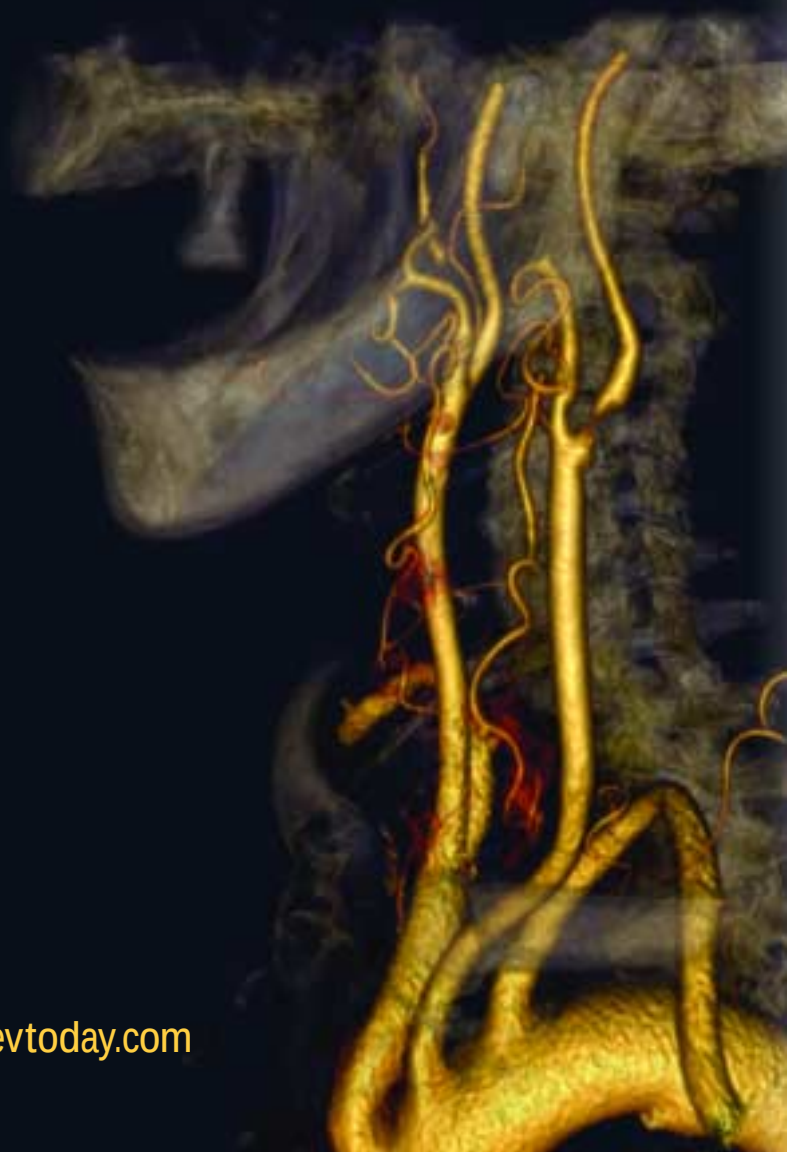
The Carotid Issue

Now approved by the FDA, carotid stenting moves into the spotlight in endovascular care.

Please visit our CAS Center at www.evtoday.com



Carotid Revascularization in 2004

A look at the most recent data from historic and ongoing CEA and CAS trials.

BY THOMAS G. BROTT, MD; JAMIE ROBERTS, LPN, CRC;
ROBERT W. HOBSON II, MD; AND SUSAN HUGHES, BSN

Carotid revascularization continues to be a very effective intervention to prevent ischemic stroke. Randomized trials of carotid endarterectomy (CEA) have shown that the degree of stroke prevention is superior to that of alternative medical treatments. During the last decade, carotid angioplasty and carotid artery stenting (CAS) have been developed as less-invasive treatments. CAS is also more easily adapted to special clinical circumstances, such as patients with high cervical carotid bifurcations, patients with serious medical comorbidities, and patients with previous CEA or irradiation to the neck.[1]

