

# Angioplasty and Stenting of the Cervical Carotid Artery with Embolic Protection of the Cerebral Circulation



Assessment  
Program  
Volume 22, No. 1  
June 2007

## Executive Summary

### Background

Atherosclerotic lesions in the cervical carotid artery can result in luminal narrowing (stenosis) and increase the risk of disabling or fatal ischemic stroke—carotid endarterectomy (CEA) can diminish this risk. However, even in the best hands, the CEA is accompanied by periprocedural complications. Whether a patient ultimately accrues a net health benefit from CEA is based primarily on: magnitude of risk reduction accompanying CEA, periprocedural risk (stroke/death rate), expected event rate with best medical therapy alone, and the patient's anticipated life expectancy. Results from several large multicenter trials have established periprocedural stroke/death rates accompanied by a net health benefit and recommended life expectancy:

Symptoms	% Stenosis	Acceptable Periprocedural Stroke/Death Rate	Recommended Anticipated Life Expectancy
No	60–99%	<3%	≥5 years
Yes	50–69%	<6%	≥5 years
	70–99%	<6%	≥2 years

A potential alternative to CEA is carotid angioplasty and stenting (CAS) used with an embolic protection device (EPD)—particularly for patients with increased medical or anatomic risk. If CAS and CEA are equally safe and effective given similar patient characteristics and can be performed with periprocedural stroke/death rates accompanied by a net health benefit, then CAS is an alternative to CEA. CAS could also be superior to CEA, particularly under some conditions, such as inaccessible lesions or adverse anatomic conditions.

### Objective

To review and evaluate available evidence concerning outcomes of CAS with EPD alone and compared to alternatives (CEA and best medical therapy) for reducing stroke risk in patients with carotid artery stenosis. The Assessment specifically seeks the following evidence:

1. Can CAS be performed with periprocedural stroke/death rates established as clinically acceptable and associated with an overall net health benefit among symptomatic and asymptomatic patients at:
  - a) average medical and anatomic risk, b) increased medical risk, and c) increased anatomic risk?<sup>1</sup>
2. How do CAS, CEA, and best medical therapy compare in each of the above subgroups?

<sup>1</sup> There is theoretically a fourth group at increased anatomic and medical risk, but anatomic risk is presumed to be of greater clinical importance.

NOTICE OF PURPOSE: TEC Assessments are scientific opinions, provided solely for informational purposes. TEC Assessments should not be construed to suggest that the Blue Cross Blue Shield Association, Kaiser Permanente Medical Care Program or the TEC Program recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service; any particular course of treatment, procedure, or service; or the payment or non-payment of the technology or technologies evaluated.



An Association  
of Independent  
Blue Cross and  
Blue Shield Plans



### Search Strategy

MEDLINE® was searched (via PubMed) for articles indexed under the MeSH® headings “stents” AND “carotid artery diseases” OR “carotid stenosis” from 1994 through April 2007 and was limited to articles published in English that reported on human subjects.

### Selection Criteria

Randomized, controlled trials and prospective registries with predefined endpoints and inclusion/exclusion criteria published in peer-reviewed journals.

### Main Results

Three randomized, controlled trials compared CAS directly to CEA (with best medical therapy) using a noninferiority approach. The “Stent-Protected Angioplasty versus Carotid Endarterectomy” (SPACE) and “Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis” (EVA-3S) trials enrolled average-risk symptomatic patients ( $\geq 50\%$  and  $60\text{--}99\%$  stenosis, respectively), while the “Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy” trial (SAPPHIRE) enrolled symptomatic ( $\geq 50\%$  stenosis) and asymptomatic ( $\geq 80\%$  stenosis) patients at increased medical or anatomic risk—stratifying randomization according to the presence or absence of symptoms. None of the trials met targeted enrollments.

SPACE and EVA-3S were terminated early: SPACE due to lack of funding and a larger-than-anticipated projected sample size; EVA-3S for reasons of safety and futility. Neither demonstrated noninferiority. Periprocedural stroke/death rates with CAS in both trials exceeded those established as clinically acceptable and associated with an overall net health benefit in symptomatic patients: in SPACE, 7.7% (95% CI: 6.1–9.7); in EVA-3S, 9.6% (95% CI: 6.4–14.0).

SAPPHIRE found CAS noninferior to CEA for a composite primary endpoint of stroke, death or myocardial infarction (MI). The dominant difference between arms was MI occurrence—almost all non-Q wave. Few symptomatic patients were enrolled ( $\leq 50$  in each arm). The 5.1% (95% CI: 2.4 to 10.7) and 3.3% (95% CI: 1.3 to 8.2) periprocedural stroke rates among asymptomatic CAS and CEA patients, respectively, and exceeded the 3% stroke/death rate established as clinically acceptable and associated with an overall net health benefit in asymptomatic patients.

Publications from 7 registries and the lead-in phase of CREST (Carotid Revascularization Endarterectomy vs. Stent Trial) reported outcomes after CAS with EPD (6,712 patients). All enrolled symptomatic and asymptomatic patients. Six registries enrolled patients at increased risk. Three registries enrolling patients at increased medical or anatomic risk reported 30-day periprocedural complication rates according to the presence or absence of symptoms that exceeded those established as clinically acceptable and associated with an overall net health benefit following CEA:

Periprocedural Outcomes in 3 Registries Enrolling Increased-Risk Patients

Symptoms	Stroke	Stroke/Death/MI
Symptomatic	7.4% to 10.9%	7.9% to 12.1%
Asymptomatic	3.4% to 3.8%	5.0% to 5.4%

A single registry reported a 3.9% periprocedural stroke/death/MI rate for patients with or without symptoms at increased anatomic risk. Interim results from the CREST lead-in phase enrolling average-risk patients reported 30-day stroke/death rates following CAS in symptomatic and asymptomatic patients of 5.7% and 3.7%, respectively.

The lack of outcomes clearly distinguished according to factors increasing medical risk or anatomic risk hinders interpreting the evidence—both from trials and registries. No studies comparing CAS to current best medical therapy were identified.

### **Author's Conclusions and Comments**

Available evidence does not support concluding that CAS is performed with acceptable periprocedural stroke/death rates for symptomatic or asymptomatic patients, that it provides a net health benefit to patients at increased medical risk, or that it is equally effective as CEA. There is a clinical rationale and limited evidence suggesting CAS may be beneficial in the group of patients at increased anatomic risk; however, current evidence has not clearly differentiated outcomes for this subgroup according to symptomatic status.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about whether carotid artery angioplasty and stenting (CAS) with or without distal embolic protection (EPD) meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to reduce stroke risk from symptomatic or asymptomatic carotid stenosis.

#### **1. The technology must have final approval from the appropriate governmental regulatory bodies.**

CAS with or without EPD is a procedure and thus does not require U.S. Food and Drug Administration (FDA) approval. However, the devices used for CAS and for EPD require FDA approval. As of this writing, five manufacturers' stents are FDA approved and indicated specifically for use in carotid arteries. The FDA has mandated postmarketing studies for these devices, including longer follow-up for patients already reported to the FDA, and additional registry studies primarily to compare outcomes as a function of clinician training and facility experience. The devices are indicated for combined use of a stent and EPD to reduce stroke risk in patients at increased risk for perioperative complications from CEA who are symptomatic with  $\geq 50\%$  stenosis or asymptomatic with  $\geq 80\%$  stenosis. CAS with these devices for patients outside these indications is an off-label use.

#### **2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

Available evidence permits conclusions regarding periprocedural complication rates (particularly stroke or death) following CAS in patients of average risk and increased medical risk. Periprocedural stroke/death rates surpassed those established as clinically acceptable and associated with an overall net health benefit following CEA. There is limited evidence and a clinical rationale to suggest CAS may be beneficial in the group of patients at increased anatomic risk, but present evidence has not clearly differentiated outcomes for this subgroup according to symptomatic status. Thus, there is insufficient evidence to draw conclusions regarding patients at increased anatomic risk.

A number of large ongoing trials will yield more evidence in the near future (e.g., "Carotid Revascularization Endarterectomy versus Stent Trial" [symptomatic and asymptomatic]; "International Carotid Stenting Study" [symptomatic]; and the "Asymptomatic Carotid Surgery Trial," ACT-1).

#### **3. The technology must improve the net health outcome.**

Available evidence does not support concluding that CAS with EPD improves the net health outcome among patients at average or increased medical risk. Evidence regarding patients at increased anatomic risk is suggestive of benefit, but insufficient to draw conclusions.

#### **4. The technology must be as beneficial as any established alternatives.**

Available evidence does not support concluding that CAS with or without EPD is as beneficial as CEA for symptomatic patients at average risk or increased medical risk. Whether CAS with EPD is as beneficial as CEA for asymptomatic patients at average medical or anatomic risk cannot be

determined because available evidence is insufficient to permit conclusions. There is no evidence comparing best medical therapy for symptomatic or asymptomatic patients at increased medical or anatomic risk, preventing conclusions.

##### 5. The improvement must be attainable outside the investigational settings.

Whether CAS with EPD improves health outcomes has not yet been demonstrated in the investigational setting.

Based on the above, use of carotid artery angioplasty and stenting with or without embolic protection of the cerebral circulation for patients with carotid artery stenosis does not meet the TEC criteria.

#### Contents

<b>Assessment Objective</b>	<b>5</b>	<b>Review of Evidence</b>	<b>14</b>
<b>Background</b>	<b>8</b>	<b>Summary of Application of the Technology Evaluation Criteria</b>	<b>26</b>
<b>Methods</b>	<b>12</b>	<b>References</b>	<b>28</b>
<b>Formulation of the Assessment</b>	<b>13</b>	<b>Appendix</b>	<b>33</b>

#### Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

##### TEC Staff Contributors

**Author**—Mark D. Grant, M.D., M.P.H.; **TEC Executive Director**—Naomi Aronson, Ph.D.; **Managing Scientific Editor**—Kathleen M. Ziegler, Pharm.D.; **Research/Editorial Staff**—Claudia J. Bonnell, B.S.N., M.L.S.; Maxine A. Gere, M.S.

##### Blue Cross and Blue Shield Association Medical Advisory Panel

**Allan M. Korn, M.D., F.A.C.P.**—Chairman, *Senior Vice President, Clinical Affairs/Medical Director, Blue Cross and Blue Shield Association*; **Alan M. Garber, M.D., Ph.D.**—Scientific Advisor, *Staff Physician, U.S. Department of Veterans Affairs*; **Henry J. Kaiser, Jr., Professor, and Professor of Medicine, Economics, and Health Research and Policy, Stanford University**; **Steven N. Goodman, M.D., M.H.S., Ph.D.**—Scientific Advisor, *Associate Professor, Johns Hopkins School of Medicine, Department of Oncology, Division of Biostatistics (joint appointments in Epidemiology, Biostatistics, and Pediatrics)*—American Academy of Pediatrics Appointee. ■ **Panel Members** **Peter C. Albertsen, M.D.**, *Professor, Chief of Urology, and Residency Program Director, University of Connecticut Health Center*; **Sarah T. Corley, M.D.**, *Physician Consultant, NexGen Healthcare Information Systems, Inc.*—American College of Physicians Appointee; **Helen Darling, M.A.**, *President, National Business Group on Health*; **Josef E. Fischer, M.D., F.A.C.S.**, *William V. McDermott Professor of Surgery, Harvard Medical School and Chair, Department of Surgery, Beth Israel Deaconess Medical Center*—American College of Surgeons Appointee; **Willard K. Harms, M.D., M.M.**, *Medical Director, Medical Policy and Adjudication, Blue Cross Blue Shield of Illinois*; **I. Craig Henderson, M.D.**, *Adjunct Professor of Medicine, University of California, San Francisco*; **Mark A. Hlatky, M.D.**, *Professor of Health Research and Policy and of Medicine (Cardiovascular Medicine), Stanford University School of Medicine*; **Walter A. Hollinger, M.D., M.M., M.H.P.E., F.A.C.P.**, *Senior Medical Director, Care Management, Blue Cross and Blue Shield of Florida*; **Bernard Lo, M.D.**, *Professor of Medicine and Director, Program in Medical Ethics, University of California, San Francisco*; **Barbara J. McNeil, M.D., Ph.D.**, *Ridley Watts Professor and Head of Health Care Policy, Harvard Medical School, Professor of Radiology, Brigham and Women's Hospital*; **Joel Owerbach, Pharm.D.**, *Vice President and Chief Pharmacy Officer, Excellus Health Plans*; **William R. Phillips, M.D., M.P.H.**, *Clinical Professor of Family Medicine, University of Washington*—American Academy of Family Physicians' Appointee; **Maren T. Scheuner, M.D., M.P.H.**, *Natural Scientist in the Division of Behavioral and Social Sciences, RAND Corporation, Adjunct Associate Professor, UCLA School of Public Health*—American College of Medical Genetics Appointee; **J. Sanford Schwartz, M.D.**, *Professor of Medicine, Department of Medicine, University of Pennsylvania School of Medicine and Professor, Health Care Systems, Health Management & Economics, The Wharton School*; **Earl P. Steinberg, M.D., M.P.P.**, *President and CEO, Resolution Health, Inc.*; **A. Eugene Washington, M.D., M.Sc.**, *Executive Vice Chancellor and Provost, University of California, San Francisco*; **Jed Weissberg, M.D.**, *Associate Executive Director for Quality and Performance Improvement, The Permanente Federation.*

CONFIDENTIAL: This document contains proprietary information that is intended solely for Blue Cross and Blue Shield Plans and other subscribers to the TEC Program. The contents of this document are not to be provided in any manner to any other parties without the express written consent of the Blue Cross and Blue Shield Association.

## Assessment Objective

Atherosclerotic lesions in the cervical carotid artery can result in luminal narrowing (stenosis) and increase the risk of disabling or fatal ischemic stroke—carotid endarterectomy (CEA) can diminish this risk. In the 1990s, results reported from pivotal randomized, controlled trials comparing CEA with the best available medical therapy to best medical therapy alone established the benefit of CEA. These trials further defined the efficacy of CEA according to the presence or absence of neurologic symptoms, degree of stenosis, and procedural expertise required to improve net health outcome (North American Symptomatic Carotid Endarterectomy Trial [NASCET] Collaborators/Steering Committee 1991a, 1991b; European Carotid Surgery Trial [ECST] Collaborative Group 1991; Barnett et al. 1998; European Carotid Surgery Trial [ECST] Collaborative Group 1998; Mayberg et al. 1991; ACAS Executive Committee 1995; Hobson et al. 1995; Halliday et al. 2004).

