". No consensus regarding proper training of those physicians already in practice has been reached by various societies. The indications for treating asymptomatic carotid disease are not without controversy. In addition, the definition for "high risk" remains opaque. In short, there is no bench mark.

The comments to follow represent my personal thoughts based on my collective experience with CAS. Enclosed find copies of two randomized trials completed in a single community hospital setting comparing carotid endarterectomy (CEA) and CAS. Initially, I was engaged in the Schneider Wallstent trial and was a Principle Investigator on ARCHeR and BEACH registries. These were industry sponsored registries for "high risk" patients. The data from these registries have been presented/published. Unfortunately, the data from the Wallstent trial never will be published. Nevertheless, the information gathered from that trial provides clear insight into the potential problems associated with CAS and the general community where this procedure is not routinely performed and experience required to acquire the sufficient skills to safely be engaged in CAS are suspect and often lacking.

It is clear the request for changes in funding practices that currently exist as developed by CMS is industry driven. Contacts from industry requesting providers to lobby CMS for change of funding have been received. Obviously, providers wish to have appropriate reimbursement for the services that are delivered. Nevertheless, this particular challenge has been led by industry. Why? To expand a market share and wealth, no doubt. Why else would

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industry send information that states "or, it might craft overly restrictive coverage regulations on the patients to be served, physician competency, or facility experience. This could severely limit physician and patient access to this service". It is my view that it is these restrictive coverage's that lie at the heart of considering reimbursement. My intention is not to present a dissenting message, rather one that expresses the concerns as experienced in the community hospital setting with hopes to offer an approach that might have been overlooked given the politics of the technique and the various providers that will be or wish to be engaged.

As a preamble to further explication of my position, review the Asymptomatic Carotid Artery Stenosis trial (ACAS) and the information gathered from the Schneider Wallstent Trial. The ACAS Trial demonstrated the benefits of CEA, in asymptomatic individuals with stenosis of 60% or greater, if and only if, the individual was anticipated to live more than five years and a provider morbidity and mortality was less than 3%. Actually, the surgeons involved in this trial were carefully selected with a surgical risk significantly less than 3%. Once this study was published those engaged in CEA proscribed surgery for individuals with carotid stenosis such that the numbers of CEAs increased by 10 fold within one year. Subsequent data gathered by the Federal Government revealed the surgical risks, morbidity and mortality, were far in excess of those proscribed by ACAS guidelines. Still, the practice continues without constraint. The literature is replete with articles and opinions condemning the blatant overuse of CEA in asymptomatic individuals. Nevertheless, CEA is beneficial in an appropriate clinical setting with an acceptable surgical risk. CMS must be aware that similar to the consequences of release of the ACAS trial, the numbers of CAS will dramatically increase with a potential for a marked increase in rates of complications and abuse.

The Schneider Wallstent Trial was discontinued because the complications associated with CAS were far in excess of those associated with CEA. One of the reasons for the failure of this trial was that there were little, if any, selection criteria for those to become engaged in CAS. Subsequently, it has been suggested that an individual must perform 50 – 100 CAS to become thoroughly qualified and trained. Clearly, the numbers wishing to adopt this technique far exceed those actively engaged at this time.

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The trials on which industry has based the argument that CAS warrants funding approval is based on "high risk" registries. Presently, there are no randomized trials comparing CEA with CAS that have been published other than those from our community hospital. Although these trials show that CEA and CAS may be equivalent, this data is obtained in only one clinical setting where a team approach was utilized. This cannot and should not be taken as a definitive study. CREST will serve as a definitive study similar to what NASCET did for endarterectomy and symptomatic disease. The definition for "high risk" is clearly in the eyes of the surgeon. Personally, I believe there is a small group of individuals who actually are placed at increased risk for carotid re-vascularization by "open surgery". Most, if not all, surgeons and those engaged in CAS would include:

1. Severe pulmonary insufficiency and/or cardiac disease with reduced ejection fraction;
2. Previous eradiation of the neck;
3. Surgically difficult access to the area of interest such as high bifurcation of the common carotid artery; and
4. Previous CEA.

These are similar to those proscribed and detailed in high risk trials that have been published or presented. This group of patients, however, represents the vast minority of those presenting with carotid stenosis. Most reports of CAS in the literature contain large numbers of asymptomatic individuals.

Provider qualification and training also is a key issue that must be carefully considered before funding. The "learning curve" for safely performing CAS has been suggested to be between 50 – 100 cases. Those physicians best prepared to adopt this technique at present seem to be cardiology and radiology "interventionalist" or those with catheter based skills. Providers without these skills are poorly prepared for CAS. Additionally, those without experience in manipulation of small (0.014m) guide wires are poorly prepared. Thorough knowledge of cerebrovascular anatomy and management of stroke is mandatory. To be partially competent equals partially incompetent. Although competition for these patients will be fierce among the various disciplines, it is doubtful that the numbers of providers wishing to become involved with CAS, at present, are trained appropriately. Clearly the numbers wishing to adopt this technique far exceeds those actively engaged at this time. Academic training programs are providing experience with CAS that will serve the needs of the public in an

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appropriate fashion in the near future. Yet the problem is current and the issues of proper qualifications to perform CAS in the interim need to be addressed. I am unaware of any guideline that generally would be acceptable without reserve and dissent. CORDIS manufacturer has proposed a training profile that seems reasonable. Certainly, this is a place from which to start. The stratification of providers provides for immediate approval as well as a proscription for training and proctoring. Strict monitoring of outcome, however, is lacking. It is my understanding that carotid stents will be provided only to those physicians who have met the criteria of CORDIS. Such an approach seems reasonable as long as outcomes are measured in context of appropriateness and acceptable morbidity and mortality as compared to CEA. I might suggest that you look at there criteria. It is not perfect, but at least an attempt and may be relevant until adequate numbers of academically trained provides enter the market. Nevertheless, the issues of local credentialing remain local and problematic. CMS funding will only add to that problem unless federally mandated constraints are in place.

Industry has expressed concern that CMS may propose "overly restrictive covered regulations" based on facility experience. Personally, I welcome such an approach. Those facilities that offer CAS must also offer acute stroke intervention. Anyone engaged in CAS must be prepared to suddenly become responsible for stroke therapy. Those of us engaged in CAS keenly are aware of the potential for a therapeutic endeavor to become a procedure of rescue. Thus, CAS cannot separate prevention from stroke therapy. Therefore, a facility without a documented acute stroke interventional protocol in place and functioning is an inappropriate setting for CAS. The guidelines for accreditation must be set higher than perhaps all can attain less the complication rates associated with CAS become unacceptable in comparison to CEA. This is an evolving technique with great potential, yet I fear, the technique may be discarded unless the early introduction to healthcare services is strictly controlled until sufficient data is obtained to warrant unrestricted use.

The use of embolic protection devices is an example of the evolution of this technique. The trials that I have presented did not use embolic protection devices as they were not available. Those of us involved in CAS as a protective measure, however, have adopted the use of these devices. However, the embolic protection device is not a safeguard against misuse, abuse, and a lack of appropriate training.

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The most difficult problem that CMA faces (not that those mentioned above are not problematic) is to insure appropriate patient selection by providers once CAS is funded. Personally, I do not believe that there is any methodology that would serve this function other than regionalization of services and strict federal oversight. The history of medicine is replete with examples of appropriate use and abuse of surgical procedures by healthcare providers. The consequences of ACAS trial are merely one example that may be applicable and serve as a warning of that potential with CAS.