In the 1980s, experience with CEA was marked by excess perioperative stroke and death. Early experience with carotid angioplasty without stenting also showed unacceptably high rates of periprocedural stroke and death. During the last 5 years, CAS has become the standard of care for carotid endovascular intervention. In addition, embolic capture devices have been developed, and endovascular interventionalists have become more experienced. Consequently, the periprocedural safety of CAS has improved. In fact, the most recent data on CAS indicate that rates of periprocedural stroke, myocardial infarction, and death continue to decline and may be approaching the best rates report-

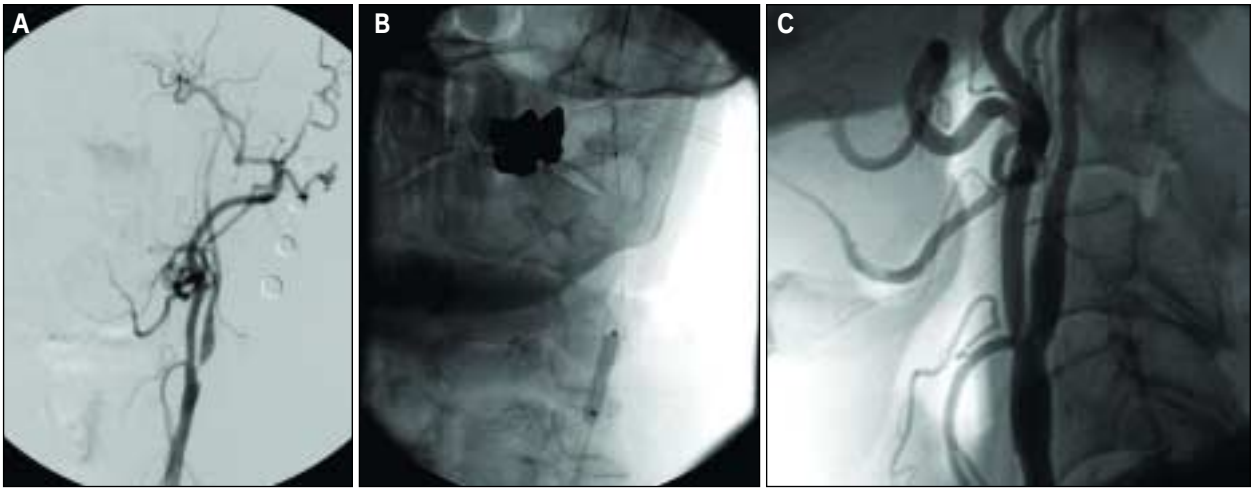


Figure 1. A carotid lesion, before angioplasty (A). The lesion undergoing angioplasty and stenting (B). The same lesion now open and flowing freely (C).

ed for CEA.[1] Benefit from medical treatments may also be increasing with better treatment of hypertension and diabetes, and more widespread use of statins. However, the best available evidence does not indicate any major shift. In the medical arm of the Asymptomatic Carotid Atherosclerosis Study (ACAS),[2] the rate of ipsilateral stroke over 5 years was essentially identical to that in the Asymptomatic Carotid Surgery Trial (ACST). ACAS was completed almost 10 years before ACST.[3]

RANDOMIZED CEA TRIALS

Results of the larger trials of CEA are listed in Table 1. The North American Symptomatic Endarterectomy Trial (NASCET)[4,5] and the European Carotid Surgery Trial (ECST)[6] merit special attention. The 30-day combined stroke and death rate for patients with ≥70% stenosis was 5.8% for NASCET and 6.8% for ECST. In the long-term, the surgical patients showed significant benefit in the high stenosis category.

NASCET and ECST, in addition to the other large randomized trials of CEA for symptomatic carotid stenosis,[1,7] did not provide answers regarding questions of CEA benefit, gender, minority status, advancing age, medical comorbidities, and degree of stenosis. Rothwell et al pooled the electronic data files from NASCET, ECST, and the Veterans Affairs Cooperative Studies Program 309,[8] and their analysis indicated that CEA increased the 5-year risk for ipsilateral stroke patients with less than 30% stenosis, and had no effect for patients with 30% to 49% stenosis. A modest benefit for CEA was detected for patients with 50% to 69% stenosis. CEA was highly beneficial for those with ≥70% stenosis without near occlusion.