The results, trial protocols (e.g., inclusion and exclusion criteria, required surgeon skill), further analyses, and subsequent studies have delineated the factors influencing CEA outcome and whether the benefit of surgery ultimately outweighs its risks, including:

- Patient-related factors
  - Whether a patient is symptomatic or asymptomatic
  - Degree of carotid stenosis
  - Medical risks (e.g., surgical and anesthesia risk)
  - Anatomic risks (e.g., prior carotid endarterectomy, radiation therapy to neck, high lesion, spinal immobility, contralateral recurrent laryngeal nerve paralysis)
- Procedure-related factors
  - Surgeon skill
  - Facility experience
  - Type of anesthesia: local/regional versus general anesthesia

Whether a patient ultimately accrues a net health benefit from CEA is based primarily on 4 factors:

1. Magnitude of risk reduction accompanying CEA
2. Perioperative (periprocedural) risk

3. Expected event rate with best medical therapy alone
4. Patient's anticipated life expectancy

Levels of acceptable periprocedural stroke/death rates and anticipated life expectancy are based on risk reduction achieved with CEA in pivotal trials, trial duration, and event rates with best medical therapy alone (Tables 1 and 2).

Excluded from pivotal trials were individuals judged unlikely to benefit from CEA due to increased perioperative risk (e.g., recent myocardial infarction [MI] or surgery) or limited anticipated life expectancy (<5 years) (for example, Appendix Table A details inclusion/exclusion criteria for NASCET). Due to improved surgical and anesthetic techniques, some patients not meeting inclusion criteria for those pivotal trials may now undergo CEA with acceptable periprocedural risk (Gasparis et al. 2003).

A potential alternative to CEA is carotid angioplasty and stenting (CAS)—particularly for patients who would have been ineligible for the pivotal CEA trials. Not requiring open access to the atherosclerotic lesion, CAS could pose less risk—particularly under certain conditions, such as patients whose anatomy is not conducive to CEA. That CAS poses less anesthetic risk presumes CEA is performed under general as opposed to local or regional anesthesia. If the interventions are equally safe and effective given similar patient characteristics, anesthetic approach, and can be performed with acceptable periprocedural stroke/death rates, then CAS is an alternative to CEA. CAS may also be superior to CEA, particularly under some conditions (e.g., inaccessible or judged increased risk because of adverse anatomic conditions).

Figure 1 graphically depicts determinants of patient- and procedure-related risks (CAS or CEA) and benefit.

Because the U.S Food and Drug Administration- (FDA-) approved indications for carotid stents stipulate use with embolic protection devices (EPD) to trap thromboemboli dislodged during the procedure, this Assessment focuses on CAS with EPD. Thus, the Assessment objective is to review and evaluate available evidence concerning outcomes of CAS with EPD and in comparison to the alternatives of CEA and

**Table 1.** Acceptable Levels of Periprocedural Risk and Anticipated Life Expectancy

Symptoms	Stenosis (%)	Acceptable Periprocedural Stroke/Death Rate	Anticipated Life Expectancy
No	60–99%	<3% <sup>1</sup>	≥5 years <sup>1</sup>
Yes	50–69%	<6% <sup>1</sup>	≥5 years <sup>1</sup>
	70–99%	<6% <sup>1</sup>	≥2 years <sup>2</sup>

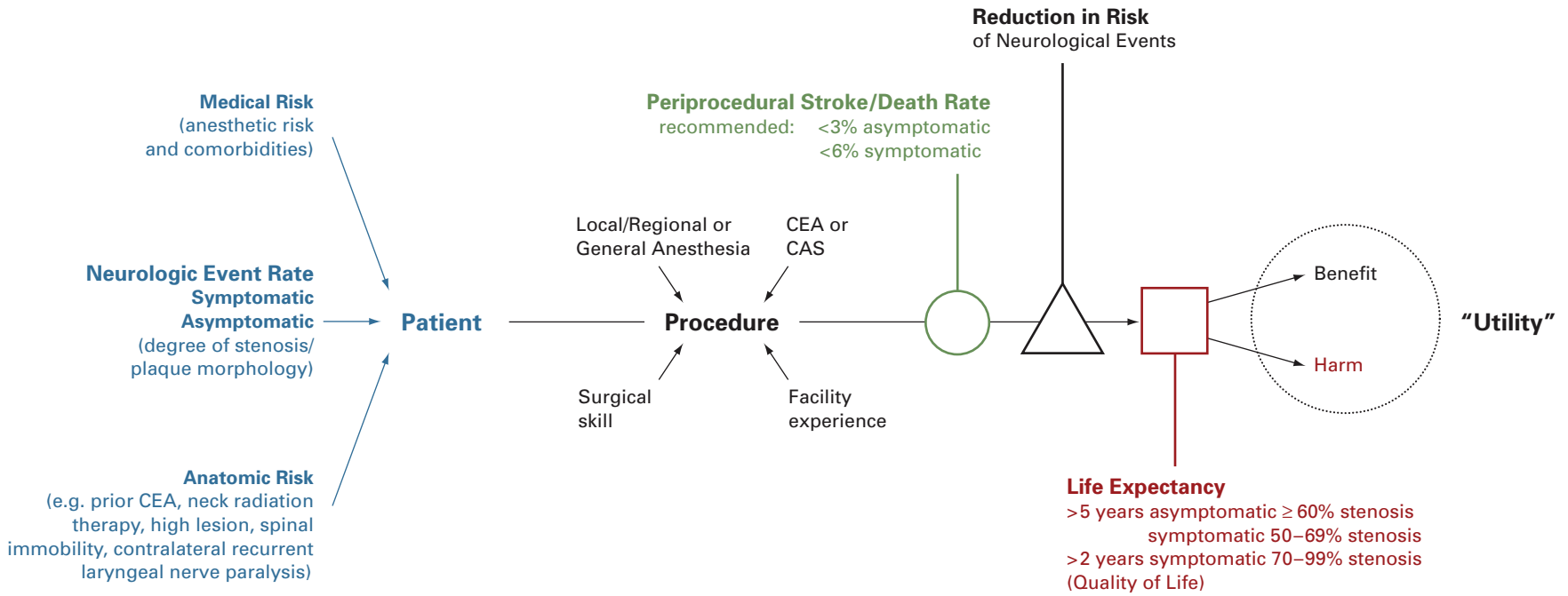
1 Chaturvedi et al. (2005)

2 Chaturvedi et al. (2005) recommend a 5-year life expectancy, however, NASCET (1991a) demonstrated benefit by 2 years.

**Table 2.** Event Rates with Best Medical Therapy from Representative Pivotal Trials

Trial	Symptoms	Stenosis (%)	Event	Time	Cumulative Event Rate	Annualized (per year)
ACAS	No	60–99%	Ipsilateral stroke/ Perioperative death	5 years	11%	2.2%
NASCET	Yes	50–69%	Ipsilateral stroke	5 years	25%	5.0%
		70–99%	Ipsilateral stroke	2 years	26%	13.0%

**Figure 1.** Interplay of Patient- and Procedure-related Risks for CEA or CAS and Relationship to Benefit or Harm (Bolted are the Primary Determinants of Net Health Benefit)



best medical therapy for reducing stroke risk in patients with carotid artery stenosis. The Assessment specifically seeks the following evidence:

1. Can CAS be performed with periprocedural stroke/death rates accompanied by a net health benefit among symptomatic and asymptomatic patients at: a) average medical and anatomical risk, b) increased medical risk, and c) increased anatomic risk.<sup>2</sup>
2. How do CAS, CEA, and best medical therapy compare in each of the above subgroups?<sup>3</sup>

## Background

Stroke is the third leading cause of death and leading cause of long-term disability in the U.S. (Faxon et al. 2004; Pasternak et al. 2004). The American Heart Association estimates 700,000 new or recurrent strokes occur in the U.S. annually (Rosamond et al. 2007). Approximately 85% of strokes are ischemic and the remainder hemorrhagic. Carotid atherosclerosis and accompanying stenosis accounts for roughly 20% of all strokes (Faxon et al. 2004; Pasternak et al. 2004).

### Carotid Stenosis

Narrowing of the internal carotid and accompanying atherosclerotic plaque occurs most frequently near the carotid bifurcation (Albers et al. 1999) and may generate emboli resulting in stroke. Carotid artery stenosis is also associated with an increased risk of coronary events (Faxon et al. 2004; Pasternak et al. 2004; Creager et al. 2004). Furthermore, the magnitude of risk for stroke, MI or death increases with decreasing carotid artery luminal diameter (Goldstein et al. 2001; Goldstein 2003; Faxon et al. 2004; Pasternak et al. 2004; Creager et al. 2004; Brott et al. 2004). Neurologic event rates depend on presence or absence of symptoms, attributable carotid atherosclerosis, and degree of narrowing (Goldstein et al. 2001; Goldstein 2003; Faxon et al. 2004; Pasternak et al. 2004; Creager et al. 2004; Brott et al. 2004) (Table 2).

### Medical Therapy and Stroke Risk

In recent years, pharmacologic therapies have improved substantially together with understanding the role of lifestyle factors in stroke

risk. Addressing both are recommended to reduce risks of disabling stroke, MI, and death in patients with carotid artery atherosclerosis (Wolf et al. 1999; Albers et al. 1999; Goldstein et al. 2001; Creager et al. 2004). Lifestyle alterations include smoking cessation, dietary changes (addressing obesity and hypertension, blood lipids, maintaining glycemic control in diabetics [UKPDS Study Group 1998]), and increasing physical activity when possible.

Medications reducing the risk of stroke, MI and death from carotid atherosclerosis include antihypertensive, lipid-lowering, and antiplatelet drugs (Wolf et al. 1999; Albers et al. 1999; Goldstein et al. 2001; Creager et al. 2004). Meta-analyses of randomized, controlled trials show that lowering systolic blood pressure by 10 mm Hg is associated with relative risk reductions for stroke of between 25% and 36%, depending upon age (Lawes et al. 2004). Multiple trials report that statins lower blood lipid concentrations, stabilize plaque, reduce risks of all cardiovascular events, and decrease stroke risk in patients with coronary artery disease (Scandinavian Simvastatin Survival Study 1994; Pfeffer et al. 1995; Shepherd et al. 1995; The LIPID Study Group 1998; Hess et al. 2000; Heart Protection Study Collaborative Group 2002). The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) randomized 4,731 patients with prior stroke or transient ischemic attack (TIA) to either aggressive lipid lowering or placebo (Amarenco et al. 2006). Active treatment was accompanied by a relative risk (RR) reduction for fatal or nonfatal stroke of 16% (RR 0.84, 95% CI: 0.71 to 0.99) and a 5-year absolute risk reduction of 2.2%. However, there was no overall mortality reduction with lipid lowering.

Antiplatelet drugs are perhaps the most important medication class reducing stroke risk, particularly among those with prior TIA or non-disabling stroke (Biller et al. 1998; Wolf et al. 1999; Albers et al. 1999; Goldstein et al. 2001; Creager et al. 2004). A meta-analysis of 287 separate randomized trials (pooled N=135,000) yielded a 22% reduction in fatal and nonfatal strokes (Antithrombotic Trialists' Collaboration 2002). Aspirin, the antiplatelet drug used most commonly for secondary prevention in patients with prior TIA, reduced the risk of

<sup>2</sup> There is theoretically a fourth group at increased anatomic and medical risk, but is presumed to have the anatomic risk of greater clinical importance and so concerted here.

<sup>3</sup> Recognizing comparison of CAS or CEA to current best medical therapy among symptomatic patients with severe stenosis (>70%) would unlikely be performed due to benefit accrued with CEA in this subgroup.

all cardiovascular events (including fatal and nonfatal MI) by 23%. Ticlopidine, clopidogrel and dipyridamole alone or, sometimes, combined with aspirin are also effective (Goldstein et al. 2001), but may be accompanied by more adverse effects.

### CEA with Best Medical Therapy Versus Best Medical Therapy Alone

In selected patients, CEA combined with best medical therapy can reduce the risks of stroke accompanying carotid stenosis over best medical therapy alone (Moore et al. 1992, 1995; Moore 1995; Perry et al. 1997; Biller et al. 1998; Benavente et al. 1998; Chassin 1998; Tu et al. 1998; Albers et al. 1999; Goldstein et al. 2001; Goldstein 2003; Halm et al. 2003; Rothwell et al. 1996a, 1996b, 2003, 2004; Creager et al. 2004; Bettman et al. 2004; Brott et al. 2004). NASCET and ECST first reported outcomes for symptomatic patients with 70–99% stenosis (NASCET Steering Committee 1991a, 1991b; ECST Collaborative Group 1991). A third trial by the Department of Veterans Affairs (VA309) closed early when NASCET and ECST reported that CEA benefited patients with 70–99% stenosis, but published results on patients randomized before it closed (Mayberg et al. 1991). However, the NASCET and ECST trials continued to enroll symptomatic patients with less-severe stenosis and reported final results in 1998 (ECST Collaborative Group 1998; Barnett et al. 1998). Subsequently, 3 additional trials (ACAS, the VA Study, and MRC ACST) enrolled asymptomatic patients with  $\geq 60\%$  (ACAS Executive Committee 1995; Halliday et al. 2004) or  $\geq 50\%$  stenosis (VA Study; Hobson et al. 1995). (Appendix Table B summarizes results from these trials).

The American Heart Association (AHA) and the American Academy of Neurology (AAN) developed evidence-based clinical guidelines for CEA indications. The most current and relevant statements follow.

### Symptomatic Carotid Artery Stenosis

**AHA** (Sacco et al. 2006)

“For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA by a surgeon with a perioperative morbidity and mortality of  $<6\%$  (Class I, Level of Evidence A) is recommended. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms (Class I, Level of Evidence A). When the degree of stenosis is  $<50\%$ , there is no indication for CEA (Class III, Level of Evidence A)”<sup>4</sup>

**AAN** (Chaturvedi et al. 2005)

“CE[A] is established as effective for recently symptomatic (within previous 6 months) patients with 70 to 99% ICA [internal carotid artery] angiographic stenosis (Level A). CE[A] should not be considered for symptomatic patients with less than 50% stenosis (Level A). CE[A] may be considered for patients with 50 to 69% symptomatic stenosis (Level B) but the clinician should consider additional clinical and angiographic variables (Level C, see below). It is recommended that the patient have at least a 5-year life expectancy and that the perioperative stroke/death rate should be  $<6\%$  for symptomatic patients (Level A). Medical management is preferred to CE[A] for symptomatic patients with  $<50\%$  stenosis (Level A).”<sup>5</sup>

### Asymptomatic Carotid Stenosis

**AHA** (Biller et al. 1998)

“Proven”<sup>6</sup>:  $\geq 60\%$  stenosis,  $<3\%$  risk of surgical complications, and  $\geq 5$  years life expectancy; “Acceptable”<sup>7</sup>:  $\geq 60\%$  stenosis with  $<3\%$  [perioperative] risk and simultaneous coronary artery bypass graft surgery (CABG), or  $\geq 75\%$  stenosis with 3-5% [perioperative] risk and  $\geq 75\%$

<sup>4</sup> Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective. Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Level of Evidence A: Data derived from multiple randomized controlled trials.