In summation, one option, although obviously not palatable to industry, is to defer full funding until the results of CREST have been obtained. I would suggest that CMS approve and fund high risk registries sponsored by industry and provide coverage only in the context of these registries or randomized, prospective trials. Reimbursement for CAS in the context of randomized, prospective trials does not need to be confined to those sponsored by industry, but also may include those sponsored in a local academic or community hospital setting. The trials that we conducted were unfunded and no reimbursement either for the hospital or physician services was received or expected. This is by far the better route, in my opinion, than releasing CAS to any physician holding the belief that because he is a surgeon with CEA experience, radiologist with the belief that all endovascular procedures are similar, and the cardiologist suggesting the coronary skills translate to knowledge of cerebrovascular anatomy and indications for cerebral re-vascularization.

Thanks for your time, I generally do not become engaged in these debates, but the potential for abuse is so high I was obliged.

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CLINICAL STUDIES **Interventional Cardiology**

Carotid Angioplasty and Stenting Versus Carotid Endarterectomy: Randomized Trial in a Community Hospital

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OBJECTIVES The goal of this study was to determine whether carotid angioplasty and stenting (CAS) is equivalent to carotid endarterectomy (CEA) in patients with symptomatic carotid stenosis >70% by a randomized, controlled trial in a community hospital.

BACKGROUND Carotid angioplasty and stenting has been suggested to be as effective as CEA for treatment of symptomatic carotid artery stenosis.

METHODS A total of 104 patients presenting with cerebrovascular ischemia ipsilateral to carotid stenosis were selected randomly for CEA or carotid stenting and followed for two years.

RESULTS Stenosis decreased to an average of 5% after CAS. The patency of the reconstructed artery remained satisfactory regardless of the technique as determined by sequential ultrasound. One death occurred in the CEA group (1/51); one transient ischemic attack occurred in the CAS group (1/53); no individual sustained a stroke. The perception of procedurally related pain/discomfort was similar. Hospital stay was similar, although the CAS group tended to be discharged earlier (mean = 1.8 days vs. 2.7 days). Complications associated with CAS prolonged hospitalization when compared with those sustaining a CEA-related complication (mean = 5.6 days vs. 3.8 days). Return to full activity was achieved within one week by 80% of the CAS group and 67% of the patients receiving CEA. Hospital charges were slightly higher for CAS.

CONCLUSIONS Carotid stenting is equivalent to CEA in reducing carotid stenosis without increased risk for major complications of death/stroke. Because of shortened hospitalization and convalescence, CAS challenges CEA as the preferred treatment of symptomatic carotid stenosis if a reduction in costs can be achieved. (J Am Coll Cardiol 2001;38:1589–95) © 2001 by the American College of Cardiology

The efficacy of endarterectomy for the treatment of patients with symptomatic high-grade stenosis of the extracranial carotid artery has been established through a series of randomized, controlled trials (1–4). The absolute reduction in the occurrence of cerebral ischemic events is dependent, however, on perioperative complication rates (5,6). A combined stroke (major or minor) and death rate exceeding 6% for patients with symptomatic stenosis eliminates the benefit of stroke reduction gained through operation. Although varying according to operator and hospital experience (7), the overall incidence of major disabling stroke approaches 2% with mortality rates of <1% (8,9), thereby supporting the therapeutic advantages of carotid endarterectomy (CEA) in treating symptomatic carotid stenosis. Despite this reduction in serious complications, CEA has limitations (10–14). Minor strokes and/or complications remain significant and can be disabling. Cranial or cervical nerve palsies occur in 7.6% to 27% of patients undergoing CEA (15–17). Complications associated with concurrent cardiac disease and hypertension occur perioperatively in about 8% of patients (18). In addition, individuals with contralateral carotid occlusion or advanced coronary vascular disease are considered poor candidates for CEA (1,19–22). Other well-known anatomical considerations, which increase morbidity and mortality, include the presence of an extremely high carotid bifurcation (C1 to C2), tracheotomy, recurrent stenosis after previous CEA and radical neck dissection with or without radiation-induced carotid stenosis.

See page 1596

The advent of percutaneous endovascular techniques has the potential for being safer, less traumatic and more cost-effective in patients with symptomatic carotid occlusive disease. The therapeutic advantage of carotid angioplasty and stenting (CAS) has been demonstrated in patients with contralateral occlusion, restenosis and surgically inaccessible lesions (23–25). Although it has been suggested that CAS is an acceptable (26–30), if not preferred, alternative to CEA, the clinical experience has been less enthusiastic. Data accrued from various centers report a major stroke and death rate of 4.7% after CAS (30). Others report a "minor" stroke rate associated with CAS of 6.5% compared with a CEA-related risk of 0.6% (31). Although these complications may be lessened through operator experience after an as yet to be

From the Central Baptist Hospital, Lexington, Kentucky. The endovascular device (Wallstent) was kindly provided by Boston Scientific Inc.

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Abbreviations and Acronyms

ACT	= activated clotting time
CAS	= carotid angioplasty and stenting
CEA	= carotid endarterectomy
CVA	= cerebral vascular accident
MRI	= magnetic resonance imaging
NIH	= National Institute of Health
NASCET	= North American Symptomatic Carotid Endarterectomy Trial
TIA	= transient ischemic attack

defined "learning curve" and optimal patient selection, the theoretical benefits of endoluminal revascularization in treating symptomatic or asymptomatic carotid stenosis have not been realized fully or documented in randomized comparative trials. Indeed, the only published randomized study of CAS versus CEA was stopped because of the occurrence of strokes, three of which were considered major, in five of the seven patients who underwent CAS (32).

The purpose of this prospective, randomized trial was to compare the efficacy and benefits of CAS with CEA in the treatment of symptomatic carotid stenosis in a community hospital.

METHODS

This two-arm randomized clinical trial was approved by the Institutional Review Board to include patients experiencing symptoms and/or signs of cerebral ischemia confined to the ipsilateral internal carotid artery. All patients were informed that the Food and Drug Administration has not approved deployment of stents within the carotid artery for the treatment of carotid stenosis. Patients with symptoms of vertebral-basilar insufficiency or intracranial occlusive disease shown by cerebral angiography were excluded. The inclusion criteria included those sustaining events confined to the carotid circulation within three months of evaluation; >70% stenosis of the ipsilateral carotid bifurcation as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (33); anticipated life expectancy of five years; willingness to complete treatment within two weeks and ability to sign informed consent. Exclusion criteria included: National Institute of Health (NIH) stroke scale of >4; cardiac arrhythmia; allergy and/or sensitivity to aspirin, heparin, ticlopidine or clopidogrel; history of bleeding diathesis or coagulopathy or history of intracranial hemorrhage within two months of randomization. A total of 104 individuals met these criteria, agreed to participation and were selected randomly to undergo CEA (51 individuals) or CAS (53 individuals). The presence of contralateral total occlusion and/or the angiographic appearance of the stenotic lesion were not factors in treatment selection. All patients received 325 mg aspirin and 75 mg clopidogrel before CAS or CEA. A neurologist (T. C.) and the research clinical nurse coordinator (L. B.) provided independent oversight and neurologic examination before and subsequent to each procedure.

Carotid endarterectomy was performed using standard operative techniques under general anesthesia with intraoperative electroencephalogram monitoring. All patients were observed in intensive care for 24 h.