For asymptomatic patients, benefit has also been established (Table 2) for those with ≥60% stenosis.[1-3,9,10] Remarkably, the results of the two largest randomized trials, ACAS and ACST, are nearly identical. CEA decreases overall risk by approximately 50% over 5 years compared to medical therapy. In addition, the very large ACST confirmed that CEA prevents disabling strokes, fatal strokes, and strokes in women—important extensions of the results from ACAS.

TABLE 1. SELECTED RANDOMIZED TRIALS OF CAROTID ENDARTERECTOMY FOR SYMPTOMATIC CAROTID ARTERY STENOSIS

Trial	No.	Stenosis	Primary Endpoint		*P* Value
			Medical	Surgical	
NASCET	659	≥70%	26%*	9%*	<.001
NASCET	858	50-69%	22.2%*	15.7*	.045
NASCET	1,368	≤50%	18.7%*	14.9*	NS
ECST	3,008†	≥70% 50-69%	Ipsilateral stroke and surgical death or stroke (only proportions were analyzed)		<.001 NS
VASST	189	>50%	19.4%‡	7.7%‡	.011

**Ipsilateral stroke; †Reanalysis using NASCET definition of stroke and method used in NASCET to determine stenosis; ‡Stroke or crescendo TIAs; NS=not statistically significant.*

TABLE 2. SELECTED RANDOMIZED TRIALS OF CAROTID ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID ARTERY STENOSIS

Trial	No.	Stenosis	Primary Endpoint		*P* Value
			Medical	Surgical	
VA	444	≥50%	20.6%*	8%*	<.001
ACAS	1,662	≥60%	11%†	5.1%†	.004
CASANOVA	410	50-90%	No significant differences		
ACST	3,120	≥60%	11.8%‡	6.4%‡	.0001

**Ipsilateral neurologic events including TIAs; †Ipsilateral stroke or any perioperative stroke or death. ‡Any type of stroke or perioperative death.*

TABLE 3. SELECTED LARGE DATABASE RESULTS OF CAROTID ENDARTERECTOMY

Study	Years	No.	Outcome	Result
Canada-wide	1994-1997	14,268	In-hospital stroke or death	4.1%
US, 10 states		10,561	Perioperative stroke or death in 226 with combined CEA/CABG	17.7%
Ontario	1994-1997	6,038	30-day stroke or death	6%
Medicare	1992-1993	113,000	Perioperative mortality	
NASCET and ACAS hospitals (n=86)				1.4%
Other hospitals (n=2,613)				1.7%

TABLE 4. LARGE RANDOMIZED TRIALS OF CAROTID STENTING

Trial	No.	Stenosis	Primary Endpoint at 1 Year		*P* Value
			Stent	CEA	
SAPPHIRE (symptomatic)	96	≥50%	16.3%*	20%*	NS
SAPPHIRE (asymptomatic)	219	≥80%	9.9%*	21.3%*	.02
WALLSTENT (symptomatic)	219	60-99%	12.1%†	3.6%†	.022

**Stroke, myocardial infarction, or death at 1 year; †Ipsilateral stroke, procedure-related death, or vascular death within 1 year.*

RESULTS FROM LARGE CEA DATABASES AND LARGE CASE SERIES

Results from randomized trials are often limited with regard to application to clinical practice because each set of inclusion and exclusion criteria excludes segments of the population of patients with carotid artery disease. Large databases of carotid surgery, such as those of Medicare and registries in Canada,[1] have been reported that provide real-world results for comparisons to the results of the randomized trials (Table 3). The majority of carotid operations are performed in the setting of asymptomatic disease. Risks are lower in centers with large numbers of operations and lower for surgeons with higher numbers of operations. Risks are not higher for women, appear to be higher for octogenarians, and may be particularly high for combined CEA and coronary artery bypass graft surgery (CABG).

Large case series of CEA[1] report information on patient populations that were not included in the randomized trials or on populations for whom data were insufficient in the randomized trials. Perioperative risks appear to be trending downward, but perioperative mortality may be higher for African Americans and for Hispanics.

The durability of CEA is also addressed in the large case series of CEA.[1] Reoperation for recurrent stenosis has been reported ranging from 1% or lower to as high as 9%. Recurrent stenosis rates of 0.1% to 1.6% for ≥70% stenosis have been reported for CEAs in which arteriotomies were repaired with a vein or patch graft.