<sup>5</sup> Level A: Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies or prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.)

<sup>6</sup> Proven: “...the strongest indication for carotid endarterectomy and strongly implies that to withhold surgery in the presence of this indication would be inappropriate under normal circumstances. Indications classified as proven are generally supported by data from contemporary, prospective, randomized clinical trials.”

<sup>7</sup> Acceptable: “...general agreement that this represents a good indication for surgery, with the expectation that benefits outweigh the risks. This rank is supported by promising, but not scientifically certain, data. Indications in this category may be the subject of ongoing prospective randomized trials. In that case, it is expected that patients will be offered the opportunity to participate in the trial. However, when this is not possible, either by geography or patient preference, surgery would be an acceptable alternative at the present level of knowledge.”

stenosis of the contralateral carotid artery; “Uncertain”<sup>8</sup>: all others with asymptomatic stenosis not proven inappropriate for CEA; “Inappropriate”<sup>9</sup>: risk of surgical complications  $\geq 5\%$  without need for simultaneous CABG.

AAN (Chaturvedi et al. 2005)

“It is reasonable to consider CE [CEA] for patients between the ages of 40 and 75 years and with asymptomatic stenosis of 60 to 99% if the patient has an expected 5-year life expectancy and if the surgical stroke or death frequency can be reliably documented to be  $< 3\%$  (Level A). The 5-year life expectancy is important since perioperative strokes pose an up front risk to the patient and the benefit from CE emerges only after a number of years.”

Still, uncertainties remain concerning the risk/benefit ratio of CEA for many patients with carotid stenosis. Medical therapies have improved considerably since the completion of pivotal CEA trials. Recent reviews have emphasized the need to conduct new randomized, controlled trials of current best medical therapy with versus without CEA (Barr et al. 2003; Goldstein 2003; Creager et al. 2004; Bettmann et al. 2004; Brott et al. 2004). Nevertheless, substantial numbers are managed surgically in the U.S. (Tu et al. 1998; Chasin 1998; Halm et al. 2003).

Four uncontrolled reviews compared CEA outcomes in patients considered at increased risk for periprocedural complications to those achieved in average-risk patients (Table 3). The rates of periprocedural adverse events reported (including or excluding MI) generally were higher among patients with increased risks. Still, approximately 37–54% of these patients were symptomatic, yet the frequency of periprocedural complications in 3 of them was near or below the 3% limit recommended for asymptomatic CEA candidates. Event rates were not reported separately for symptomatic and asymptomatic patients. Authors of the studies listed in Table 3 conclude that experienced surgical teams and institutions can achieve acceptable periprocedural outcomes in carefully selected patients who would have been ineligible for CEA trials. However, these studies lacked predefined protocols and endpoints, potentially resulting in under ascertainment of neurologic events (Rothwell et al. 1996a; Ouriel

et al. 2001) compared to contemporary trials and registries.

### **Carotid Angioplasty and Stenting (CAS)**

CAS is a procedure designed to enlarge the stenotic lumen and similar in principle to angioplasty performed at other vascular sites (Bettmann et al. 1998, 2004; Barr et al. 2003; Goldstein et al. 2003; Higashida et al. 2004; Brott et al. 2004; Cambria 2004; Coward et al. 2004; NICE 2004). CEA removes the atherosclerotic lesion by excising plaque while CAS leaves it in place (Cambria 2004). Because CAS does not require a surgical incision, it is accompanied by a lower risk of cranial nerve injury. However, those injuries may not be permanent and infrequently result in permanent deficits (Taylor et al. 2003). Overall, therefore, one must consider failure rates, repeat interventions, permanent adverse events, and patency when comparing CAS to CEA.

### **Embolic Protection of the Cerebral Circulation**

Embolic protection devices (EPD) utilized in the U.S. are filters deployed distal<sup>10</sup> to the atherosclerotic target lesion before balloon expansion, if lumen diameter allows. Stent placement follows with a second balloon inflation. The filter is collapsed and withdrawn once angioplasty and stent placement are complete, trapping contained emboli, although microemboli can escape (Macdonald 2006). A systematic review pooling results from 40 studies employing CAS alone (N=2,357) and 14 studies employing CAS with EPD (N=839) concluded the devices reduced thromboembolic complications (Kastrup et al. 2003a). Nevertheless, some clinicians disagree that EPD should be used for all CAS procedures (Ohki and Veith 2003; Eckert and Zeumer 2003; Forsting 2004). Emphasized is the lack of randomized, controlled trial evidence, and problems with use of EPDs. These include difficulties manipulating the devices through target lesions and with deployment, varying effectiveness at capturing emboli, vessel injury caused by the devices, and difficulties with device retrieval (Cremonesi et al. 2003; Ohki and Veith 2003). However, nearly all ongoing pivotal trials for as-yet unapproved carotid stents used EPDs for all stented patients. Furthermore, the Centers for Medicare and Medicaid Services (CMS) covers CAS only when used with an EPD. Consequently, this Assessment focuses on

<sup>8</sup> Uncertain: “...insufficient data to define the risk/benefit ratio. These potential indications should be evaluated in clinical trials.”

<sup>9</sup> Inappropriate: “...current database is adequate to indicate that the stated risks of carotid endarterectomy outweigh the benefits.”

<sup>10</sup> So-called distal embolic protection devices.

**Table 3.** Endarterectomy Outcomes in Increased- versus Average-Risk Patients

Study (Design)	Sample Characteristics	CEA Risk Groups, n	All Perioperative Events	Perioperative Deaths	Perioperative Strokes	Perioperative MIs
Ouriel et al. 2001 (prospective registry single-institution, multi-surgeon)	2,662 CEA alone, 1988–98; 37% symptomatic, 63% asymptomatic	increased risk, 195 <sup>1</sup>	5.1%	2.6%	1.0%	1.5%
		average risk, 2,467	2.9%	0.3% <sup>5</sup>	1.7%	1.1%
Lepore et al. 2001 (retrospective single-institution, multi-surgeon)	366 CEAs in 348 patients, 1997–98; 40% symptomatic, 60% asymptomatic	increased risk, 169 <sup>2</sup>	3.6% <sup>2</sup>	n=1	3.6%	n=1
		average risk, 197	1.5% <sup>2</sup>	n=1	1.5%	n=1
Gasparis et al. 2003 (retrospective, two institutions, multi-surgeon)	788 CEA alone, 1996–2001; 39% symptomatic, 61% asymptomatic	increased risk, 228 <sup>3</sup>	1.3% <sup>3</sup>	0.4%	0.9%	0.9%
		average risk, 560	1.1% <sup>3</sup>	0.4%	0.7%	0.9%
Illig et al. 2003 (retrospective single-institution, multi-surgeon)	859 CEA alone <sup>4</sup> , 1993–2000; 54% symptomatic, 46% asymptomatic	increased risk, 372 <sup>2</sup>	2.7% <sup>2</sup>	NR	NR	NR
		comorbidities, 242	2.9% <sup>2</sup>			
		average risk, 487	1.6% <sup>2</sup>			

1 defined by CAD, CHF, COPD, or renal disease; n=399 others underwent CEA and open cardiac surgery at same sitting

2 defined by NASCET/ACAS ineligibility; excludes MIs

3 defined by comorbidities (63%; age>80, CAD, CHF, COPD, or renal disease), anatomic features (28%), or both (9%); excludes MIs

4 from total n=1230; remainder lacked adequate data in charts to evaluate risk factors, trial eligibility or indication for CEA; 30-day rate similar for all 1,230 patients as for 859 with adequate data for analysis of risks and eligibility.

5 statistically significant difference p<0.0001

comparing CAS with EPD versus alternatives for patients with carotid stenosis.

### Restenosis after CEA and CAS

The durability of carotid patency after either CEA or CAS is critical for benefit to be maintained. Recurrent stenosis within 3 years of CEA is typically attributed to neointimal hyperplasia (Lal and Hobson 2006). Subsequently, recurrent atherosclerosis is felt responsible. Reported restenosis rates following CEA range from 0.1% recurrent stenosis  $\geq 70\%$  at 7.1 years' median follow-up (1,000 CEAs in 975 patients) (Ecker et al. 2003); to 7.7% (4.5% severe restenosis or occlusion, 3.2% repeat CEA) at 5.9 years' median follow-up (n=2,236) (LaMuraglia et al. 2004). While these results are consistent with contemporary CEA studies tabulated by Ecker et al. (2003), many of the cohorts were followed either prior to or during a period when aggressive lipid lowering became a standard of practice. LaMuraglia et al. (2004) found elevated cholesterol levels associated with early restenosis.

Following CAS, the ARChR registry (Gray et al. 2006) reported that of 581 patients, at 12 months, 5% had restenosis greater than 70% and 26% had restenosis of 50 to 69%. Only 166 patients were followed to 2 years or more; however, rates did not appear to change. The Global Carotid Artery Stent Registry, a survey of 53 centers (11,243 patients), reported a 3-year restenosis rate of 2.4% (Wholey et al. 2003). However, these data were both retrospective and collected voluntarily. Christiaans et al. (2007) followed 217 patients after CAS with serial ultrasound exams. At 1 year, the prevalence of restenosis ( $\geq 50\%$ ) was 18% and 21% at 2 years (with 48 patients evaluated at 2 years). Accurate and representative CAS restenosis rates will be established in the near future as long-term registry data are collected and reported.

**FDA Status.** CAS with or without EPD is a procedure and thus does not require FDA approval. However, devices used for CAS and for EPD require FDA approval. As of this writing, a number are FDA-approved and indicated specifically for use in carotid arteries.

- ACCULINK™ and RX ACCULINK™; ACCUNET™ and RX ACCUNET™; Guidant Corp.
- XACT® EMBOSHIELD®; Abbott Corp.

- PRECISE® ANGIOGUARD®; Cordis Corp.
- NEXSTENT™ and FILTERWIRE™; Boston Scientific
- PROTÉGÉR® and SPIDERX®; ev3 Inc, Arterial Evolution Technology

The FDA has mandated postmarketing studies for these devices, including longer follow-up for patients already reported to the FDA and additional registry studies primarily to compare outcomes as a function of clinician training and facility experience. Devices are indicated for combined use of a stent and EPD to reduce stroke risk in patients at increased risk for perioperative complications from CEA who are symptomatic with  $\geq 50\%$  stenosis or asymptomatic with  $\geq 80\%$  stenosis. CAS with these devices for patients outside these indications is an off-label use.

## Methods

### Search Methods

Studies were identified by searching the MEDLINE® (via PubMed) database for articles indexed under the MeSH® headings “stents” AND “carotid artery diseases” OR “carotid stenosis.” The search was performed for the period of 1994 through April 2007 and was limited to articles published in English that reported on human subjects. Computerized searches were supplemented by manual bibliography review of selected references.

### Study Selection

Randomized, controlled trials were included if they met the following criteria:

- directly compared outcomes of CAS with outcomes of CEA or best medical therapy;
- used embolic protection devices;
- included at least 10 patients per arm;
- studied homogeneous populations, or stratified patients providing subgroup analyses for
  - symptomatic patients
  - asymptomatic patients
    - at average medical and anatomical risk
    - increased medical risk alone
    - increased anatomic risk

Prospective CAS registry studies with predefined endpoints and inclusion/exclusion criteria were included if results were published in peer-reviewed journals.

**Trial Data Abstraction and Calculations**

Trial results were abstracted together with relevant 95% confidence intervals. If confidence intervals were not presented, they were calculated using the method of Wilson (Agresti and Coull 1998). Negative risk differences indicate CAS harmful compared to CEA (or for relevant comparison).

**Medical Advisory Panel Review**

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on February 21, 2007. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

**Formulation of the Assessment**

**Patient Indications**

The target populations are symptomatic patients at risk for stroke due to moderate (50% to 69%) or severe (70% to 99%) carotid artery stenosis, and asymptomatic patients with stenosis ≥60%. Two indications are considered:

1. Symptomatic patients for whom CEA provides a net health benefit, i.e., moderate (50% to 69%) or severe (70% to 99%) and can be performed with less than a 6% periprocedural stroke/death rate.
2. Asymptomatic patients for whom CEA provides a net health benefit, i.e., stenosis ≥60% and can be performed with less than a 3% periprocedural stroke/death rate.

**Technologies to be Compared**

Table 4 outlines the technologies to be compared together with potential combinations of medical and anatomic risk.

**Carotid Artery Angioplasty and Stenting (CAS) with Embolic Protection Device (EPD).**

CAS with EPD most often involves insertion of a multi-catheter system into the femoral artery. Under fluoroscopy or X-ray visualization, a guide wire is navigated through the aorta to the stenotic lesion in the carotid artery. The EPD is delivered past the site and expanded to trap embolic material dislodged during the procedure. A dilating balloon catheter is used to expand the stenosis, followed by placement of a self-expanding stent (with a second balloon inflation in some devices). If the stenosis is severe, balloon expansion can be required prior to placing the EPD. After stent placement, the distal protection device is collapsed to trap any filtered material and removed. The catheters are then removed, leaving the expanded stent in place. The procedure is most commonly performed with the patient awake.

**Carotid Endarterectomy.** During carotid endarterectomy, plaque and debris are removed from the carotid artery through a neck incision. The procedure can be performed under either general or local/regional anesthesia (Jordan et al. 1998) and the latter may be accompanied by lower perioperative risks. For example, an analysis of 13,622 CEAs from the National Surgical Quality Improvement Program database found procedures performed under local compared to general anesthesia accompanied by an adjusted relative odds for stroke or death at 30 days of 0.59 (95% CI: 0.41 to 0.86); the overall rate of stroke or death in the cohort was 3.4% (Stoner et al. 2006). A Cochrane review pooled results from 7 randomized, controlled

**Table 4.** Technologies to be Compared Together with Potential Combinations of Medical and Anatomic Risk

Symptoms	Periprocedural Risk	Degree of Stenosis	Medical Risk	Anatomic Risk	Groups for Comparison
Yes	<6%	50–69% ≥70%	Average & Increased	Average & Increased	CEA/best medical therapy CAS/best medical therapy best medical therapy
No	<3%	≥60%	Average & Increased	Average & Increased	CEA/best medical therapy CAS/best medical therapy best medical therapy

CEA Carotid Endarterectomy  
CAS Carotid Artery Stent with Embolic Protection Device (EPD)

trials comparing local to general anesthesia in CEA yielding an odds ratio for stroke or death of 0.63 (95% CI 0.25 to 1.62) (Rerkasem et al. 2004). However the pooled result was based on only 18 events. The General Anesthesia vs. Local Anesthesia for CEA in progress should provide more definitive evidence having recruited over 3,030 patients, with a target of 3,500 (<http://www.dcn.ed.ac.uk/gala/>).