Carotid angioplasty and stenting was performed using a standard percutaneous retrograde femoral approach via an 8F Super-S Arrowflex sheath (Arrow International, Inc., Reading, Pennsylvania). After heparinization with 100 μ/kg, carotid angiography was performed with a 5F/125-cm VTK (Cook, Inc.) catheter over a 0.035-in angled-tip glide wire. Subsequent to guiding angiography, an 0.18-in Steel-core wire (Guidant-ACS, Inc., Indianapolis, Indiana) was placed in the external carotid artery for support. The Arrowflex sheath then was advanced over either the VTK catheter or the Arrowflex dilator into the common carotid artery. Activated clotting time (ACT) was maintained >300. Distal protection was not used in any case. Although not routinely used, ReoPro (0.25 mg/kg bolus over 20 min followed by a continuous infusion of 0.125 μg/kg/min for 12 h to a maximum of 10 μg/min) was administered to three individuals who sustained cerebral vascular accidents (CVA) with persistent defects (NIH < 4) associated with ulcerative lesions and possible residual thrombus. In all cases, the stenosis was crossed using a 0.014-in Sport wire (Guidant-ACS, Inc.) and placed in the petrous portion of the internal carotid artery. All stenoses were predilated with a 4.0 × 20 mm Symmetry balloon (Medi-Tech, BSC, Inc.) inflated to 8 atms for 5 s before placement of a 10 × 20 mm Wallstent (Boston Scientific, Inc.). Postdilation was completed with an appropriately sized balloon meeting a balloon:artery ratio of 1:1 by visual estimate. Pan cerebral angiography was performed before withdrawal of the Arrowflex sheath from the common carotid artery.

A 6F femoral venous sheath was placed at the initiation of the procedure for placement of a temporary pacemaker if bradycardia was observed. Systolic arterial pressure was maintained between 120 mm Hg to 160 mm Hg throughout the procedure. All patients were admitted and observed in the neurovascular intensive care for 24 h. The sheaths were removed when the ACT was <170.

Carotid duplex scanning was performed within 24 h of either procedure and at 1, 3, 6, 12 and 24 months and expressed as the ratio of internal carotid artery/common carotid artery velocity. Sequential neurologic examinations, Rankin and Barthel scorings were performed concurrent with Duplex scanning. Magnetic resonance imaging (MRI) was obtained at 6 and 12 months to detect the presence of asymptomatic ischemic events in the distribution of the treated vessel (34).

Perception of pain was assessed in accordance with guidelines commissioned by the Agency for Health Care Policy and Research (35). No specific posthospitalization instructions were provided in reference to activities; each individual determined return to "full activity."

Table 1. Baseline Characteristics of Study Patients

	CAS (n = 53)	CEA (n = 51)
Mean age (yrs)	66.4 (36–78)	69.6 (56–81)
Presenting symptom		
Stroke (NIH < 4)	9	8
Transient ischemia	32	33
Amaurosis fugax	12	10
Risk factors		
Hypertension	45	48
Diabetes mellitus	19	12
Cholesterol (>200)	34	24
Smoking	38	40
>2 risk factors	38	32
Coronary vascular disease	39	31
Family history		
Stroke	27	31
Cardiac disease	48	48

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

Hospital variable costs included operating room or catheterization laboratory, nursing, pharmacy, laboratory and radiology. Professional charges were not assessed for stenting; hence, no physician's fees were included in determination of any costs or charges. Costs/charges for the single patient requiring amputation necessitated by complications attendant with femoral artery access were not included.

Results are expressed as average ± SEM. Statistical comparisons were performed using Student *t* test. Two-way repeated measures of analysis of variance were used to compare sequential testing of carotid duplex scanning. A p value of <0.05 was considered statistically significant.

RESULTS

Demographics. The inclusion criteria, average ages and numbers of men and women of those randomized for CEA or CAS were similar (Table 1). The most common presenting event was a TIA. Those sustaining a CVA were functionally independent (NIH scores of <4 and Barthel Index >90). No patient experienced speech or comprehension dysfunction. Risk factors for stroke included hypertension, elevated cholesterol, smoking and diabetes. More than two risk factors were observed in more than 50% (70/104) of patients.

Results of treatment. Most patients (87/104) were treated within one month (range: 7 to 42 days.) of the presenting symptom. All received definitive treatment by six weeks. Diagnostic cerebral angiography indicated the average pretreatment stenosis in the CEA group (88.2 ± 13.2%) to be similar (p > 0.05) to the CAS group (82.4 ± 7.1%). The mean cross-sectional diameter as determined by the greatest stenosis observed on anteroposterior, lateral or oblique angiographic view was 1.6 ± 1.1 mm (range: 0.8 mm to 2.4 mm) in the CAS group and 1.7 ± 0.46 mm (range: 1.0 mm to 3.0 mm) in those undergoing CEA. The contralateral, asymptomatic carotid artery was found to have <50% stenosis in 70/104 patients, although total occlusion

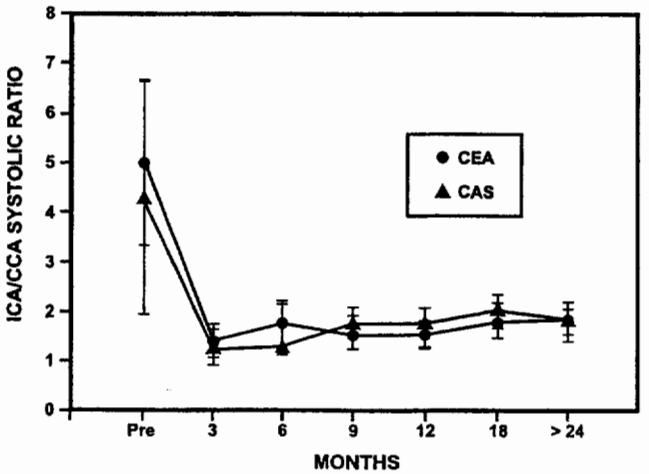

Figure 1. Patency of carotid artery before revascularization and after 3, 6, 9, 12, 18 and >24 months expressed as average internal carotid artery/common carotid artery (ICA/CCA) systolic ratio. CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

was observed in five and two individuals undergoing CAS or CEA, respectively. The average postangioplasty and stenting stenosis decreased to 5.0 ± 2.7% (range: 0% to 10%). The 24-month patency of the reconstructed artery remained satisfactory as determined by carotid ultrasound (Fig. 1). No MRI evidence of asymptomatic focal cerebral ischemia was found in any patient (data not shown).

Complications. No patient sustained a CVA, although one individual died from an immediate postoperative myocardial infarction subsequent to CEA (Table 2). This was the only procedurally related mortality experienced during this study. One patient experienced transient confusion associated with left sensory loss subsequent to postdilation of the stent that resolved within 10 min with elevation of the systolic blood pressure. Complications associated with CEA included wound hematoma requiring re-exploration (one patient) and peripheral nerve injury manifest as hoarseness (one patient) or lower facial and diminished sensations in the neck (three patients). These nerve injuries resolved within three months.