CAS FOR PREVENTION OF STROKE

Endovascular treatment of carotid artery disease with CAS[1] is less invasive than surgical treatment, hence its potential application to situations in which CEA may be of higher risk, also explaining the appeal of CAS to patients. Figure 1 depicts a carotid, with approximately 90% stenosis, from diagnosis through treatment. The question to be answered is whether CAS provides equivalent prevention of stroke, compared to CEA, as well as equivalent safety and durability. Complications of CEA, such as cranial nerve injury, are not a consideration with CAS, and high clinical-risk or anatomical-risk patients with severe carotid disease might be more safely treated

TABLE 5. LARGE PROSPECTIVE REGISTRIES OF CAROTID STENTING

Trial	No.	Stenosis	Symptomatic	Stroke and Death at 1 Month
SAPPHIRE	124	≥50%	Yes	8.1%
CREST	465	≥50%	Yes	5.6%
		≥70%	No	2.4%
SAPPHIRE	280	≥80%	No	5%
CARESS	143	≥50%	38%	2.1% (same as that for concurrent CEA cohort)
ARCHeR 1-3	581	≥50% for symptomatic ≥80% for asymptomatic	24%	6.8%

with CAS. For example, CAS may be safer in selected patients with severe coronary artery disease, heart failure, or severe chronic obstructive pulmonary disease.

RANDOMIZED TRIALS

The first large randomized trial of carotid angioplasty was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS),[11] but only 55 of the 251 patients in the endovascular group were treated with a stent, and an embolic capture device was not used.

In the next randomized trial, the WALLSTENT study, patients were eligible if they were symptomatic and had 60% to 99% carotid stenosis by cerebral angiogram. An embolic protection device was not used. At 1 year, ipsilateral stroke, procedure-related death, or vascular death occurred in 12.1% in the stent group, and in 3.6% in the CEA group (P=.022).[1]

The most recently completed randomized trial of carotid stenting compared to CEA is the SAPPHIRE trial (Table 4).[12] The primary objective of SAPPHIRE was to compare the safety and effectiveness of CAS with embolic protection to CEA in high-risk patients. CAS was done with the Cordis Precise Nitinol Stent and the Angioguard XP emboli capture system (Cordis Corporation, a Johnson & Johnson company, Miami, FL). High-risk symptomatic patients were eligible if they had ≥50% stenosis by carotid ultrasound or angiography, and high-risk asymptomatic patients were eligible if they had ≥80% stenosis by carotid ultrasound or angiography. High-risk was defined as patients with at least one of the following: contralateral carotid occlusion, radiation therapy to the neck, previous CEA with recurrent stenosis, difficult surgical access, contralateral laryngeal nerve palsy, severe tandem lesions, heart failure, CABG or open heart surgery within 6 weeks, myocardial infarction 1 day to 4 weeks prior, angina at low workload or unstable angina, severe pulmonary disease, or age >80.

The outcomes were not good for either CAS or CEA for any of the treatment subgroups (Table 4). For asymptomatic patients, the stroke and death rate at 30 days after either CEA or CAS exceeded the ≤3% recommended as the maximum by guideline statements. The question is raised whether outcomes for the symptomatic or asymptomatic high-risk patients in SAPPHIRE would have been different with medical therapy only.

An Advisory Panel to the FDA convened in April 2004 and voted 6-5 in favor of the premarket approval application of the Cordis Corporation, allowing the Precise stent and the Angioguard Emboli Capture System to be used in SAPPHIRE-eligible patients. FDA approval of the PMA is pending.

Randomized clinical trial data comparing CEA to CAS for conventional risk symptomatic and asymptomatic patients are not yet available. The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is underway. CREST is a prospective, randomized trial of symptomatic patients with carotid stenosis ≥50% by angiography or ≥80% stenosis by carotid ultrasound. Prior to being approved to perform CAS in the randomized phase of CREST, interventionists have monitored performance of up to 20 procedures using the Acculink stent and Acculink embolic protection system. Two other randomized trials comparing CEA to CAS are also underway. The SPACE trial has randomized more than 500 patients in Europe; CAVATAS II is underway in Europe, North America, and Australia.