**Best Medical Therapy.** Best medical therapy for patients with elevated stroke risk relies on blood pressure control, antiplatelet agents, lipid lowering, and lifestyle interventions including smoking cessation, glycemic control in diabetics, weight loss in obese individuals, and increased physical activity, when possible.

### Health Outcomes

Primary outcomes of interest include:

- proportion of patients experiencing any stroke or death by 30 days after the procedure (stroke/death)—periprocedural stroke/death rate;
- proportion of patients experiencing any stroke, myocardial infarction (MI) or death by 30 days after the procedure (stroke/death/MI);
- separate rates by day 30 of stroke, MI and death;
- 30 day stroke/death/MI or ipsilateral stroke from day 31 to day 365.

The Assessment focuses on primary outcomes, but studies also report secondary outcomes, including:

- device success rate, defined as the proportion of devices utilized that are delivered, placed, and retrieved as described in the study protocol;
- complication rates.

### Specific Assessment Questions

1. Can CAS be performed with periprocedural stroke/death rates accompanied by a net health benefit among symptomatic and asymptomatic patients at: a) average medical and anatomical risk, b) increased medical risk, and c) increased anatomic risk
2. How do CAS, CEA, and best medical therapy compare in each of the above subgroups?

## Review of Evidence

### Overview of Available Evidence

The literature search identified 3 randomized, controlled trials (RCTs) comparing CEA to CAS: SAPPHERE “Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy” (Yadav et al. 2004); SPACE “Stent-Protected Angioplasty versus Carotid Endarterectomy” (Ringleb et al. 2006); “Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis” EVA-3S (Mas et al. 2006); 8 registry publications (CaRESS Steering Committee 2005; Coppi et al. 2005; Reimers et al. 2005; White et al. 2006; Safian et al. 2006; Gray et al. 2006, 2007), including an interim report of the lead-in phase of CREST (Carotid Revascularization Endarterectomy vs. Stent Trial) (Hobson et al. 2004), which is effectively a CAS registry. The review of evidence is organized according to study design. No study is specific to the patient subgroups identified in the specific Assessment questions. In the discussion section, we address how the available evidence pertains to the patient subgroups of interest.

### Randomized Controlled Trials

**Design and Follow-Up.** The 3 trials (SAPPHERE, SPACE, EVA-3S) were designed to test equivalence of CAS to CEA with non-inferiority margins ranging from 2–3% and 30-day to 1-year follow-up reported. Primary endpoints and patient selection also differed among the trials (Table 5).

Each trial specified or reported qualifications for interventionalists performing stenting, surgeons, and participating centers. SAPPHERE (Yadav et al. 2004) required that surgeons document CEA experience resulting in a periprocedural stroke or death risk less than 6.0%. The median annual surgeon CEA volume was 30 (range 15 to 100). Interventional physicians performing stenting had a median experience of 64 procedures (range: 20 to 700). SPACE (Ringleb et al. 2006) required interventionalists to have performed at least 25 successful CAS procedures with or without stenting and vascular surgeons 25 consecutive CEAs. EVA-3S (Mas et al. 2006) stipulated that vascular surgeons had performed at least 25 CEAs in the prior year; interventionalists at least 12 CAS or 35 other stent procedures in supra-aortic trunks, with at least 5 in the carotid artery.

**Table 5.** RCT Characteristics

Trial	Sample Size	Medical/Anatomic Risk	Symptoms	Longest Follow-Up Reported	Noninferiority Margin	Primary Endpoint
SAPPHIRE 29 centers	334	Increased	Symptomatic & Asymptomatic	1 year	3.0%	Death, stroke, MI to 30 days; ipsilateral stroke 31 days to 1 year
SPACE 35 centers	1,183	Average	Symptomatic	30 days	2.5%	Ipsilateral stroke or death
EVA-3S 30 centers	527	Average	Symptomatic	6 months	2.0%	Stroke or death within 30 days

SAPPHIRE was supported by Cordis; SPACE by the German Ministry of Education and Research, German Research Foundation, German Society of Neurology, German Society of Neuropathology, German Radiological Society, Boston Scientific, Guidant, and Sanofi-Aventis; EVA-3S by the French Ministry of Health.

**Patient Characteristics.** Inclusion criteria differed among the 3 RCTs (Table 6). Patients were considered symptomatic in SAPPHIRE and SPACE if they had experienced a TIA or non-disabling stroke in the prior 180 days; EVA-3S in the past 120 days. SAPPHIRE enrolled both symptomatic and asymptomatic individuals at either increased medical or anatomic risk requiring the presence of either clinically significant cardiac disease; severe pulmonary disease; contralateral carotid occlusion or laryngeal nerve palsy; previous radical neck surgery or radiation therapy to the neck; recurrent stenosis after endarterectomy; or age older than 80 years. EVA-3S and SPACE enrolled symptomatic patients at average medical and anatomic risk (see Appendix Table C for detailed inclusion criteria). Randomization was stratified in SAPPHIRE by the presence or absence of symptoms and in EVA-3S by degree of stenosis ( $\geq 90\%$  or  $< 90\%$ ). Finally, EPDs were used in all SAPPHIRE participants undergoing CAS, 92.3% of the CAS arm in EVA-3S, and 27% of the CAS arm in SPACE (although outcomes in the CAS arm of SPACE were more favorable absent EPD, see following).

#### **Trial Conduct**

**SAPPHIRE.** Patients considered for enrollment in SAPPHIRE were initially reviewed by 3 clinicians including a neurologist, a vascular

surgeon or neurosurgeon, and an interventional physician. If all agreed that a patient was safely eligible for either intervention, the patient was randomized. If the surgeon concluded the risks of CEA were unacceptable, but the interventional physician concluded CAS was feasible, the patient was entered into a registry separate from the RCT and treated with CAS. Similarly, if the interventionalist judged the risks of CAS unacceptable but the surgeon concluded CEA risks acceptable, the patient entered a surgical registry and underwent CEA. Patients were enrolled from August 2000 to July 2002.

SAPPHIRE sought to randomize 600 to 900 patients before demonstrating noninferiority. Sequential analyses were planned after randomizing every 100 patients; the maximum accrual target was 2400. In the CEA arm, 90.4% were treated and in the CAS arm, 95.2%. CAS success rate was 95.6%. Patients in both arms received aspirin (81 or 325 mg/day) and those undergoing CAS also received clopidogrel 75 mg/day 24 hours prior to and 2 to 4 weeks following the procedure. Mode of anesthesia in the CEA arm was not reported, but “most procedures were done with a patch and under general anesthesia” (U.S. Food and Drug Administration 2004b, page 97). The trial closed early because accrual slowed attributed to competing registries and physician reluctance to continue randomizing patients. At closure, 747 patients had been evaluated, 334 randomized, 406 entered into the stent registry, and 7 the surgical registry. Follow-up was complete with both intention-to-treat and per protocol analyses reported for 30-day and 1-year outcomes.

**SPACE.** Treatment indications for potentially eligible patients were determined by

**Table 6.** Patient Characteristics in the CAS/EPD vs. CEA Trials (all arms included best medical therapy).

	Trial					
	SAPPHIRE		EVA-3S		SPACE	
	CAS/EPD	CEA	CAS/EPD	CEA	CAS ( $\pm$ EPD)	CEA
<b>Treatment Arm</b>						
Symptomatic (n)	50	46	261	259	599	584
<i>Stenosis (%)</i>	$\geq 50\%$		60–99%		$\geq 50\%$	
Asymptomatic (n)	117	120				
<i>Stenosis (%)</i>	$\geq 80\%$					
Symptomatic/ Asymptomatic	167	167 <sup>1</sup>				
Age (SD)	72.5 (8.3)	72.6 (8.9)	70.3 (10.7)	69.1 (10.2)	67.6 (8.2)	68.2 (8.7)
Female	33.1%	32.9%	22.0%	27.6%	28.0%	28.4%
Hypertension	85.5%	85.1%	72.6%	73.6%	75.1%	76.2%
Diabetes	25.3%	27.5%	25.5%	22.2%	26.0%	28.4%
Coronary Heart Disease	85.8%	75.5%			21.2%	24.0%
Prior MI	29.7%	35.3%	13.1%	10.7%		
Current/Past Smoker					70.7%	70.1%
Current Smoker	16.9%	16.4%	23.6%	24.1%		
Mean BMI (SD)			26.3 (4.1)	26.1 (4.6)	27.2 (4.1)	26.7 (3.7)
<b>Medical Risk</b>						
Age > 80 yr	19.3%	20.5%				
COPD	17.0%	13.8%				
“Severe” CHD	15.9%	16.5%				
Renal insufficiency	6.0%	7.5%				
Class 3 or 4 angina	24.1%	14.7%				
CHF	17.1%	19.6%				
<b>Anatomic Risk</b>						
Prior Endarterectomy	28.3%	26.7%	3.9% <sup>2</sup>	1.9% <sup>2</sup>		
Contralateral Occlusion	23.6%	25.3%				
Restenosis	22.6%	22.2%				
<p>1 One patient not included in FDA analysis stratified by symptoms.  2 CEA or angioplasty.</p>						

a multidisciplinary team of “neurologists, vascular surgeons and interventionalists” at each participating center. Patients were enrolled from March 2001 through February 2006. Individuals in both arms received aspirin (100 mg per day) and in the CAS arm, 75 mg clopidogrel daily for at least 3 days before and 30 days following stent placement. EPD use was optional (deployed in 27% of CAS procedures). Both local and general anesthesia were used for CEA, but rates were not reported. To achieve 80% power for establishing noninferiority, 950 patients per arm were sought. The trial terminated early due to funding issues and an interim analysis projecting that 2,500 patients per arm would be required to achieve the desired power. All randomized patients were accounted for and 98.6% included in intention-to-treat analyses.

**EVA-3S.** Patients deemed eligible for either CAS or CEA were enrolled between November 2000 and September 2005. Initially, whether to use EPD or not was left to the treating interventionalist and patient. However, unprotected CAS was ended after randomizing the first 80 patients to the CAS arm, when an interim analysis found an age-adjusted relative odds for stroke or death of 3.8 (0.5 to 31.6) with CAS alone compared to CAS with EPD. Ultimately, 20 patients underwent CAS without EPD. Stenting was successful in 95% of attempted interventions. Daily aspirin (100 to 300 mg) was recommended for both arms and for CAS patients, clopidogrel (75 mg) or ticlopidine (500 mg) 3 days prior and for 30 days following stenting. Local or regional anesthesia was used for 27% of CEAs; general anesthesia was in 6.5% of stenting procedures. Initial power estimates targeted a sample size of 872. In September 2005, enrollment was halted “for reasons of both safety and futility.” At that point, more than 4,000 patients would have been required to test noninferiority given the 2% margin with adequate power (and one-sided alpha of 0.05). Of those randomized, 95.6% were included in intention-to-treat analyses and all withdrawals identified.

### **Trial Results and Comment**

**SAPPHIRE.** The composite endpoint reported included myocardial infarction limiting comparisons with combined stroke and death rates reported by pivotal CEA trials (Table 7). Outcomes for asymptomatic and symptomatic subgroups (accompanying stratified randomization) while unpublished, were reported to

the FDA. Outcomes were not reported separately according to increased medical or anatomic risk.

While SAPPHIRE generated considerable controversy and lengthy commentaries, to address the Assessment objectives, we focus on whether the results: 1) support a favorable risk/benefit ratio in symptomatic and asymptomatic patients and therefore 2) allow comparing CAS to CEA. Mortality rates differences are also examined.

The symptomatic group was small in size and events few. The 6.5% (95% CI: 2.2–17.5) 30-day mortality rate in the CEA arm reflected 3 deaths; at 1 year, 8 of 46 patients had died. Corresponding rates in the CAS arm were 0% (95% CI: 0–7.1); at 1 year 6 deaths in 50 patients. Although the mortality rate was lower in the CAS arm, there is considerable uncertainty owing to small subgroup size—the trial was not powered to examine subgroup differences. Still, the 30-day mortality rate in the CEA arm exceeded the 6% combined stroke and death rate accepted to accompany a favorable risk/benefit ratio. The absence of mortality at 30 days in the CAS arm must be considered uncertain in light of the subgroup size. In the asymptomatic group, 30-day stroke rates in both arms exceeded the 3% combined stroke and death rate accompanying a favorable risk/benefit ratio. At 1 year, stroke rates were similar (7.5% and 7.7%) in the CEA and CAS arms, respectively.

The mortality rate was lower in the CAS arm at 30 days and 1 year for symptomatic and asymptomatic patients as well as for the entire sample. In the asymptomatic group, 1-year mortality rates in the CAS and CEA arms were 5.1% (95% CI: 2.4 to 10.7) and 10.8% (95% CI: 6.4 to 17.6), respectively. Although cause of death data according to the presence or absence of symptoms are unavailable, FDA documents indicate the differential mortality between arms primarily attributable to non-neurologic causes (Table 8).

Noninferiority of CAS to CEA was demonstrated for the composite primary endpoint ( $p=0.004$ ), which included MI. However, of 17 infarctions, 15 were non-Q wave and MI was more than twice as common in the CEA arm (where general anesthesia was primarily used). Additionally, cranial nerve palsies were significantly more common in the CEA arm—4.9%—compared to none with CAS.