The most common occurrence associated with CAS was transient bradycardia (7/53) and/or hypotension (12/53) concurrent with angioplasty as a result of carotid body stimulation. None persisted more than 24 h. Initially, a

Table 2. Complications

	CAS	CEA
Death/cerebral ischemia		
Death	0	1
Stroke	0	0
Transient cerebral ischemia	1	0
Other		
Arterial thrombosis/amputation	1	0
Hematomas requiring treatment	3	1
Cranial/cervical nerve injury	0	4
Bradycardia (temporary pacing)	7	0
Hypotension (requiring treatment)	12	3

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

JACC Vol. 38, No. 6, 2001
November 15, 2001:1589–95

Table 3. Days Length of Hospital Stay*

	CAS	CEA
All patients	5.2 ± 11.4 days (1–68)†	3.7 ± 3.1 days (1–14)
Without complications	1.8 ± 0.58 days (1–4)	2.7 ± 1.2 days (1–13)
With complications	13.3 ± 21 days (3–68)†	3.8 ± 3.5 days (1–14)

*Avg ± SEM (range); †Exempting the single patient with major vascular complication, overall length of stay for CAS = 2.6 ± 1.6 days. Average length of stay for patients undergoing CAS who experienced other complications = 5.6 ± 3.7 days (3–11). CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

temporary pacemaker was inserted prophylactically. However, in efforts to contain cost and due to infrequent use, this has been abandoned. Currently, severe and/or prolonged bradycardia and/or flux in blood pressure were treated pharmacologically. These events are anticipated and frequently resolve without treatment. Complications associated with CAS were contingent with femoral artery access similar to other routine interventional approaches used for coronary artery disease (36). Retroperitoneal hemorrhage occurred in the three patients who received the platelet IIb/IIIa receptor antibody, abciximab (ReoPro, Eli Lilly and Co., Indianapolis, Indiana) in conjunction with heparin. This complication can be avoided by adhering closely to recommendations for the use of heparin with this monoclonal antibody provided by the Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome with Abciximab Glycoprotein IIa/IIIb Blockade (EPILOG) protocol (37). One individual with previously undiagnosed advanced generalized peripheral vascular occlusive disease sustained popliteal artery thrombosis, which necessitated below-the-knee amputation. This was the only major complication in the CAS group.

Length of hospital stay. The length of hospitalization was similar for both groups, although those undergoing CAS without complication tended to be discharged sooner (Table 3). As the study progressed, patients in the CEA group remained in the hospital for shorter periods, most being discharged the day after surgery. Forty-four patients (44/53) in the CAS group (83%) and 34 patients (34/51) in the CEA group (67%) were discharged from the hospital the day after the procedure. Excluding the single patient requiring below-the-knee amputation whose hospitalization extended to 68 days, overall hospital stays tended to be shorter in the CAS group (2.6 ± 1.6 days vs. 3.7 ± 3.1 days). Nevertheless, complications prolonged hospital care slightly more in the CAS group (5.6 ± 3.7 days vs. 3.8 ± 3.5 days). The primary complication associated with CAS was related to femoral artery access (3/53), which prolonged hospitalization because of continued bed rest and/or transfusion. Cranial/peripheral nerve injuries associated with CEA (4/51) did not prolong hospitalization. Hospitalization was extended secondary to concurrent or subsequent coronary bypass surgery in five patients. This procedure added an average of 10 ± 2 days to hospitalization. Neither CAS nor CEA afforded an advantage in terms of shortened stay in this small group of patients.

Patient's perception of pain and return to activity. The perception of pain was similar in both groups; neither experienced pain beyond a rating of 5/10 (Table 4). Most symptoms resolved by one month. Return to full activity was achieved within one week by 43 of the 53 patients undergoing CAS and 34 of the 51 patients randomized to CEA. All individuals in the CEA group resumed full activity by one month. However, complications in the CAS group significantly prolonged convalescence (57 to 120 days).

Cost/charges. Variable costs reflect the actual expenditures of performing a specific procedure, thus provide an accurate accounting of CEA and CAS. The total variable costs associated with CAS and CEA are similar ($p = 0.89$) (Table 5). As anticipated, individual hospital costs and charges resulting from the occurrence of complications varied widely, although they were higher for the CAS group secondary to prolonged hospitalization. Charges to patients, which did not include any professional fees, were higher in the CAS group ($p = 0.01$).

DISCUSSION

Endovascular technology has advanced to include treatment of carotid occlusive disease (23,24,26–29,38). Although proponents suggest that stenting may be effective in reducing carotid stenosis, its use has been recommended without testing its "clinical equipoise" (39) against the standard of care, endarterectomy. The single published randomized study designed to address this issue was suspended because of significant numbers of disabling strokes associated with

Table 4. Perception of Perioperative Pain and Activity

	CAS	CEA
Pain scale (0–10)		
24 h postprocedure (avg)	1.2 (range 0–5)	2.7 (range 0–5)
1 month postprocedure	<1.0 (0–4)	<1.0 (0–4)
Return to full activity (average days)		
Without complication	12 days (2–30)	16 days (7–30)
With complications	120 days (57–140)	21 days (9–30)

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy.

Table 5. Comparison of Variable Costs/Patient Charges*

	Total Costs	Nursing Costs	Cath/OR Lab	Pharmacy Costs	Lab Costs	Radiology Costs	Charges (Excluding Doctor Fees)
CAS	4,077 ± 460	327 ± 39	3,550 ± 286	66 ± 16	81 ± 26	105 ± 11	6,653 ± 367
CEA	3,415 ± 1,289	1,187 ± 101	1,159 ± 359	470 ± 229	79 ± 41	108 ± 58	5,594 ± 166

*Expressed as Avg ± SEM.
CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; OR = operating room.

stenting (32). Other multicenter prospective, randomized trials comparing CAS with CEA have been suspended (40) or have yet to be initiated (41). This report presents initial observations of a clinical trial designed to investigate the safety and effectiveness of carotid stenting compared with CEA in treating symptomatic carotid occlusive disease in a community hospital.

Equipoise of stenting and endarterectomy. Our results agree that carotid stenting is equally as effective as CEA in correcting and maintaining postprocedure patency of carotid stenosis (24,26,28,42). Equipoise is further supported by MRI, indicating that no asymptomatic ischemic events occurred in the distribution of the treated vessel subsequent to either revascularization technique (data not shown). The occurrence of major or minor stroke or death associated with CAS or CEA was well within the limits of acceptable risk delineated by the NASCET (1,4) and Asymptomatic Carotid Arteriosclerosis study (43) yet markedly differed from previous reports of nonrandom series indicating a risk for major or minor stroke associated with CAS approaching 6% (31). Although the "learning curve" for CAS is about 50 cases (31,42), the occurrence rates for serious complications in series involving an excess of 100 patients is higher than those associated with CEA (26,28,31,43,44). The low number of neurologic complications observed in this trial reflects a "cerebral endovascular team" comprised of neurosurgeons possessing skills in endarterectomy and catheter-based techniques, experienced interventional cardiologists and neurologists.

Economic issues of carotid stenting versus endarterectomy. Economic evaluation of stroke prevention and treatment is an important factor in the heath care sector (45–47). Thus, the deference toward evidence-based medicine now includes a demand for "cost-effectiveness" of new and existing technologies. This trial addresses these issues as characterized by length of hospital stay, the return to full activity, patient's perception of pain associated with the procedure and hospital costs. The occurrence of major or minor stroke was not observed in this trial regardless of the revascularization procedure. Thus, in contradistinction to Jordan et al. (31), these cerebrovascular complications cannot be deployed in an economic argument favoring CEA over CAS. Initially, stenting resulted in a shortened hospital stay with most patients being discharged within 24 h. However, based on our experience and that of others, that complications associated with endarterectomy occur within 6 h, a growing tendency toward shorter hospitalization after CEA has evolved (48–50). Most patients undergoing CEA are discharged within 24 h. Although, the theoretical advantage of "early" hospital discharge supposed through percutaneous technology has yet to be determined, hospital stay subsequent to CAS may be lessened in the future through miniaturization of technology and routine use of arterial closure devices.