MULTICENTER CAS STUDIES AND REGISTRIES

In the development of a new treatment technique such as CAS, single-center case series, multicenter registries, and multicenter trials of the new technique can lay the needed groundwork (Table 5) for randomized clinical trials. The preliminary short- and longer-term results can aid in sample size calculations, estimates of safety, and in identification of productive centers.

The CREST Lead-In study is the credentialing arm of the trial. Interventionalists must submit results from up to 20 cases of CAS using the stent and protection device used in the CREST randomized phase. If the results are excellent, they can then proceed to randomization. Symptomatic patients with ≥50% stenosis and asymptomatic patients with ≥80% stenosis by angiogram are eligible. Patients are examined after the procedure by neurologists.

The results of the CREST lead-in are encouraging in that the 30-day stroke and death rates for the symptomatic patients have been slightly lower than those reported from NASCET and ECST. For asymptomatic patients, 30-day stroke and death has been higher than that reported for ACAS but very similar to that just reported for ACST. Similar periprocedural morbidity has been observed for women compared to men. For octogenarians, the 30-day stroke and death rate has been 11.9%, significantly higher than for those aged 79 and younger. Hence, enrollment of octogenarians into the CREST lead-in has been halted.

LARGE CAS CASE SERIES

Large case series have been reported from cardiology, neurosurgery, and interventional radiology centers. Results have suggested that CAS can be accomplished safely in women, after neck irradiation, patients with stenosis involving high cervical carotid bifurcations, and in patients with high surgical risk. Additional clinical studies of CAS are underway (Table 6).

DURABILITY OF CEA COMPARED TO CAS

Durability and recurrent carotid stenosis are concerns for both CEA and CAS. Case series are available for comparison to CEA, but inference is limited because of differences in patient populations and concurrent medical treatments. Differences in CAS and CEA are best detected in a randomized trial. In SAPPHIRE at 1 year, 0.8% of the stented patients had ≥70% stenosis compared to 4.2% of the CEA patients (P=.17); 20% of the stented patients studied had ≥50% stenosis compared to 31% of the CEA patients (P=.06). For the long-term, CEA has an established record of good durability. The long-term durability of CAS is not yet established.

CAS COMPARED TO CEA

For symptomatic and asymptomatic patients with the conventional risk factors of the cohorts studied in NASCET, ECST, ACAS, and ACST, the indications for CEA are relatively well defined:

- Symptomatic men and women, age ≤80, with ≥50% carotid stenosis if surgical risk for stroke and death is ≤6% to 7%.
- Asymptomatic men and women, age ≤80, with ≥60% carotid stenosis if surgical risk for stroke and death is ≤3%.

TABLE 6. CLINICAL TRIALS OF CAROTID STENTING

Trial	Sponsor	Design	Stent	Protection Device
ARCHeR	Guidant	Registry, high-risk	AccuLink	AccuNet
BEACH	Boston Scientific	Registry, high-risk	Wallstent, monorail	FilterWire EX
CABERNET	Boston Scientific, EndoTex	Registry, high-risk	NexStent	EPI Filter
CARESS	ISIS	Registry, stent and endarterectomy	Originally Wallstent, now not specified	Originally PercuSurge, now not specified
CREST	Guidant, NIH, NINDS	Randomized, lower risk	AccuLink	AccuNet
ICSS (CAVATAS-2)	UK Stroke Association	Randomized	Not specified	Not specified
MAVErIC	Medtronic	Registry, high risk	Medtronic/AVE Self-Expanding Carotid Stent	PercuSurge, GuardWire plus
SECURITY	Abbott	Registry, high risk	Xact Stent	Formerly MedNova NeuroShield, now "Emboshield" rapid exchange version

• For these patients, the results of CREST, SPACE, and CAVATAS II will provide comparison results for CAS.

• For higher-risk patients, only SAPPHIRE provides randomized clinical trial data. These data and the CEA and CAS registry and case series results suggest the following:

• CEA and CAS may be comparable with regard to 30-day morbidity and durability.

• CEA would be favored where vessel tortuosity, degree of stenosis, or other anatomic features make safe deployment of the embolic protection device or carotid stent technically difficult.