**Table 7.** Death, Stroke, MI, and Composite Outcome at 30 days and 1 year in SAPHIRE<sup>1</sup>

	% Stenosis (NASCET)	n		Outcome (%)	
				Absolute Risk Reduction (ARR, 95% CI) <sup>2</sup>	
				30-day	1-year
<b>Death</b>					
Symptomatic (≥50%) or Asymptomatic (≥80%)		167	CEA	2.5% (1.0 to 6.1)	13.5% (9.1 to 19.5)
		167	CAS/EPD	1.2% (0.3 to 4.3)	7.4% (4.3 to 12.4)
			ARR	1.3% (-2.1 to 5.0)	6.1% (-0.5 to 12.9)
Symptomatic ≥50%		46	CEA	6.5% (2.2 to 17.5)	17.4% (9.1 to 30.7)
		50	CAS/EPD	0% (0 to 7.1)	12.0% (5.6 to 23.8)
			ARR	6.5% (-1.8 to 17.5)	5.4% (-9.0 to 20.2)
Asymptomatic ≥80%		120	CEA	0.8% (0.1 to 4.5)	10.8% (6.4 to 17.6)
		117	CAS/EPD	1.7% (0.5 to 6.0)	5.1% (2.4 to 10.7)
			ARR	-0.9% (-5.3 to 3.0)	5.7% (-1.4 to 13.0)
<b>Stroke</b>					
Symptomatic (≥50%) or Asymptomatic (≥80%)		167	CEA	3.1% (1.3 to 7.0)	7.9% (4.7 to 13.0)
		167	CAS/EPD	3.6% (1.7 to 7.6)	6.2% (3.4 to 10.9)
			ARR	-0.5% (-4.9 to 3.8)	1.7% (-0.4 to 7.5%)
Symptomatic ≥0%		46	CEA	2.2% (0.4 to 11.4)	6.5% (2.2 to 17.5)
		50	CAS/EPD	0% (0 to 7.1)	2.0% (0.1 to 10.5)
			ARR	2.2% (-5.2 to 11.4)	4.5% (-0.5 to 15.6)
Asymptomatic ≥80%		120	CEA	3.3% (1.3 to 8.2)	7.5% (4.0 to 13.6)
		117	CAS/EPD	5.1% (2.4 to 10.7)	7.7% (4.1 to 14.0)
			ARR	-1.8% (-7.8 to 3.8)	0.2% (-7.4 to 6.9)
<b>MI</b>					
Symptomatic (≥50%) or Asymptomatic (≥80%)		167	CEA	6.1% (3.4 to 10.8)	7.5% (4.4 to 12.5)
		167	CAS/EPD	2.4% (0.9 to 6.0)	3.0% (1.3 to 6.8)
			ARR	3.7% (-0.8 to 8.6)	4.5% (-0.4 to 9.8)
Symptomatic ≥50%		46	CEA	4.3% (1.2 to 14.5)	4.3% (1.2 to 14.5)
		50	CAS/EPD	2.0% (0.1 to 10.5)	4.0% (1.1 to 13.5)
			ARR	2.3% (-6.8 to 12.6)	0.3% (-9.7 to 10.9)
Asymptomatic ≥80%		120	CEA	6.7% (3.4 to 12.6)	8.3% (4.6 to 14.6)
		117	CAS/EPD	2.6% (0.9 to 7.3)	2.6% (0.9 to 7.3)
			ARR	4.1% (-1.6 to 10.3)	5.7% (-0.3 to 12.2)
<b>Stroke/Death/MI</b>					
Symptomatic (≥50%) or Asymptomatic (≥80%)		167	CEA	9.8% (6.2 to 15.3)	20.1% (14.7 to 26.8)
		167	CAS/EPD	4.8% (2.5 to 9.2)	12.2% (8.1 to 18.0)
			ARR	5.0% (-0.7 to 10.9)	7.9% (-0.7 to 16.4) <sup>3</sup>
Symptomatic ≥50%		46	CEA	10.9% (4.8 to 23.1)	19.6% (10.7 to 33.2)
		50	CAS/EPD	2.0% (0.1 to 10.5)	16.0% (8.3 to 28.5)
			ARR	8.9% (-1.6 to 21.2)	3.6% (-11.8 to 19.2)
Asymptomatic ≥80%		120	CEA	9.2% (5.2 to 15.7)	19.2% (13.2 to 27.2)
		117	CAS/EPD	6.0% (2.9 to 11.9)	10.3% (6.0 to 17.1)
			ARR	3.2% (-3.9 to 10.4)	8.9% (-0.2 to 17.9)

1 from FDA intention-to-treat analyses

2 when not presented from Kaplan-Meier estimates, proportions reported from ITT analyses and 95% CI calculated

3 (see methods); p=0.004 for noninferiority

**Table 8.** Deaths at 1-year by Cause in SAPPHIRE

Non-Neurologic Causes	Group/Arm		
	CEA/CAS	CEA	CAS
Cardiac	18	10	8
Respiratory	4	3	1
Cancer	3	1	2
Renal Failure	1	1	0
Multisystem Failure	3	3	0
Neurologic Causes	4	3	1
<b>Total</b>	<b>33</b>	<b>21</b>	<b>12</b>
<b>Total (non-neurologic)</b>	<b>29</b>	<b>18</b>	<b>11</b>

The FDA's statistical reviewers concluded results did not meet prespecified objective performance criteria because confidence intervals using the analyses specified in the trial protocol crossed the line for no difference between treatment arms (U.S. Food and Drug Administration 2004a). The reviewers judged it remained uncertain whether the trend towards noninferiority would have continued with additional patient accrual and randomization.

The range of 1-year primary endpoint rates across sites, 6.9% to 21.1%, was not accounted for in the analyses. Also lacking are data to compare sites for differences in complication rates with the two treatments. Although patients were stratified by treatment center before randomization, results might have been influenced by larger differences between arms in early complication rates at centers that enrolled more patients than at centers that enrolled fewer patients.

Since perioperative and periprocedural risks in SAPPHIRE were greater than those in RCTs of CEA with or without best medical therapy, the time to treatment benefit relative to best medical therapy alone from either intervention likely is longer in the SAPPHIRE sample. Thus, SAPPHIRE should require even longer follow-up than the CEA trials which reported outcomes at 2-7 years after, treatment and excluded such higher surgical risk candidates. A separate issue is that 1 year is inadequate to provide evidence on durability of benefits from CAS with EPD, relative to available evidence on durability of benefit from CEA from other studies.

Finally, absent was a third arm treated with best medical therapy. Consequently, the SAPPHIRE trial does not permit conclusions on the relative benefits of CAS with EPD and best medical therapy versus best medical therapy alone for increased medical/anatomic risk patients.

While SAPPHIRE's published result found CAS noninferior to CEA (both with best medical therapy) for the combined outcome including MI, a majority of the cardiac events were non Q-wave MIs occurring in the CEA arm. Moreover, the result must be considered in concert with periprocedural event rates in the trial. For asymptomatic and symptomatic patient enrolled in SAPPHIRE, lack of comparison with best medical therapy, small number of symptomatic patients, and high periprocedural stroke rates in the asymptomatic group do not support a conclusion that benefit from CAS (or even CEA) outweighs procedural risk in this patient population.

**SPACE.** Including only symptomatic individuals at average medical and anatomic risk, SPACE found no difference between CEA and CAS (with or without EPD) in the primary outcome specified: 30-day ipsilateral stroke and death rates (Table 9). While EPDs were used in only one-quarter of patients, the primary outcome was slightly less frequent without the devices; results were consistent with or without EPDs. The periprocedural stroke and death rate in the CEA group exceeded 6% slightly and was 7.7% in the CAS arm. Among individuals older than 75 years, the primary endpoint was reached at 30 days in 12 of 109 (11.0%, 95% CI: 6.4 to 18.3).

**Table 9.** SPACE 30-day Ipsilateral Stroke and Death (overall, with or without EPD) and any Stroke and Death Rates (Intention to Treat)

	% Stenosis (NASCET)	n		30-day Outcome (%) Absolute Risk Reduction (95% CI)
<b>Ipsilateral Stroke/Death</b>				
Symptomatic	>50%	584	CEA	6.3% (4.6 to 8.6)
		599	CAS/+EPD	6.8% (5.1 to 9.2)
			ARR	-0.5% (-3.4 to 2.4)
<b>Any Stroke/Death</b>				
		584	CEA	6.5% (4.8 to 8.8)
		599	CAS/+EPD	7.7% (5.8 to 10.1)
			ARR	-1.2% (-4.1 to 1.8)
<b>Ipsilateral Stroke/Death</b>				
		151	CAS w/EPD	7.3% (4.1 to 12.6)
		416	CAS no/EPD	6.7% (4.7 to 9.6)
			ARR	0.6% (-3.7 to 6.2)

A number of issues are important to consider interpreting these results particularly since the trial was prematurely terminated. First, per-protocol analyses were consistent. The primary endpoint definition included deficits lasting 24 hours or more, even if they later resolved—possibly more liberal than other trials. While EPDs were not used in all patients, their use did not appear to impact results. Nevertheless, it is possible that EPDs were effective and selectively used in higher risk patients. However, the SPACE steering and endovascular-therapy quality committees were aware of the EVA-3S decision to require EPDs in 2004 and elected not to alter their protocol. Cardiac complications were also not ascertained and multiple stent systems used in the trial.

The accompanying editorial (Naylor 2006) highlighted that the 30-day stroke and death rate in both trial arms exceeded currently acceptable rates and approximately one quarter of potential investigators failed to qualify. Others have questioned the experience required (a minimum of 25 procedures) of interventionalists included in the trial (Setacci and Cremonesi 2007). However, this level of experience is not inconsistent with requirements for CREST (20 procedures with a single device (Hobson et al. 2005). The experience of interventionalists was otherwise not described.

Potential shortcomings of the trial must be considered. However, the trial's early termination, failure to demonstrate noninferiority, perioperative complication rates in the CAS arm exceeding acceptable levels support concluding that CAS is neither equivalent to CEA, nor accompanied by, acceptable perioperative complication rates.

**EVA-3S.** In a sample of symptomatic patients at average medical and anatomic risk, the EVA-3S trial results favored CEA over CAS (Table 10). In absolute terms, the results imply that at 30 days, for every 17 trial-eligible patients undergoing CAS instead of CEA, 1 will experience a stroke or death; for every 52 CAS procedures, 1 patient will experience a disabling stroke or death. Results were similar at 6 months.

The investigators found no association between center volume (categorized as less than 21, 21 to 40, and more than 40 patients) and outcomes. Additionally, no relationship was found between interventionalist experience and 30-day incidence of stroke or death (Mas and Chatellier 2007). Although EPDs were not used in all patients, in the CAS with EPD group the 30-day stroke/death rate was 7.9% (95% CI: 5.1 to 12.2). Thirty-six patients undergoing stenting did not receive dual antiplatelet therapy as recommended and event rates were slightly higher

**Table 10.** EVA-3S Stroke and Death Rates (Intention to Treat)

	% Stenosis (NASCET)	n		Outcome (%) Absolute Risk Reduction (95% CI)	
				<b>Any Stroke/Death</b>	
				30-days	6-months
Symptomatic	60-99%	259	CEA	3.9% (2.0 to 7.2)	6.1% (3.8 to 9.7)
		261	CAS	9.6% (6.4 to 14.0)	11.7% (8.4 to 16.1)
			ARR	-5.7% (-10.2 to -1.4)	-5.6% (-10.6 to -0.7)

in that group (11.1% vs. 9.0%). Cranial nerve injuries were significantly more frequent in the CEA arm (7.7%, n=20 vs. 1.1%, n=3); 2 of the 20 nerve injuries in the CEA arm were categorized as severe compared to none in the CAS arm.

Concerns regarding the EVA-3S results have been raised centering primarily on interventionalist experience and center volume. The number of CAS procedures per site was relatively low—10 sites contributed fewer than 10 patients and largest number of procedures performed at any site was 52 (Bonvini and Righini 2007). A nonrandomized study of 182 patients found higher volume associated with improved outcomes and shorter procedure times (Lin et al. 2005). The 30-day death or stroke rate in the CEA arm (possibly attributed to surgical experience and medical therapy) was lower than in pivotal CEA trials of symptomatic individuals potentially accentuating the difference in outcomes between arms. Finally, 5 different stents and 7 EPDs were used by interventionalists.

Although the trial's limitations temper conclusiveness of inference, the results do not support the use of CAS in symptomatic individuals at average medical or anatomic risk with carotid stenosis >60%—or equivalence with CEA.

### Registries

Published reports from 7 prospective CAS registries and interim results from the CREST lead-in phase were reviewed representing 6,712 patients. Seven reports included only 30-day outcomes, a single registry reported 1-year follow-up. Table 11 outlines study characteristics. In only PRIAMUS was a majority symptomatic (see Appendix Table D for other patient characteristics). In the CREST lead-in study, EPDs were not used in all patients. Six of the 8 studies applied increased-risk enrollment criteria.

Outcomes at 30-days are summarized in Table 12. When reported, conventional stroke/death rates ranged from 2.1% to 6.9%. In 5 of the 7 registries enrolling a substantial majority (69% to 86%) of asymptomatic patients, reported rates of stroke or death with or without MI exceeded 5.7%. It is therefore unlikely that the periprocedural complication rate in the asymptomatic groups was less than the 3% judged needed to accrue benefit. Three registries enrolling patients at increased medical or anatomic risk reported 30-day periprocedural complication rates according to the presence or absence of symptoms. In these registries, complication rates exceeded 3% in asymptomatic and 6% in symptomatic individuals (Tables 13 through 15). Only CaRESS and ARChER reported 1-year outcomes including a 10.9% stroke/death/MI rate (CaRESS); 9.6% 30-day death/stroke/MI combined with ipsilateral stroke between 30 days and 1 year (ARChER). Both are comparable to SAPPHERE's results. The interim lead-in phase of CREST (average-risk patients) also reported periprocedural stroke/death rates according to symptom status (Table 16) with rates greater than 3% in asymptomatic, and slightly less than 6% in symptomatic patients.

A single registry (BEACH) reported 30-day event rates distinguishing patients by whether they were at increased medical or anatomic risk. The periprocedural event rate in the group with increased anatomic risk was lower than among those at increased medical risk for any stroke or major stroke and death.