As expected, hospitalization is prolonged by procedural complications. Cranial or peripheral nerve injury or neck hematomas that are rapidly recognized and appropriately treated do not influence hospital stay (1,16); however, the occurrence of clinically significant retroperitoneal hemorrhage does prolong hospitalization (36). Although anticoagulation is necessary, the paradigm used in stenting probably can be lessened because most cerebral ischemic events are associated with post-stent dilation, at which time atheromatous material may be released from the arterial wall rather than hematologic emboli (51). Routine use of distal protection devices in conjunction with less anticoagulation may reduce the risk of both excessive retroperitoneal and intraprocedural ischemic events. However, the addition of distal protection devices designed to prevent cerebral embolization of atheromatous material actually may increase cost/charges.

The evaluation of pain and return to full activity also judges the economic efficiency of a procedure. The frequent bias that "open" surgical techniques are less well tolerated in terms of pain and discomfort than percutaneous approaches is not supported by this trial. Both procedures seem equally well tolerated in terms of pain and discomfort. Moreover, return to full activity was achieved in about two weeks regardless of the procedure. However, return to full activity was delayed by complications particularly after CAS. Pain associated with groin complications is more limiting than those involving incisions in the neck in terms of active daily living.

Whereas, this study shows that the effectiveness of CAS is equivalent to CEA in terms of the ability to correct symptomatic carotid stenosis without increased risk for major or minor stroke, fiscal considerations tend to favor CEA (52). Although pharmacy and "routine" hospital costs and charges may be similar, expenditures associated specifically with cardiac catheterization laboratories compared with standard operating rooms are higher. Stents, angioplasty balloons, catheters, guiding wires, sheaths and the use of temporary pacemakers are costly and nonreusable. If the use of a distal protection device becomes a "standard of care," the costs will escalate further. These data suggest that, from a perspective of an economic evaluation, the potential

effect gained through percutaneous carotid stenting may be lessened by increased incremental cost/charges.

Study limitations. This trial is limited to a single institution, and a select "team" with experience in cerebral vascular disease and endovascular techniques, thus, cannot advocate that CAS replace CEA as a primary revascularization procedure in patients with symptomatic carotid stenosis. However, it is the first randomized prospective study to demonstrate that carotid angioplasty and stenting is equivalent to endarterectomy for the treatment of symptomatic carotid stenosis without added risk for major or minor stroke. If the economic constraints of incremental costs associated with stenting can be overcome, this trial indicates that CAS has reached clinical equipoise with CEA.

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Carotid Angioplasty and Stenting versus Carotid Endarterectomy for Treatment of Asymptomatic Carotid Stenosis: A Randomized Trial in a Community Hospital

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OBJECTIVE: Carotid endarterectomy (CEA) is effective in reducing the risk of stroke in individuals with more than 60% carotid stenosis. Carotid angioplasty and stenting (CAS) has been proffered as effective and used in treating individuals with asymptomatic carotid stenosis despite the absence of proven clinical equivalency. This randomized trial was designed to explore the hypothesis that CAS is equivalent to CEA for treating asymptomatic carotid stenosis.

METHODS: A total of 85 individuals presenting with asymptomatic carotid stenosis of more than 80% were selected randomly for CAS or CEA and followed up for 48 months.

RESULTS: Stenosis decreased to an average of 5% after CAS. The patency of the reconstructed artery remained satisfactory regardless of the technique, as determined by carotid ultrasonography. No major complications such as cerebral ischemia or death occurred. Procedural complications associated with CAS (n = 5) were hypotension and/or bradycardia; those concomitant with CEA (n = 3) were cervical nerve injury or complications related to general anesthesia (n = 4). Both procedures were well tolerated in the context of pain and discomfort. Hospital stay was similar in the two groups (mean, 1.1 versus 1.2 d). The occurrence of complications associated with CAS or CEA prolonged hospitalization by 3 days (mean, 4.0 versus 4.5 d). Return to full activity was achieved within 1 week by more than 85% of patients; all returned to their usual lifestyle by 2 weeks. Although hospital charges were slightly higher for CAS, costs were similar.

CONCLUSION: CAS and CEA may be equally effective and safe in treating individuals with asymptomatic carotid stenosis.

KEY WORDS: Asymptomatic carotid stenosis, Carotid angioplasty and stenting, Carotid endarterectomy

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Carotid endarterectomy (CEA) has been proved to significantly reduce the risk of stroke in patients with symptomatic carotid stenosis (19, 43, 48). However, the role of CEA in asymptomatic carotid stenosis remains controversial, partly because of uncertainty about the natural history of carotid stenosis treated with aggressive medical management alone as well as the inherent risks associated with the surgical procedure (6, 7, 18, 21, 33, 34, 41, 46). The Asymptomatic Carotid Atherosclerosis Study (ACAS) recorded a statistical benefit favoring CEA in reducing the risk of stroke if the combined surgical morbidity and mortality is less than 3% and the prognosis for healthy life expectancy is at least 5 years (12, 27). Although some surgical series have achieved complication rates similar to those of ACAS (17, 54), others have abrogated these benefits because of excessively higher occurrences of major stroke and/or death (10, 18, 22, 26, 31, 33, 37, 55, 58). In addition, minor strokes and other complications associated with endarterectomy remain significant and often disabling. Perioperative complications resulting from exacerbation of concurrent, asymptomatic cardiac and hypertensive disease occur in approximately 8% of patients (44). Cranial and/or cervical nerve injury occurs in 7.6 to 27% of patients undergoing CEA (5, 51). Thus, in addition to the risk for major cerebral ischemic complications, CEA has other potential con-

sequences that require consideration when surgical treatment is recommended for asymptomatic carotid stenosis.

Carotid angioplasty and stenting (CAS) represents a relatively new technique offering a theoretical advantage of being less traumatic, safer, and more cost-effective in patients with asymptomatic carotid stenosis (2, 28, 49, 60). The therapeutic benefit of CAS has been demonstrated in patients with contralateral occlusion, restenosis, and surgically inaccessible lesions (35, 39, 61). However, despite observations that angiographic results comparable to those of CEA are achievable, major complications in most early CAS series exceeded those acceptable in the context of ACAS (23, 30, 38, 57); hence, CAS has been considered unacceptable for routine treatment of symptomatic carotid stenosis and clearly inappropriate and unethical for consideration in treating asymptomatic carotid stenosis (8, 9, 40, 42, 53). Recently, a randomized, prospective trial comparing CAS with CEA demonstrated clinical equivalence of these procedures for treating symptomatic carotid stenosis (11). CAS was demonstrated to be equivalent to CEA without increased risk for such major complications as stroke or death. Moreover, the shortened hospitalization and convalescence attendant on CAS challenges CEA as the preferred treatment of symptomatic carotid disease. This prospective randomized trial compares the efficacy and benefits of CAS and CEA in the treatment of asymptomatic carotid stenosis in a community hospital.

PATIENTS AND METHODS

This two-arm randomized clinical trial was approved by our institutional review board to include asymptomatic individuals referred for revascularization to the neurosurgical, neurology, and/or cardiology services and having digital subtraction angiography-documented internal carotid stenosis of more than 80%, as determined by the North American Symptomatic Carotid Endarterectomy Trial (45). Persons with any symptom of cerebrovascular ischemia were excluded. All patients were informed that the United States Food and Drug Administration has not approved deployment of stents in the carotid artery for treatment of carotid stenosis. The presence of contralateral total occlusion of the internal carotid artery, the angiographic appearance (smooth versus ulcerative) of the stenotic lesion, or the presence of an intracranial aneurysm was not a factor in treatment assignment. In addition to angiographic criteria, inclusion criteria included an anticipated life expectancy of 5 years, willingness to complete treatment within 1 month, and ability to sign an informed consent. Exclusionary criteria included allergy or sensitivity to aspirin, heparin, or clopidogrel; a history of bleeding diathesis or coagulopathy; or cardiac arrhythmia.