• CAS would be favored when a consensus exists that general or local anesthesia and a surgical procedure would pose excess risk. Such circumstances would include, for example, heart failure, serious angina, and severe obstructive pulmonary disease.

• CAS would be favored in situations in which anatomic characteristics put the patient at higher risk for CEA, including previous CEA with recurrent stenosis, difficult surgical access, previous radiation therapy to the neck, previous radical neck dissection, and contralateral laryngeal palsy.

The SAPPHIRE and ARCHeR 30-day results are not ideal, particularly for asymptomatic patients. These results raise the question as to whether medical therapy alone may be superior to carotid revascularization in high-risk patients, whether CEA or CAS. For high-risk patients, higher periprocedural morbidity, concurrent illness, and higher stroke risk outside the territory of the treated carotid could counterbalance or even exceed the benefits of revascularization. In asymptomatic patients at high risk, data suggesting urgent need for carotid artery revascularization are lacking.

For example, the stroke and death rates of the high-risk asymptomatic patients in SAPPHIRE and ARCHeR at 1 month are well above the recommended American Heart Association Guidelines of a 30-day stroke and death rate of ≤3%. In addition, the 1-year stroke rates for asymptomatic SAPPHIRE patients of 7.7%, and the composite 1-year endpoint rate for asymptomatic ARCHeR 1 and 2 patients of 8.3% and 10.2%, respectively, approach the 5-year ipsilateral stroke rates of the patients treated medically in ACAS and ACST. Accordingly, best medical treatment alone in high-risk asymptomatic patients may be superior to revascularization. Better antihypertensive treatments, including the availability of ACE inhibitors and ACE receptor antagonists, improved antiplatelet regimens, potential for tighter glucose control in diabetes, and well-tolerated lipid-lowering regimens provide a potent armamentarium for the medical approach to treatment of asymptomatic carotid artery disease in high-risk patients. ■

Thomas G. Brott, MD, is a Professor of Neurology at the Mayo Clinic College of Medicine and Co-Principal Investigator for the CREST Trial. He has disclosed no financial interest in any product or manufacturer mentioned herein. Dr. Brott may be reached at (904) 953-7228; Brott.Thomas@Mayo.edu.

Jamie Roberts, LPN, CRC, works in the Department of Neurology at Mayo Clinic Jacksonville and is the Director of Recruitment for the CREST Trial. She has disclosed no financial interest in any product or manufacturer mentioned herein. Ms. Roberts may be reached at (904) 953-7742; Roberts.Jamie@Mayo.edu.

Susan Hughes, BSN, works at University of Medicine and Dentistry in New Jersey and is Senior Clinical Research Associate for the CREST Trial. She has disclosed no financial interest in any product or manufacturer mentioned herein. Ms. Hughes may be reached at (973) 972-2128; Hughesse@UMDNJ.edu

Robert W. Hobson II, MD, is Program Director in Vascular Surgery at the University of Medicine and Dentistry in New Jersey, New Jersey Medical School and Principal Investigator of the CREST Trial. Dr. Hobson has disclosed that he receives financial and/or material support from Guidant. Dr. Hobson may be reached at (973) 972-6633; HobsonRW@UMDNJ.edu.

1. Brott TG, Brown RD, Meyer FB, et al. Carotid revascularization for prevention of stroke: carotid endarterectomy and carotid artery stenting. *Mayo Clin Proc*. 2004;79:1197-1208.
2. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421-1428.
3. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491-1502.
4. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445-453.
5. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415-1425.
6. Rothwell PM, Gutnikov SA, Warlow CP. Reanalysis of the final results of the European Carotid Surgery Trial. *Stroke*. 2003;34:514-523.
7. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA*. 1991;266:3289-3294.
8. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107-116.
9. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1993;328:221-227.
10. The CASANOVA Study Group. Carotid Surgery versus medical therapy in asymptomatic carotid stenosis. *Stroke*. 1991;22:1229-1235.
11. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357:1729-1737.
12. Circulatory System Devices Panel Precise (OTW and RX) and Angioguard (OTW and RX) Nitinol Carotid Stent and Emboli Capture Guidewire by Cordis Corp. P030047 April 21, 2004 http://www.fda.gov/ohrms/dockets/ac/04/questions/4033q1_01_Draft%20Panel%20Pack%20questions.htm.