Finally, the interim report from the CREST lead-in phase described death or stroke rates according to age (Table 17). There was a prominent trend of increasing death/stroke rate with age, particularly among those 80 years of age

**Table 11.** Characteristics, Patient Demographics, and Symptomatic or Asymptomatic Subgroups.

	CREST (2004) (lead-in)	Mo.Ma (Reimers et al., 2005)	CaRESS (2005)	PRIAMUS (2005)	BEACH (2005) Pivotal	Combined	CREATE (2006) Pivotal	ARCHeR (2006)	CAPTURE (2006)
Dates	1/2000– 3/2004	3/2002– 3/2003	4/2001– 12/2002	10/2001– 3/2005	2/2002– 12/2003	2/2002– 12/2003	4/2004– 10/2004	3/2000– 9/2003	10/2004– 3/2006
Centers	51	14	14	4	47	47	32	48	144
Location	US	European	US	Italy	US	US	US	US/Europe	US
n	749	157	143	416	480	747	419	581	3500
Stent	ACCULINK	Any	Wallstent	Any	Wallstent	Wallstent	Protégé	ACCULINK	ACCULINK
EPD	ACCUNET (in 88.1%)	Mo.Ma	Guardwire Plus	Mo.Ma	FilterWire	FilterWire	SPIDER	ACCUNET	ACCUNET
Mean Age (SD)	69.5 (4)	68 (8.3)	71.2 (9.6)	71.6 (9)	70.9 (9.3)	≈70.7	73.6 (9.1)	70.3 (9.5)	72.7
Male	64%	77%	60%	72%	65%	64%	61%	67%	61%
Increased Risk Enrollment Criteria	<b>No<sup>1</sup></b>	<b>Yes</b>	<b>Yes</b>	<b>No</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
Asymptomatic (Stenosis %)	<b>69%</b> ≥70%	<b>80%</b> >70%	<b>69%</b> ≥75%	<b>37%</b> >70%	<b>76%</b> >80%	<b>75%</b> >80%	<b>83%</b> ≥70%	<b>76%</b> ≥80%	<b>86%</b> ≥80%
Symptomatic (Stenosis %)	<b>31%</b> ≥50%	<b>20%</b> >50%	<b>31%</b> ≥50%	<b>63%</b> >50%	<b>24%</b> >50%	<b>25%</b> >50%	<b>17%</b> ≥50%	<b>24%</b> ≥50%	<b>14%</b> ≥50%

1 Included 12.1% aged 80 years and older.

**Table 12.** 30-day Outcomes and Procedure Success Rates Reported from CAS Registries

	CREST (2004) (lead-in)	Mo.Ma (Reimers et al., 2005)	CaRESS (2005)	PRIAMUS (2005)	BEACH (2005) Pivotal	Combined	CREATE (2006) Pivotal	ARChER (2006)	CAPTURE (2006)
Procedural Success Rate	99.7%	100%	96.5%	99.0%	98.3%	98.2%	97.4%	98.8%	
<b>30-Day Outcomes</b>									
Death	0.8%	0.6%	0%	0.5%	1.5%	1.5%	1.9%	2.1%	1.8%
Major Stroke		0.6%		0.2%	1.9% <sup>1</sup>	2.1% <sup>2</sup>	3.5%	1.5%	2.0%
Minor Stroke		4.5%		3.8%	2.5%	2.5%	1.0%	4.0%	2.9%
TIA				0.7%					
Stroke	4.0%		2.1%	4.1%	4.4%	4.7% <sup>3</sup>	4.5%	5.5%	4.8%
MI			0%	0%	1.0%	0.8%	1.0%	2.4%	0.9%
Death/Stroke/MI			2.1%	4.6%	5.8%	5.8%	6.2%	8.3%	6.3%
Death/Stroke	4.4%	5.7%	2.1%	4.6%				6.9%	5.7%

1 Including 3 hemorrhagic and subarachnoid hemorrhage not recorded in publication as major stroke.

2 Including 6 hemorrhagic and subarachnoid hemorrhage not recorded in publication as major stroke.

3 Percentage includes 35 strokes from Table 4 in publication, although total reported was 33.

**Table 13.** 30-day Outcomes and 95% CIs for Subgroups Reported from BEACH (2005)

Subgroup	Any Stroke	MI	Death/Stroke/MI
Symptomatic (n=189)	7.4% (4.5 to 12.0)	1.1% (0.3 to 3.8)	7.9% (4.9 to 12.7)
Asymptomatic (n=558)	3.4% (2.2 to 5.3)	0.7% (0.3 to 1.8)	5.0% (3.5 to 7.2)
Increased Medical/Surgical Risk (n=289)	5.9% (3.7 to 9.2)	1.0% (0.4 to 3.0)	8.7% (5.9 to 12.5)
Increased Anatomic Risk (n=456)	3.5% (2.2 to 5.6)	0.7% (0.2 to 1.9)	3.9% (2.5 to 6.2)

**Table 14.** 30-day Outcomes and 95% CIs for Subgroups Reported from ARChER (2006)

Subgroup	Any Stroke	MI	Stroke/Death
Symptomatic (n=136)	10.9% (6.2 to 17.3)	2.2% (0.5 to 6.2)	11.6% (6.8 to 18.1)
Asymptomatic (n=439)	3.8% (2.3 to 6.1)	2.5% (1.2 to 4.4)	5.4% (3.5 to 8.0)

**Table 15.** 30-day Outcomes and 95% CIs for Subgroups Reported from CAPTURE (2006)

Subgroup	Death/Stroke/MI
Symptomatic (n=482)	12.1% (9.4 to 15.2)
Asymptomatic (n=3018)	5.4% (4.6 to 6.3)

**Table 16.** 30-day Outcomes and 95% CIs for Subgroups Reported from the Interim Lead-in Phase of CREST (2006)

Subgroup	Death/Stroke
Symptomatic (n=229)	5.7% (3.3 to 9.5)
Asymptomatic (n=516)	3.7% (2.4 to 5.7)

**Table 17.** Interim CREST Lead-in 30-day Death or Stroke Rates According to Age

Age	n	Events	Death/Stroke
<60	120	2	1.7%
60-69	229	3	1.3%
70-79	301	16	5.3%
80+	99	12	12.1%

or older. The 30-day stroke/death rate in the oldest age group is similar to that reported in SPACE among those 75 years of age and older (11.0%).

While not comparative, these 30-day outcomes are informative. Periprocedural event rates, sample compositions (predominantly asymptomatic patients), and event rates reported according to patient symptoms indicate 30-day stroke/death rates exceeding acceptable levels for both asymptomatic and symptomatic increased-risk patients in the 3 registries reporting by subgroup. The interim publication from the CREST lead-in phase, reported periprocedural complication rates just under 6% in average risk symptomatic patients, but exceeded 3% in those who were asymptomatic. Periprocedural stroke/death rates reported in the oldest age group in CREST and SPACE were substantial. Finally, although not categorized according to the presence of symptoms, BEACH suggests that a group of individuals at high risk for CEA due to anatomic reasons may obtain acceptable benefit and should be targeted for further study—particularly within ongoing registries.

## Discussion

This Assessment sought evidence pertaining to two questions:

1. Can CAS be performed with periprocedural stroke/death rates accompanied by a net health benefit among (I) symptomatic and (II) asymptomatic patients at: a) average medical and anatomical risk, b) increased medical risk, and c) increased anatomic risk?
2. How do CAS, CEA, and best medical therapy compare in each of the above subgroups?

Specific evidence exists pertaining only to the symptomatic group at average risk addressed in question 1. Evidence pertaining to the remaining groups overlaps among them. While specific evidence is most desirable, that relevant to the overlapping groups is also addressed, according to the presence of symptoms.

1. Can CAS be performed with periprocedural stroke/death rates accompanied by a net health benefit among (I) symptomatic and (II) asymptomatic patients at: a) average medical and anatomical risk, b) increased medical risk, and c) increased anatomic risk?

## I. Symptomatic

**A. (Average risk).** SPACE and EVA-3S examined symptomatic patients at average risk. The trials were prematurely stopped: SPACE due to funding and interim analysis projecting a sample size unlikely attainable; EVA-3S because of safety and futility. In both trials, periprocedural stroke/death rates in the CAS arms exceeded the 6% level established as clinically acceptable and associated with an overall net health benefit for CEA in symptomatic patients (7.7% in SPACE, 9.6% in EVA-3S). Interim results from the CREST lead-in phase reported a 5.7% periprocedural stroke/death rate in symptomatic average risk patients.

One interim CREST report described periprocedural stroke/death rates in average risk symptomatic patients slightly less than 6%. However, considered together with results of SPACE and EVA-3S current evidence does not support concluding benefit of CAS in this group.

**B. (Increased medical risk).** No study adequately directly addressed this subgroup. Evidence pertaining to this group is insufficient.

In the group of symptomatic patients from SAPPHIRE the periprocedural stroke/death or MI rate was 2.0%, less than the 6% rate acceptable for CEA. However, there were only 50 patients in the CAS symptomatic arm and the rate represents just 1 event. The BEACH registry reported a 5.9% periprocedural stroke rate in the increased medical risk group (n=289) but did not distinguish symptomatic individuals (24% of the overall registry) in the subgroup. From the overall BEACH sample (patients at increased medical or anatomic risk), in the symptomatic group the periprocedural stroke, death or MI rate was 7.9%, any stroke 7.4%. The ARChER registry enrolled individuals at increased medical or anatomic risk; among symptomatic patients (n=136) the periprocedural stroke/death rate was 11.6%. In CAPTURE, a postapproval study enrolling patients similar to ARChER, the periprocedural death/stroke or MI rate among symptomatic patients (n=482) was 12.1%.

Available evidence indirectly informs regarding outcomes in the symptomatic increased medical risk group. The evidence indicates that periprocedural death/stroke rates following CAS exceed levels judged to provide benefit.

**C. (Increased anatomic risk).** No study reported outcomes specific to this group. However, in BEACH, the periprocedural stroke rate in the increased anatomic risk group (symptomatic and asymptomatic) was 3.5% and death/stroke or MI rate was 3.9%. While the result is suggestive, the absence of reporting according to the presence of symptoms and being a single registry, precludes conclusions.

## II. Asymptomatic

**A. (Average risk).** Interim results from the CREST lead-in phase found a periprocedural stroke/death rate of 3.7% in this subgroup exceeding the 3% acceptable rate for asymptomatic patients. Limited evidence does not support benefit in this group.

**B. (Increased medical risk).** The BEACH results cited above (symptomatic IB, increased medical risk) apply; evidence is insufficient.

SAPPHIRE included 117 individuals falling into the increased medical and anatomic risk groups with stenosis  $\geq 80\%$ . The reported periprocedural stroke rate was 5.1%. In ARCHER the periprocedural stroke/death rate in this group was 5.4%. CAPTURE reported a stroke/death or MI rate of 5.4% (the periprocedural MI rate in the overall registry was 0.9%). These exceed the 3% rate of stroke/death recommended for CEA in asymptomatic patients.

**C. (Increased anatomic risk).** The BEACH results cited above (symptomatic IC, increased anatomic risk) apply; evidence is insufficient.

### 2. How do CAS, CEA, and best medical therapy compare in each of the above subgroups?

Both SPACE and EVA-3S compared outcomes of CAS to CEA (both with best medical therapy) in patients of average medical and anatomic risk. Neither trial found CAS equivalent to CEA. While EPDs were not used in all patients in SPACE and a small number in EVA-3S, it is highly unlikely to alter their conclusions. SAPPHIRE compared CAS to CEA (both with best medical therapy). For asymptomatic and symptomatic patients combined, CAS was not inferior to CEA. However, as previously noted, periprocedural complication rates in the asymptomatic arm exceeded levels judged to provide patient benefit; the small number of events and patients in the symptomatic arm preclude conclusions.

No studies compared CAS with best medical therapy to best medical therapy alone among symptomatic or asymptomatic patients.

Available evidence does not support concluding that CAS is performed with acceptable periprocedural stroke/death rates for symptomatic or asymptomatic patients, that it provides a net health benefit to patients at increased medical risk, or that it is equally effective as CEA. There is limited evidence and a clinical rationale to suggest CAS may be beneficial in the group of patients at increased anatomic risk, but current evidence has not clearly differentiated outcomes for this subgroup according to symptomatic status.

## Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about whether carotid artery angioplasty and stenting (CAS) with or without distal embolic protection (EPD) meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to reduce stroke risk from symptomatic or asymptomatic carotid stenosis.

### 1. The technology must have final approval from the appropriate governmental regulatory bodies.

CAS with or without EPD is a procedure and thus does not require U.S. Food and Drug Administration (FDA) approval. However, the devices used for CAS and for EPD require FDA approval. As of this writing, five manufacturers' stents are FDA approved and indicated specifically for use in carotid arteries. The FDA has mandated postmarketing studies for these devices, including longer follow-up for patients already reported to the FDA, and additional registry studies primarily to compare outcomes as a function of clinician training and facility experience. The devices are indicated for combined use of a stent and EPD to reduce stroke risk in patients at increased risk for perioperative complications from CEA who are symptomatic with  $\geq 50\%$  stenosis or asymptomatic with  $\geq 80\%$  stenosis. CAS with these devices for patients outside these indications is an off-label use.

**2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

Available evidence permits conclusions regarding periprocedural complication rates (particularly stroke or death) following CAS in patients of average risk and increased medical risk. Periprocedural stroke/death rates surpassed those established as clinically acceptable and associated with an overall net health benefit following CEA. There is limited evidence and a clinical rationale to suggest CAS may be beneficial in the group of patients at increased anatomic risk, but present evidence has not clearly differentiated outcomes for this subgroup according to symptomatic status. Thus, there is insufficient evidence to draw conclusions regarding patients at increased anatomic risk.

A number of large ongoing trials will yield more evidence in the near future (e.g., “Carotid Revascularization Endarterectomy versus Stent Trial” [symptomatic and asymptomatic]; “International Carotid Stenting Study” [symptomatic]; and the “Asymptomatic Carotid Surgery Trial” ACT-1).

**3. The technology must improve the net health outcome.**

Available evidence does not support concluding that CAS with EPD improves the net health outcome among patients at average or increased medical risk. Evidence regarding patients at increased anatomic risk is suggestive of benefit, but insufficient to draw conclusions.

**4. The technology must be as beneficial as any established alternatives.**

Available evidence does not support concluding that CAS with or without EPD is as beneficial as CEA for symptomatic patients at average risk or increased medical risk. Whether CAS with EPD is as beneficial as CEA for asymptomatic patients at average medical or anatomic risk cannot be determined because available evidence is insufficient to permit conclusions. There is no evidence comparing best medical therapy for symptomatic or asymptomatic patients at increased medical or anatomic risk, preventing conclusions.

**5. The improvement must be attainable outside the investigational settings.**

Whether CAS with EPD improves health outcomes has not yet been demonstrated in the investigational setting.

Based on the above, use of carotid artery angioplasty and stenting with or without embolic protection of the cerebral circulation for patients with carotid artery stenosis does not meet the TEC criteria.

---

NOTICE OF PURPOSE: TEC Assessments are scientific opinions, provided solely for informational purposes. TEC Assessments should not be construed to suggest that the Blue Cross Blue Shield Association, Kaiser Permanente Medical Care Program or the TEC Program recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service; any particular course of treatment, procedure, or service; or the payment or non-payment of the technology or technologies evaluated.

CONFIDENTIAL: This document contains proprietary information that is intended solely for Blue Cross and Blue Shield Plans and other subscribers to the TEC Program. The contents of this document are not to be provided in any manner to any other parties without the express written consent of the Blue Cross and Blue Shield Association.