A total of 85 individuals met these criteria in the initial year of the trial, agreed to participate, and were selected randomly to undergo CEA (42) or CAS (44); the patients were evaluated sequentially for 48 months. All patients received 325 mg aspirin and 75 mg clopidogrel before CAS or CEA. A neurologist (TLC) and a clinical coordinator (LB) provided neurological examinations and independent oversight before and after each procedure and at specified intervals in conjunction with carotid duplex scanning.

CEA was performed by standard techniques under general anesthesia with electroencephalographic monitoring. All patients were observed in the intensive care unit after surgery.

CAS was performed as described previously (11). Conscious sedation was not used. Activated clotting time was maintained at more than 250 seconds. Distal protection devices were not used. All lesions were predilated before placement of either a 10 × 20-mm Wallstent (Boston Scientific/Medi-tech, Natick, MA) or a 10 × 38-mm Dynalink (Guidant Corp., Indianapolis, IN) stent (kindly provided by the manufacturers). Postdilation was completed with an appropriately sized balloon meeting a balloon-to-artery ratio of 1:1 by visual estimate. Ipsilateral cerebral angiography was performed before withdrawal of the sheath from the common carotid artery.

Carotid duplex scanning was performed within 24 hours and at specified intervals and expressed as the ratio of internal carotid artery to common carotid artery velocity. Rankin and Barthel scorings and independent neurological evaluations were performed concurrently with sequential duplex examinations. Inversion recovery magnetic resonance imaging was performed on all patients the day after either procedure.

Perception of pain was assessed as described previously (11, 36). No specific posthospitalization instructions were provided in reference to activity; each patient determined return to "full activity." Hospital variable costs included operating room or catheterization laboratory, pharmacy, nursing, laboratory, and radiology. Professional fees were not assessed for CAS; hence, no physician's fees were included in computing costs/charges.

Results are expressed as average ± standard error of the mean. Statistical comparisons were performed with Student's t test. Two-way repeated-measures analysis of variance was used to compare sequential testing of carotid duplex scanning. A value of $P < 0.05$ was considered significant.

RESULTS

The average ages, numbers of women and men, and risk factors for stroke of those randomized for CEA or CAS were similar (*Table 1*). Risk factors for stroke included hypertension, smoking, elevated cholesterol level, and diabetes. More than two risk factors and family history of symptomatic cerebrovascular or coronary vascular disease were present in most individuals (81 of 85 patients).

Results of Treatment

Treatment was completed in all individuals within 4 weeks after randomization. Diagnostic cerebral angiography indicated the average pretreatment stenosis in the CEA group (85.6 ± 3.5%) to be similar ($P > 0.05$) to that in the CAS group (86.3 ± 3.5%). The mean cross sectional stenosis observed on anteroposterior, lateral, or oblique angiographic view was 1.4

TABLE 1. Baseline characteristics of patients[a]

	CAS (n = 43)	CEA (n = 42)
Mean age, yr (range)	66.6 (49–85)	69.9 (48–84)
Risk factor		
Hypertension	35	41
Smoking	40	37
Coronary vascular disease	35	20
Diabetes mellitus	7	5
Cholesterol (>200 mg/dl)	9	8
Family history of stroke/coronary vascular disease	40	41
>2 risk factors	39	37

[a] CAS, carotid angioplasty and stenting; CEA, endarterectomy.

± 0.6 mm (range, 0.8–3.2 mm) in the CEA group and 1.6 ± 0.3 mm (range, 1.0–3.1 mm) in those undergoing CAS. The average untreated contralateral carotid artery stenosis was 33.3 ± 10.6% in the CEA group and 45.0 ± 21.0% in the CAS group; total occlusion was observed in three and four individuals undergoing CEA and CAS, respectively. The average postprocedural stenosis for CAS decreased to 5.0 ± 3.5% (range, 0–15%).

The 48-month patency of the reconstructed artery, regardless of technique, remained satisfactory as determined sequentially by carotid ultrasonography and expressed as the internal carotid artery to common carotid artery ratio of peak systolic velocity (*Fig. 1*). During the follow-up period (48 mo), no individual in either group experienced symptoms of cerebral ischemia.

Complications

There were no procedurally related transient cerebral ischemic events, strokes, or deaths (*Table 2*). No evidence of asymptomatic focal cerebral ischemia was found in any patient after treatment as determined by fluid-attenuated inversion recovery magnetic resonance imaging (data not shown).

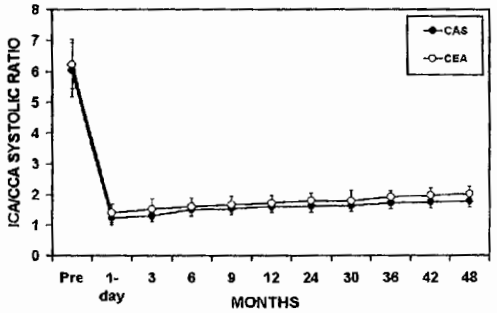

FIGURE 1. *Graph showing patency of carotid artery before revascularization and after 24 hours and monthly intervals expressed as average internal carotid artery to common carotid artery (ICA/CCA) systolic ratio.*

TABLE 2. Complications[a]

	CAS	CEA
Stroke/TIA	0	0
Cervical nerve injury	NA	3
Bradycardia/hypotension	5	0
Related to anesthesia	NA	4

[a] CAS, carotid angioplasty and stenting; CEA, endarterectomy; TIA, transient ischemic attack; NA, not applicable.

Five patients required treatment for marked bradycardia and hypotension concurrent with angioplasty as a result of carotid body stimulation. All responded to pharmacological management. Placement of a cardiac pacemaker was not required in any individual. There were no complications associated with femoral artery access. Complications associated with CEA were limited to cervical nerve injury, manifested as diminished sensation in the mandible or neck. These symptoms resolved within 3 months. One patient developed atrial fibrillation after CEA. Three patients experienced minor complications related to general anesthesia, e.g., nausea, vomiting, or general malaise.

Length of Hospital Stay

The overall length of hospital stay was similar for the two groups (*Table 3*). Thirty-seven of 43 patients in the CAS group and 32 of 42 patients in the CEA group were discharged the day after the procedure. None were discharged the day of the procedure. Forty (93%) of the 43 individuals undergoing CAS and 38 (90%) of the 42 in the CEA group were discharged from the hospital within 48 hours. Cervical nerve injury associated with CEA did not prolong hospitalization, although side effects of general anesthesia and the single occurrence of atrial fibrillation resulted in extended stays (mean, 4.5 ± 6.4 d). Complications associated with CAS prolonged stay because of continued bed rest and/or adjustments of antihypertensive medicines (mean, 4.0 ± 3.0 d). Neither CAS nor CEA afforded a decisive advantage in terms of shortened hospital stay.

TABLE 3. Length of hospital stay[a]

	Days, mean (range)	
	CAS	CEA
All patients	1.5 ± 0.8 (1–10)	1.7 ± 2.5 (1–14)
Without complications	1.1 ± 0.35 (1–2)	1.2 ± 0.42 (1–2)
With complications	4.0 ± 3.0 (2–10)	4.5 ± 6.4 (1–14)

[a] Values are average ± standard error of the mean (range); CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy.

Perception of Pain and Return to Activity

Perception of pain was similar; neither group experienced pain rated higher than 5 on a scale of 0 to 10 (*Table 4*). Few patients (CAS, 3 patients; CEA, 2 patients) indicated the presence of discomfort beyond 1 month. Typically, return to full activity as determined by the individual patient was achieved within 1 week but was prolonged slightly when complications occurred. No significant differences were observed with respect to return to full activity.

Costs/Charges

Variable costs reflect the actual hospital expenditures of performing a specific procedure and thus provide an accurate accounting of hospital cost for providing CEA or CAS. The total variable costs generated by CAS and CEA are similar ($P = 0.79$) (*Table 5*). These data indicate that the hospital expenditures attendant on these procedures do not favor either one. Actual charges to patients, which did not include any professional fees, were slightly higher in the CAS group ($P = 0.04$).

DISCUSSION

Endovascular treatment of carotid disease is rapidly gaining popularity as an alternative to endarterectomy (2, 16, 24, 49, 56, 59, 60). Despite the enthusiasm and the obvious advantage over CEA by avoiding a neck incision and dissection of the carotid bifurcation, only a single prospective, randomized trial has demonstrated the equivalence of these procedures in the treatment of symptomatic carotid stenosis (11). Although the Carotid and Vertebral Artery Transluminal Angioplasty Study reported similar success and complication rates for CEA and angioplasty, stents were deployed in only 26% of cases (13). More recently, a randomized comparison of CEA with CAS using a distal protection device in high-risk patients (59) has reported that CAS is superior to CEA in treating carotid stenosis in both symptomatic and asymptomatic individuals. Although the 30-day death or stroke complication rates of CAS (5.8%) in asymptomatic individuals were indeed lower than those of CEA (6.8%), neither was within the constraints of ACAS. The occurrence of transient cerebral ischemia (CAS, 3.8%; CEA, 2.0%) was similar for the two groups. Other multicenter trials comparing CAS with CEA in symptomatic patients either have failed to show equivalence (42) or have been suspended (1). Despite the absence of confirmatory multicenter randomized trials demonstrating the therapeutic equivalence of CAS and CEA for treatment of symptomatic carotid stenosis, carotid stents have been deployed in large numbers of asymptomatic individuals (2, 38, 49, 59, 60). Thus, carotid stenting has been recommended and used despite the conspicuous absence of demonstrated "clinical equipoise" (20) of CAS and CEA in the management of asymptomatic individuals with critical carotid stenosis. This clinical trial was designed to address this issue by assessing the safety and effectiveness of carotid stenting compared with CEA in treating asymptomatic carotid occlusive disease in a community hospital.

The results of this trial are comparable to those of our previous study (11) and others (2, 49) indicating that carotid stenting and CEA are equally effective in correcting and maintaining postprocedure patency of the treated carotid artery. The occurrence of major complications associated with CAS or CEA was well within the constraints of risk prescribed by the ACAS (17, 27). Moreover, the absence of any cerebral ischemic event in the CAS patients differs from previously reported nonrandom series that found a risk for minor stroke approaching 6% (30, 57, 59). The notable reduction of neurological complications in this and the previous trial may reflect the advantages of developing a cerebrovascular interventional team consisting of neurosurgeons, neurologists, and interventional cardiologists who possessed experience in cerebrovascular disease as well as surgical and interventional skills before initiating a community hospital-based program providing CAS as a treatment choice for carotid stenosis. Given the difficulties and controversies in proper patient selection for treating asymptomatic carotid stenosis, a team approach is important to avoid selection bias and to provide the best medical and/or surgical management before and after CAS or CEA.

In addition to safety and effectiveness, cost constraints and economic evaluation of any prescribed protocol designed to lessen the prevalence of stroke are important factors in the healthcare sector (3, 14, 15, 25, 50, 52). Issues of cost-effectiveness can be addressed by comparing the length of hospital stay and patient perception of pain in addition to hospital costs and charges associated with these procedures. Although Al-Mubarak et al. (2) have reported the safety and short-term results of ambulatory carotid stenting, the majority of patients (approximately 70%) still required hospitalization, indicating that same-day discharge is not as yet appropriate. In the present trial, most

TABLE 4. Perception of perioperative pain and activity[a]

	Mean (range)	
	CAS	CEA
Pain scale (0–10)		
24 h postprocedure (average)	1.1 (0–4)	2.0 (0–5)
1 mo postprocedure	<1.0 (0–3)	<1.0 (0–3)
Return to full activity (average days)		
Without complications	6.5 ± 2.8 (3–14)	8.3 ± 3.5 (4–14)
With complications	8.6 ± 5.9 (6–15)	9.8 ± 6.1 (4–18)

[a] CAS, carotid angioplasty and stenting; CEA, endarterectomy.

TABLE 5. Comparison of variable costs/charges[a]

	Catheterization laboratory/ operating room	Nursing	Laboratory	Radiology	Pharmacy	Total	Charges[a]
CAS	2772 ± 410	400 ± 86	55 ± 6	92 ± 4	55 ± 6	3600 ± 422	6447 ± 325
CEA	1089 ± 554	1059 ± 89	70 ± 4	109 ± 16	629 ± 43	3969 ± 557	5371 ± 112

[a] Physician fees excluded. CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy.

patients without procedure-related complications were discharged the day after CAS or CEA. Although complications associated with CAS and CEA generally occur within 6 hours after either procedure (25, 47, 50), at present, outpatient procedures for treatment of carotid stenosis should be carefully scrutinized before they are accepted as standard care. The goals of treating asymptomatic carotid stenosis by CAS must remain centered on safety and effectiveness; the postprocedure length of stay should not become the major end point of efficacy analyses.

As expected, procedural complications slightly prolonged hospitalization. Although no major adverse occurrences were experienced in this study, complications specifically associated with endovascular procedures, e.g., femoral artery thrombosis/embolism or retroperitoneal hemorrhage (32), or with endarterectomy, e.g., wound hematoma or cranial nerve injury, can occur and prolong hospitalization. Minor complications associated with CAS were typically confined to bradycardia and hypotension secondary to carotid sinus stimulation after stent placement and poststent dilation. Although not uncommon, this cardiovascular effect usually is transient or responds rapidly to pharmacological intervention (47). Nevertheless, patients may require prolonged hospitalization to accommodate to lower blood pressures and/or changes in antihypertensive medications. Interestingly, some patients continued to manifest normal blood pressures without resuming antihypertensive medication. Common complications of cervical nerve injury associated with CEA typically did not affect hospitalization. Those individuals who experienced side effects of general anesthesia, however, did require extra hospitalization. Thus, minor complications associated with either CAS or CEA similarly prolong hospitalization, albeit minimally. Although individuals undergoing CAS tended to be discharged earlier than the CEA group, at present, CAS cannot be claimed to have an advantage of a predictable shortened hospital stay compared with endarterectomy.

Other important factors to be considered in preventive therapy are the individual's perception of pain and discomfort associated with any procedure and the duration of recovery until resumption of full, unrestricted activities. Although it has been suggested that CAS affords less discomfort and facilitates a rapid return to normal function (2, 56), the present study indicates that the degree of pain and return to previous lifestyles are similar. Patients undergoing CAS seemed to have less postprocedural pain, yet the difference was not dramatic. In addition, the CAS group tended to experience a return to full activity more rapidly than those in the CEA group. However, the differences observed between the two procedures were too small to strongly favor one over the other.