# References

- ACAS Executive Committee. (1995).** Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*, 273(18):1421-8.
- Agresti A, Coull BA. (1998).** Approximate is better than “exact” for interval estimation of binomial proportions. *Am Stat*, 52:119-126.
- Albers GW, Easton JD, Sacco RL et al. (1998).** Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest*, 114(5 Suppl):683S-698S.
- Albers GW, Hart RG, Lutsep HL et al. (1999).** AHA Scientific Statement. Supplement to the guidelines for the management of transient ischemic attacks: A statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. *Stroke*, 30(11):2502-11.
- Alberts MJ. (2001).** Results of a Multicenter Prospective Randomized Trial of Carotid Artery Stenting vs. Carotid Endarterectomy. *Stroke* 32:525-d (abstract 55).
- Alberts MJ, McCann R, Smith TP et al. (1997).** A randomized trial of carotid stenting vs. endarterectomy in patients with symptomatic carotid stenosis: study design. *J Neurovascular Disease* 2(6):228-54.
- Amarenco P, Bogousslavsky J, Callahan A 3rd et al. (2006).** High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*, 355(6):549-59.
- American Heart Association (AHA). (2005).** Stroke (and Stroke in Children). In: *Heart Disease and Stroke Statistics — 2004 Update*. Dallas, TX, American Heart Association, pp. 15-16. Also available online at: <http://www.amhrt.org/downloadable/heart/1079756729696HDSStats2004UpdateREV3-19-04.pdf>. Last accessed September 27, 2004.
- Antithrombotic Trialists’ Collaboration. (2002).** Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*, 324(7329):71-86.
- Barnett HJ, Taylor DW, Eliasziw M et al. (1998).** Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*, 339(20):1415-25.
- Barr JD, Connors JJ 3rd, Sacks D et al. (2005).** Quality improvement guidelines for the performance of cervical carotid angioplasty and stent placement. Developed by a collaborative panel of the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, and the Society of Interventional Radiology. *J Vasc Interv Radiol*, 14(9 Pt 1):1079-95.
- Bates ER, Babb JD, Casey DE Jr et al. (2007).** ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting). *J Am Coll Cardiol*, 49(1):126-70.
- Benavente O, Moher D, Pham B. (1998).** Carotid endarterectomy for asymptomatic carotid stenosis: a meta-analysis. *BMJ*, 317(7171):1477-80.
- Bettmann MA, Katzen BT, Whisnant J et al. (1998).** Carotid stenting and angioplasty: a statement for healthcare professionals from the Councils on Cardiovascular Radiology, Stroke, Cardio-Thoracic and Vascular Surgery, Epidemiology, and Prevention, and Clinical Cardiology, American Heart Association. *Circulation*, 97(1):121-5.
- Bettmann MA, Dake MD, Hopkins LN et al. (2004).** Atherosclerotic vascular disease conference: Writing Group VI: revascularization. *Circulation*, 109(21):2645-50.
- Biller J, Feinberg WM, Castaldo JE et al. (1998).** Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation*, 97(5):501-9.
- Blaisdell WF, Clauss RH, Galbraith JG et al. (1969).** Joint study of extracranial arterial occlusion. IV. A review of surgical considerations. *JAMA*, 209(12):1889-95.
- Bonvini RF, Righini M. (2007).** Endarterectomy versus stenting for carotid stenosis. *N Engl J Med*, 356(3):305; author reply 306-7.
- Brooks WH, McClure RR, Jones MR et al. (2001).** Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol*, 38(6):1589-95.
- Brott TG, Brown RD Jr, Meyer FB et al. (2004).** Carotid revascularization for prevention of stroke: carotid endarterectomy and carotid artery stenting. *Mayo Clin Proc*, 79(9):1197-208.
- Cambria RP. (2004).** Stenting for carotid-artery stenosis. *N Engl J Med*, 351(15):1565-7.
- CAPRIE Steering Committee. (1996).** A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*, 348(9058):1329-39.
- CARESS Steering Committee. (2005).** Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial. *J Endovasc Ther*, 10(6):1021-30.

- CaRESS Steering Committee. (2005).** Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg*, 42(2):213-9.
- Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) Investigators. (2001).** Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*, 357(9270):1729-57.
- Chassin MR. (1998).** Appropriate use of carotid endarterectomy. *N Engl J Med*, 339(20):1468-71.
- Chaturvedi S, Bruno A, Feasby T et al. (2005).** Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*, 65(6):794-801.
- Christiaans MH, Ernst JMPG, Suttorp MJ et al. on behalf of the Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group. (2005).** Restenosis after Carotid Angioplasty and Stenting: a Follow-up Study with Duplex Ultrasonography. *Eur J Vasc Endovasc Surg*. [In Press].
- Collins R, Peto R, MacMahon S et al. (1990).** Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*, 335(8695):827-58.
- Coppi G, Moratto R, Silingardi R et al. (2005).** PRIAMUS—proximal flow blockage cerebral protection during carotid stenting: results from a multicenter Italian registry. *J Cardiovasc Surg (Torino)*, 46(3):219-27.
- Coward LJ, Featherstone RL, Brown MM. (2004).** Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev*, (issue 2):CD000515.
- Creager MA, Jones DW, Easton JD et al. (2004).** Atherosclerotic vascular disease conference: Writing Group V: medical decision making and therapy. *Circulation*, 109(21):2634-42.
- Cremonesi A, Manetti R, Setacci F et al. (2005).** Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. *Stroke*, 34(8):1956-41.
- Diener HC, Cunha L, Forbes C et al. (1996).** European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*, 145(1-2):1-15.
- Eastcott HH, Pickering GW, Rob CG. (1954).** Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet*, 267(6846):994-6.
- Ecker RD, Pichelmann MA, Meissner I et al. (2005).** Durability of carotid endarterectomy. *Stroke*, 34(12):2941-4.
- Eckert B, Zeumer H. (2005).** Editorial comment—Carotid artery stenting with or without protection devices? Strong opinions, poor evidence! *Stroke*, 34(8):1941-5.
- Eskandari MK, Longo GM, Vijungco JD et al. (2004).** Does carotid stenting measure up to endarterectomy? A vascular surgeon's experience. *Arch Surg*, 139(7):754-8.
- European Carotid Surgery Trial (ECST) Collaborative Group. (1991).** MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet*, 337(8752):1235-45.
- European Carotid Surgery Trial (ECST) Collaborative Group. (1998).** Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*, 351(9115):1579-87.
- European Stroke Prevention Study (ESPS) Group. (1990).** European Stroke Prevention Study. ESPS Group. *Stroke*, 21(8):1122-50.
- Faxon DP, Creager MA, Smith SC Jr et al. (2004).** Atherosclerotic vascular disease conference: executive summary: atherosclerotic vascular disease conference proceeding for healthcare professionals from a special writing group of the American Heart Association. *Circulation*, 109(21):2595-604.
- Fields WS, Maslenikov V, Meyer JS et al. (1970).** Joint study of extracranial arterial occlusion. V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. *JAMA*, 211(12):1995-2005.
- Fields WS, North RR, Hass WK et al. (1968).** Joint study of extracranial arterial occlusion as a cause of stroke. I. Organization of study and survey of patient population. *JAMA*, 203(11):955-60.
- Forsting M. (2004).** Editorial comment—with or without protection? The second important question in carotid artery stenting. *Stroke*, 35(1):e20-1.
- Gasparis AP, Ricotta L, Cuadra SA et al. (2005).** High-risk carotid endarterectomy: fact or fiction. *J Vasc Surg*, 37(1):40-6.
- Goldstein LB, Adams R, Alberts MJ et al. (2006).** Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*, 37(6):1585-655.
- Goldstein LB, Adams R, Becker K et al. (2001).** Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation*, 103(1):163-82.

- Goldstein LB. (2005).** Extracranial carotid artery stenosis. *Stroke*, 34(11):2767-75.
- Gray WA, Hopkins LN, Yadav S et al. (2006a).** Protected carotid stenting in high-surgical-risk patients: the ARCHEr results. *J Vasc Surg*, 44(2):258-68.
- Gray WA, White HJ Jr, Barrett DM et al. (2002).** Carotid stenting and endarterectomy: a clinical and cost comparison of revascularization strategies. *Stroke*, 33(4):1065-70.
- Gray WA, Yadav JS, Verta P et al. (2006).** The CAPTURE registry: Results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv*, 69(3):541-548.
- Gray WA, Yadav JS, Verta P et al. (2006b).** The CAPTURE registry: Results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv*, 69(3):541-548.
- Guidant Corporation. (2004).** Acculink™ Carotid Stent System: product insert. Information for prescribers. Available online at: <http://www.fda.gov/cdrh/pdf4/P040012c.pdf>. Last accessed October 2004.
- Halliday A, Mansfield A, Marro J et al. (2004).** Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*, 363(9420):1491-502.
- Halm EA, Chassin MR, Tuhim S et al. (2005).** Revisiting the appropriateness of carotid endarterectomy. *Stroke*, 34(6):1464-71.
- Harris RP, Helfand M, Woolf SH et al. (2001).** Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*, 20(3 Suppl):21-55.
- Hass WK, Easton JD, Adams HP Jr et al. (1989).** A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med*, 321(8):501-7.
- Heart Protection Study Collaborative Group. (2002).** MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360(9526):7-22.
- Hess DC, Demchuk AM, Brass LM et al. (2000).** HMG-CoA reductase inhibitors (statins): a promising approach to stroke prevention. *Neurology*, 54(4):790-6.
- Higashida RT, Meyers PM, Phatouros CC et al. (2004).** Reporting standards for carotid artery angioplasty and stent placement. *Stroke*, 35(5):e112-54.
- Hobson RW 2nd. (2002).** Update on the Carotid Revascularization Endarterectomy versus Stent Trial (CREST) protocol. *J Am Coll Surg*, 194(1 Suppl):S9-14.
- Hobson RW 2nd. (2005).** Rationale and status of randomized controlled clinical trials in carotid artery stenting. *Semin Vasc Surg*, 16(4):311-6.
- Hobson RW 2nd, Brott TG, Roubin GS et al. (2005).** Carotid artery stenting: meeting the recruitment challenge of a clinical trial. *Stroke*, 36(6):1514-5.
- Hobson RW 2nd, Howard VJ, Roubin GS et al. (2004).** Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg*, 40(6):1106-11.
- Hobson RW 2nd, Weiss DG, Fields WS et al. (1995).** Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*, 328(4):221-7.
- Hodis HN, Mack WJ, LaBree L et al. (1996).** Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*, 124(6):548-56.
- Hodis HN, Mack WJ, LaBree L et al. (1998).** The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med*, 128(4):262-9.
- Illig KA, Zhang R, Tanski W et al. (2005).** Is the rationale for carotid angioplasty and stenting in patients excluded from NASCET/ACAS or eligible for ARCHEr justified? *J Vasc Surg*, 37(3):575-81.
- International Society for Endovascular Specialists (ISES) Steering Committee. (2004).** The CARESS trial. *Endovascular Today*; January 2004:21-22, 29.
- Inzitari D, Eliasziw M, Gates P et al. (2000).** The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*, 342(25):1695-700.
- Jordan WD Jr, Voellinger DC, Fisher WS et al. (1998).** A comparison of carotid angioplasty with stenting versus endarterectomy with regional anesthesia. *J Vasc Surg*, 28(3):397-402; discussion 402-3.
- Kastrup A, Groschel K, Krapf H et al. (2005a).** Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke*, 34(3):815-9.
- Kastrup A, Skalej M, Krapf H et al. (2005b).** Early outcome of carotid angioplasty and stenting versus carotid endarterectomy in a single academic center. *Cerebrovasc Dis*, 15(1-2):84-9.
- Lal BK, Hobson RW 2nd. (2006).** Management of carotid restenosis. *J Cardiovasc Surg (Torino)*, 47(2):155-60.
- LaMuraglia GM, Brewster DC, Moncure AC et al. (2004).** Carotid endarterectomy at the millennium: what interventional therapy must match. *Ann Surg*, 240(5):535-44; discussion 544-6.
- Lawes CM, Bennett DA, Feigin VL et al. (2004).** Blood pressure and stroke: an overview of published reviews. *Stroke*, 35(4):1024.

- Lepore MR Jr, Sternbergh WC 3rd, Salartash K et al. (2001).** Influence of NASCET/ACAS trial eligibility on outcome after carotid endarterectomy. *J Vasc Surg*, 34(4):581-6.
- Macdonald S. (2006).** The evidence for cerebral protection: an analysis and summary of the literature. *Eur J Radiol*, 60(1):20-5.
- MacMahon S, Rodgers A. (1994).** Blood pressure, antihypertensive treatment and stroke risk. *J Hypertens Suppl*, 12(10):S5-14.
- Mas JL, Chatellier G, Beyssen B et al. (2006).** Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*, 355(16):1660-71.
- Mas JL, Chatellier G, Beyssen B. (2004).** Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. *Stroke*, 35(1):e18-20.
- Mayberg MR, Wilson SE, Yatsu F et al. (1991).** Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 509 Trialist Group. *JAMA*, 266(25):5289-94.
- Moore WS. (1995).** The American Heart Association Consensus Statement on guidelines for carotid endarterectomy. *Semin Vasc Surg*, 8(1):77-81.
- Moore WS, Barnett HJ, Beebe HG et al. (1995).** Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the ad hoc Committee, American Heart Association. *Stroke*, 26(1):188-201.
- Moore WS, Mohr JP, Najafi H et al. (1992).** Carotid endarterectomy: practice guidelines. Report of the Ad Hoc Committee to the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. *J Vasc Surg*, 15(5):469-79.
- National Institute for Clinical Excellence (NICE). 2004.** Overview of carotid artery stent placement for carotid stenosis. Available online at <http://www.nice.org.uk/pdf/ip008overview.pdf> (last accessed October 8, 2004).
- Naylor AR, Bolia A, Abbott RJ et al. (1998).** Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg*, 28(2):526-54.
- North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators. (1991a).** Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*, 325(7):445-53.
- North American Symptomatic Carotid Endarterectomy Trial (NASCET) Steering Committee. (1991b).** North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke*, 22(6):711-20.
- Ohki T, Veith FJ. (2005).** Critical analysis of distal protection devices. *Semin Vasc Surg*, 16(4):517-25.
- O'Leary DH, Polak JF, Kronmal RA et al. (1999).** Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*, 340(1):14-22.
- Ouriel K, Hertzler NR, Beven EG et al. (2001).** Preprocedural risk stratification: identifying an appropriate population for carotid stenting. *J Vasc Surg*, 33(4):728-32.
- Pasternak RC, Criqui MH, Benjamin EJ et al. (2004).** Atherosclerotic vascular disease conference: Writing Group I: epidemiology. *Circulation*, 109(21):2605-12.
- Perry JR, Szalai JP, Norris JW. (1997).** Consensus against both endarterectomy and routine screening for asymptomatic carotid artery stenosis. Canadian Stroke Consortium. *Arch Neurol*, 54(1):25-8.
- Pfeffer MA, Sacks FM, Moye LA et al. (1995).** Cholesterol and Recurrent Events: a secondary prevention trial for normolipidemic patients. CARE Investigators. *Am J Cardiol*, 76(9):98C-106C.
- PROGRESS Collaborative Group. (2001).** Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*, 358(9287):1035-41.
- Psaty BM, Smith NL, Siscovick DS et al. (1997).** Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA*, 277(9):759-45.
- Reimers B, Sievert H, Schuler GC et al. (2005).** Proximal endovascular flow blockage for cerebral protection during carotid artery stenting: results from a prospective multicenter registry. *J Endovasc Ther*, 12(2):156-65.
- Rerkasem K, Bond R, Rothwell PM. (2004).** Local versus general anaesthesia for carotid endarterectomy. *Cochrane Database Syst Rev*, 2):CD000126.
- Ringleb PA, Allenberg J, Bruckmann H et al. (2006).** 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*, 368(9545):1239-47.
- Rosamond W, Flegal K, Friday G et al. (2007).** Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, 115(5):e69-171.
- Rothwell PM, Eliasziw M, Gutnikov SA et al. (2004).** Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*, 363(9415):915-24.
- Rothwell PM, Eliasziw M, Gutnikov SA et al. (2005).** Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*, 361(9352):107-16.

- Rothwell PM, Slattery J, Warlow CP. (1996a).** A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke*, 27(2):260-5.
- Rothwell PM, Slattery J, Warlow CP. (1996b).** A systematic comparison of the risks of stroke and death due to carotid endarterectomy for symptomatic and asymptomatic stenosis. *Stroke*, 27(2):266-9.
- Roubin GS, Hobson RW 2nd, White R et al. (2001).** CREST and CARESS to evaluate carotid stenting: time to get to work! *J Endovasc Ther*, 8(2):107-10.
- Sacco RL, Adams R, Albers G et al. (2006).** Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*, 37(2):577-617.
- Safian RD, Bresnahan JF, Jaff MR et al. (2006).** Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol*, 47(12):2584-9.
- Scandinavian Simvastatin Survival Study (4S). (1994).** Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*, 344(8954):1585-9.
- Setacci C, Cremonesi A. (2007).** SPACE and EVA-3S trials: the need of standards for carotid stenting. *Eur J Vasc Endovasc Surg*, 35(1):48-9.
- Shaw DA, Venables GS, Cartlidge NE et al. (1984).** Carotid endarterectomy in patients with transient cerebral ischaemia. *J Neurol Sci*, 64(1):45-55.
- Shepherd J, Cobbe SM, Ford I et al. (1995).** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*, 335(20):1501-7.
- Spence D, Eliasziw M. (2001).** Endarterectomy or angioplasty for treatment of carotid stenosis? *Lancet*, 357(9270):1722-5.
- Stoner MC, Abbott WM, Wong DR et al. (2006).** Defining the high-risk patient for carotid endarterectomy: an analysis of the prospective National Surgical Quality Improvement Program database. *J Vasc Surg*, 45(2):285-295; discussion 295-6.
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. (1998).** Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*, 339(19):1549-57.
- Tu JV, Hannan EL, Anderson GM et al. (1998).** The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med*, 339(20):1441-7.
- UK Prospective Diabetes Study (UKPDS) Group (1998).** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 54). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*, 352(9151):854-65.
- U.S. Food and Drug Administration (FDA). (2004a).** Circulatory System Devices Panel briefing information: FDA Powerpoint presentation (Lisa Kennell) and Lead Reviewer Memos. Available online at: <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4053b1.htm>. Last accessed May 25, 2007.
- U.S. Food and Drug Administration (FDA). (2004b).** U.S. Food and Drug Administration Center for Devices and Radiological Health Medical Devices Advisory Committee, Circulatory System Devices Panel meeting (April 21, 2004) transcript. Available online at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4053t1.htm>. Last accessed May 25, 2007.
- White CJ, Iyer SS, Hopkins LN et al. (2006).** Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv*, 67(4):503-12.
- Wholey MH. (2005).** Unanswered issues for carotid stenting in 2005. *Catheter Cardiovasc Interv*, 60(4):570-2.
- Wolf PA, Clagett GP, Easton JD et al. (1999).** Preventing ischemic stroke in patients with prior stroke and transient ischemic attack : a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*, 30(9):1991-4.
- Yadav JS, Wholey MH, Kuntz RE et al. (2004).** Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*, 351(15):1493-501.
- Yusuf S, Sleight P, Pogue J et al. (2000).** Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*, 342(3):145-53.

# Appendix

**Appendix Table A.** Eligibility Criteria of Representative RCTs on Best Medical Therapy with or without CEA

Selection criteria of the ECST, VA and MRC ACST studies were similar, except for acceptable limits of stenosis shown in Appendix Table B.

Trial Citation	Inclusion Criteria	Exclusion Criteria
NASCET	<ul style="list-style-type: none"> <li>- symptoms of focal cerebral ischemia (TIA or monocular blindness) in previous 120 days</li> </ul>	<ul style="list-style-type: none"> <li>- age <math>\geq</math>80 years (initial phase; included for later phase)</li> <li>- intracranial stenosis &gt; cervical stenosis</li> </ul>
NASCET Collaborators 1991a, 1991b	<ul style="list-style-type: none"> <li>- symptoms ipsilateral to stenosis of &gt;70% or &lt;70% by angiography (stratified and reported separately)</li> <li>- symptom duration &lt;24 hours or resulting in non-disabling stroke</li> </ul>	<ul style="list-style-type: none"> <li>- other illness limiting life expectancy to &lt;5 years (renal, liver or lung diseases, cardiac valve disorders or arrhythmias)</li> <li>- inability to angiographically visualize symptomatic artery</li> <li>- cerebral infarction limiting useful function in affected arterial territory</li> <li>- presence of non-atherosclerotic carotid disease</li> <li>- cardiac lesions likely to cause cardioembolism</li> <li>- history of ipsilateral CEA (recurrent stenosis)</li> <li>- lack of informed consent</li> </ul>
ACAS	<ul style="list-style-type: none"> <li>- age between 40 and 79 years</li> <li>- compatible history and findings on physical examination</li> </ul>	<ul style="list-style-type: none"> <li>- cerebrovascular event in distribution of affected artery or vertebrobasilar system</li> </ul>
ACAS 1995	<ul style="list-style-type: none"> <li>- acceptable laboratory and EKG results</li> <li>- stenosis <math>\geq</math>60% by arteriography in prior 60 days or Doppler exam in past 60 days showing frequency or velocity &gt; instrument-specific cut point with 95% positive predictive value</li> </ul>	<ul style="list-style-type: none"> <li>- symptoms referable to contralateral hemisphere within prior 45 days</li> <li>- contraindication to aspirin therapy</li> <li>- any disorders that might seriously complicate surgery</li> <li>- any condition that could prevent continuing participation or cause death or disability within 5 years</li> <li>- lack of informed consent</li> </ul>

**Appendix Table B.** Benefits and Risks of Adding CEA to Best Medical Therapy (adapted from Chassin 1998 and FDA 2004)

TRIAL	Stenosis Severity	n	Recent Symptoms	Absolute MAE Risk Reduction	Time to Reported Benefit	Perioperative MAE Rate
NASCET	≥70%	659	yes	16.5% <sup>1</sup>	2 years	5.8%
ECST	≥60%	356	yes	11.6% <sup>1</sup>	3 years	4.8%
NASCET	50–69%	430	yes	10.1% <sup>1</sup>	5 years	6.7%
VA309	>50%	189	yes	11.7% <sup>1</sup>	1–2 years	7.7%
NASCET	<50%	678	yes	0.8% <sup>2</sup>	5 years	6.7%
ECST	<40%	1,455	yes	surgery ↑ risk	3 years	7.9%
ACAS	≥60%	1,662	no	6.3% <sup>3</sup>	5 years	2.3%
MRC ACST	≥60%	3,120	no	5.4% <sup>1</sup>	5 years	3.1%
VA Study	≥50	211	no	0 <sup>4</sup>	7 years	4.7

1 p&lt;0.05

2 p=0.97

3 p=0.08

4 p=0.92

MAE major adverse events (includes perioperative and subsequent non-fatal strokes or death).

**Appendix Table C.** Detailed Inclusion and Exclusion Criteria for SAPHIRE, SPACE, and EVA-3S

Inclusion Criteria	Exclusion Criteria
<b>SAPHIRE</b>	
<b>General Criteria</b>	Ischemic stroke within previous 48 hr
Age $\geq$ 18 yr	Presence of intraluminal thrombus
Unilateral, bilateral atherosclerotic or restenotic lesions in native carotid arteries	Total occlusion of target vessel
Symptoms plus stenosis of more than 50 percent of the luminal diameter	Vascular disease precluding use of catheter-based techniques
No symptoms plus stenosis of more than 80 percent of the luminal diameter	Intracranial aneurysm >9 mm in diameter
<b>Criteria for Increased Risk (at least one required)</b>	Need for more than two stents
Clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery)	History of bleeding disorder
Severe pulmonary disease	Percutaneous or surgical intervention planned within next 30 days
Contralateral carotid occlusion	Life expectancy < 1 yr
Contralateral laryngeal-nerve palsy	
Previous radical neck surgery or radiation therapy to the neck	
Recurrent stenosis after endarterectomy	
Age >80 yr	
<b>SPACE</b>	
Symptomatic stenosis (amaurosis, transient ischaemic attack, or stroke) of carotid bifurcation or internal-carotid artery within past 180 days	Intracranial bleeding in past 90 days
Modified Rankin scale score of 3 or less	Uncontrolled arterial hypertension
Older than 50 years	Known intracranial arteriovenous malformation or aneurysm
Negative pregnancy test for women with childbearing potential	Severe concomitant disease with poor prognosis (life expectance <2 years)
Possibility for follow up examinations	Uncorrectable coagulation abnormality
Written informed consent provided	Contraindications for heparin, aspirin, or clopidogrel
Stenosis of carotid bifurcation or internal-carotid artery of at least 70% proven by duplex ultrasound or angiography corresponding to stenosis level of at least 70% according to criteria of European Carotid Surgery Trial or at least 50% according to criteria of North American Symptomatic Carotid Endarterectomy Trial.	Contraindications for contrast media
	Planned simultaneous surgical procedures
	Any condition that could impose hazards to the patient if study therapy is imitated, left to discretion of investigator
	Occlusion of common-carotid or internal-carotid artery
	Stenosis due to external compression
	Stenosis due to dissection
	Recurrent stenosis after surgery or stenting
	Radiation-induced stenosis
	Stenosis due to fibromuscular dysplasia
	Floating thrombus
	Additional intracranial stenosis with higher grade

**Appendix Table C.** Detailed Inclusion and Exclusion Criteria for SAPHIRE, SPACE, and EVA-3S (cont'd)

Inclusion Criteria	Exclusion Criteria
<b>EVA-3S</b>	
<p>18 years of age or older</p> <p>A hemispheric or retinal transient ischemic attack or a nondisabling stroke (or retinal infarct) within 120 days before enrollment, and had a stenosis of 60 to 99% in the symptomatic carotid artery, as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. (degree of stenosis 70% or more at the start of the trial, changed in 10/2003 to <math>\geq 60\%</math>)</p> <p>Ipsilateral carotid stenosis <math>\geq 60\%</math> required confirmation by angiography or both duplex scanning and magnetic resonance angiography</p>	<p>Modified Rankin score <math>\geq 3</math> (on a scale of 0 to 5)</p> <p>Nonatherosclerotic carotid disease</p> <p>Severe tandem lesions (stenosis of proximal common carotid artery or intracranial artery that was more severe than the cervical lesion)</p> <p>Previous revascularization of the symptomatic stenosis</p> <p>History of bleeding disorder</p> <p>Uncontrolled hypertension or diabetes</p> <p>Unstable angina</p> <p>Contraindication to heparin, ticlopidine, or clopidogrel</p> <p>Life expectancy of less than 2 years</p> <p>Percutaneous or surgical intervention within 30 days before or after the study procedure.</p>

**Appendix Table D.** Patient Characteristics as Reported in Published Registries

	CREST (2004) (lead-in)	Mo.Ma (2005)	CaRESS (2005)	PRIAMUS (2005)	BEACH (2005) Pivotal	Combined	CREATE (2006) Pivotal	ARCher (2006)	CAPTURE (2006)
<b>Medical/Surgical Risk</b>									
HTN	84%	79%	81%		90%	88%	90%	84%	88%
Hypercholesterolemia	82%	69%	64%					73%	78%
MI within 30 days					1%			3%	1%
Prior MI		28%	66%		36%	35%	30%	66%	
CAD		57%	66%		22%	35%		66%	67%
Prior CABG	26%	13%							
DM	31%	29%	29%		34%	33%	31%	38%	35%
Current Smoker	16%								21%
Current/Prior Smoker					75%	75%			
Unstable Angina					12%		4%	8%	4%
Renal Disease							19%	3%	8%
Pulmonary Disease						2%	4%	4%	19%
CHF			13%		22%	20%			16%
Age ≥80	12.1%	4.5%			18%			16%	24%
Age ≥75					39%		50%		
Prior Stroke					28%	27%		28%	
Prior TIA			20%					26%	
Prior Stroke or TIA			22%				38%		

**Appendix Table D.** Patient Characteristics as Reported in Published Registries (cont'd)

	CREST (2004) (lead-in)	Mo.Ma (2005)	CaRESS (2005)	PRIAMUS (2005)	BEACH (2005) Pivotal	Combined	CREATE (2006) Pivotal	ARCHeR (2006)	CAPTURE (2006)
<b>Anatomic Risks</b>									
Surgically inaccessible					9%			8%	
Unfavorable anatomy							14%	14%	11%
Prior radiation					11%			7%	
Prior neck surgery					11%			3%	
Tracheostomy					2%			2%	
Spinal immobility					7%			3%	
Laryngeal Nerve Palsy					1%			.5%	
Contralateral Occlusion					18%		10%	16%	8%
PVD			45%						36%
Prior CEA			30%		41%				
Restenosis after CEA					34%		24%	35%	
<b>Increased ("High") Risk</b>	–	75% <sup>1</sup>	84% <sup>2</sup>	–	100% <sup>3</sup>	100%	100% <sup>4</sup>	<sup>5</sup>	

1 Age greater than 80 years; ejection fraction less than 30%, severe COPD, CAD with a 70% stenosis, unstable angina, CABG or valve surgery ≤30 days, uncontrolled diabetes, restenosis after CEA, surgically inaccessible lesions, need for hemodialysis  
2 Either age 80 years or older, NYHA class III/IV for congestive heart failure, chronic obstructive pulmonary disease, contralateral stenosis >50%, prior CEA or CAS, or prior coronary artery bypass grafting.  
3 58.8% met anatomic high risk criteria  
4 76.3% met medical criteria; 52.7% anatomic; 29.1% medical and anatomic.  
5 80.6% met medical criteria; 13.9% anatomic



**Technology  
Evaluation  
Center**

**Blue Cross and  
Blue Shield Association**  
225 North Michigan Avenue  
Chicago, Illinois 60601-7680  
[www.bcbs.com/tec](http://www.bcbs.com/tec)