These data support the claim that CAS and CEA are equivalent in reducing carotid stenosis and maintaining patency, with similar risks and postoperative outcome. However, fiscal considerations tend to favor CEA (11, 29). The actual hospital expenditures required for providing these procedures are similar, yet the charges generated were higher for CAS. Indeed, costs and charges may increase in the future if the use of distal protection devices becomes an integral component required for successful, uncomplicated CAS (4, 56, 59). Perhaps the costs of expendables required for angioplasty and stenting will decrease as this technique becomes more customary. At present, however, an argument that endovascular therapy is less expensive than endarterectomy is untenable.

Although this trial, limited to a single institution, has demonstrated that CAS can achieve parity with the "gold standard," endarterectomy, for the treatment of asymptomatic carotid stenosis, the results must be interpreted with restraint. This study cannot and does not advocate that CAS replace CEA as the treatment of choice for asymptomatic carotid stenosis, nor is it empowered to address the issues of the indications for treating this condition. A multicenter randomized trial comparing the risks and benefits of CAS with medical management of asymptomatic carotid stenosis is required before stenting truly can meet the standards required by ACAS. Although the current trial indicates that at 48 months, CAS maintains carotid patency equal to that achieved by CEA, longer sequential follow-up is necessary to provide irrefutable evidence that the two carotid revascularization procedures are equivalent in maintaining carotid patency. Moreover, it must be emphasized that no revascularization procedure, CEA or CAS, is warranted in the management of asymptomatic carotid stenosis if the procedural risks of the institution and operator exceed 3%. Nevertheless, despite these reservations, this trial indicates that a select cerebrovascular team with surgical and endovascular experience in cerebrovascular disease may be effective in treating asymptomatic carotid stenosis with results similar to those achieved via CEA.

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COMMENTS

Brooks et al. report a randomized trial of asymptomatic patients with carotid stenosis who underwent either carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS). In this small series, both treatments seemed to be equally effective in establishing normal flow in the carotid artery. No significant complications were reported in either treatment arm, and no restenosis was seen in either treatment arm. The excellent results in this series attest to the high level of skill and experience of the surgeons and interventionalists who performed these procedures. In this group of patients, one or two major complications could have affected the statistical conclusions significantly. Therefore, although these results suggest that both methodologies are clearly useful in treating patients with carotid artery stenosis, this comparison may not be generalizable to the practice patterns of physicians at low-volume medical centers.

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The authors present the results of a single-center randomized trial in which CEA was compared with CAS in a group of 85 asymptomatic patients. No patients in either group experienced ischemic symptoms in the periprocedural period or during 48 months of follow-up. Given the low risk of stroke in patients with asymptomatic carotid stenosis (2.2%/yr with medical therapy) observed in the Asymptomatic Carotid Atherosclerosis Study (1), it is difficult to make inferences about the efficacy of either treatment in a patient population of this size. The data presented are encouraging. However, the results of larger multicenter trials are needed to draw meaningful conclusions about the relative efficacy and safety of CAS compared with CEA.

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1. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study: Endarterectomy for asymptomatic carotid stenosis: Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 273:1421–1429, 1995.

Brooks et al. describe their experience in a small, randomized study of 85 individuals who presented with asymptomatic stenosis greater than or equal to 80%. Patients were selected randomly to undergo CAS or CEA under an Institutional Review Board-approved protocol and were followed for 48 months. The authors' hypothesis was that CAS is equivalent to CEA in the treatment of patients with asymptomatic carotid stenosis.

The results are remarkable in that CAS could be performed in all patients who were randomized to have that procedure. Five procedural complications occurred within the CAS group; however, none were related to either temporary or significant neurological events. The length of hospital stay was virtually identical in both groups, although hospital charges were slightly higher in the CAS group.

The number of patients studied in this article is small, but the results are certainly provocative. In view of the fact that neurosurgeons are still trying to address the question whether CAS is a durable and statistically significant procedure in the treatment of symptomatic stenosis as part of the Carotid Revascularization Endarterectomy versus Stent Trial (1), Brooks et al. have taken it one step further into the asymptomatic population.

One certainly cannot argue with the authors' results, which indicate that CAS was equivalent to CEA in their patients. Remarkably, the perioperative complication rates were extremely low in both groups. Caution should be exercised, however, and as the authors themselves state, the results of this small study cannot be generalized to all centers.

Several key points in the Discussion are worth reiterating. The goals of treating asymptomatic carotid stenosis with CAS must remain centered on safety and effectiveness, not length of stay, and although cost is an issue, it should not be the determining factor in selecting the mode of treatment. The authors also make an important point when they state, "This study cannot and does not advocate that CAS replace CEA as the treatment of choice for asymptomatic carotid stenosis, nor is it empowered to address the issues of the indications for treating this condition." In addition, as the authors appropriately point out, "It must be emphasized that no revascularization procedure, CEA or CAS, is warranted in the management of asymptomatic carotid stenosis if the procedural risks of the institution and operator exceed 3%." Only

larger studies will determine its true efficacy and durability as a stroke reduction procedure.

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Brooks et al. have conducted a randomized, prospective trial comparing CAS with CEA in asymptomatic patients with significant carotid stenosis. Both procedures were effective in decreasing or eliminating the stenosis, and in no case was recurrent stenosis found during follow-up. The hospital stay and costs associated with both procedures were similar. Few complications occurred in both groups. Of note, there were no instances of transient ischemic attack or stroke in either treatment arm, and no distal protection device was used. It is interesting that there were no significant differences in either hospital stay or cost.

These results support the authors' claim of clinical equipoise between the two treatment methods at the authors' institution and in the patient population studied. Of course, as the authors correctly note, long-term follow-up is necessary to establish the durability of CEA. A randomized trial comparing CAS with medical therapy for patients with asymptomatic but significant carotid stenosis is needed. Nonetheless, this report is an important contribution to the growing literature indicating that CAS, when performed by experienced surgeons and in carefully selected patients, is a safe and effective alternative to surgery.

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The authors report the results of a randomized trial of CAS versus CEA performed at a single center. A total of 85 patients with asymptomatic, greater than 80% cervical carotid artery stenosis underwent either CAS or CEA. Distal protection was not used. The patients were followed for 48 months, and outcomes were determined in terms of angiographic results (for patients who had CAS), complications, procedural discomfort, hospital stay, hospital charges, stroke or transient ischemic attack, and return to full activity. There were no occurrences of stroke or transient ischemic attack in any patient during the periprocedural course or during the 48-month follow-up period. Complication rates for both procedures were reasonably low, which is particularly notable, given that distal protection devices were not used for the CAS procedures. Vessel patency, as measured by carotid duplex scanning, was preserved in all patients during the follow-up period.

This study is timely and important and was conducted well. A single team consisting of a neurosurgeon and an interventional cardiologist performed the procedures. A neurologist performed neurological examinations. The primary drawback of the study is the relatively small number of patients studied. Although this study has value as one of the first randomized trials to compare CAS with CEA performed in asymptomatic patients, a much larger sample size is required to determine with any degree of statistical certainty whether complication rates and outcomes associated with the two procedures are comparable. A wide array of randomized trials and registries that should answer this question are currently under way.

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Future Meetings—Congress of Neurological Surgeons

The following are the planned sites and dates for future annual meetings of the Congress of Neurological Surgeons:

2004	San Francisco, CA	October 16–21
2005	Boston, MA	October 8–13
2006	Chicago, IL	October 7–12
2007	San Diego, CA	September 15–20

Future Meetings—American Association of Neurological Surgeons

The following are the planned sites and dates for future annual meetings of the American Association of Neurological Surgeons:

2004	Orlando, FL	May 1–6
2005	New Orleans, LA	April 16–21
2006	San Francisco, CA	April 22–27
2007	Washington, DC	April 14–19