CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

CAROTID ARTERY STENTING

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum was asked to update its review of the scientific evidence for the use of carotid artery stenting for patients with coronary artery stenosis. The topic was last reviewed in October 2005. At that time, the data were concerning for an increased risk of early strokes with angioplasty and stenting, with promising data only in patients at very high risk for surgical complications. There were also concerns about whether arteries receiving stents would have higher rates of restenosis over time. Since the prior review, there has been increasing emphasis on aggressive anticoagulation and the use of distal embolization protection devices during the angioplasty and stenting procedure in order to prevent early strokes. Two to four year follow-up results have been published for the three largest randomized trials of stents. However, two large European randomized trials were stopped early because of an excess of strokes in the stenting groups or futility (inability to prove the non-inferiority of stenting to endarterectomy). Despite the equivocal data there has been increasing use of carotid stenting in the United States. Investigators using administrative data on more than 250,000 carotid revascularization procedures in the US found that carotid artery stenting had a higher rate of in-hospital postoperative stroke (2.1% vs. 0.88%, $P < .0001$) and higher postoperative mortality (1.3% vs. 0.39%) than carotid endarterectomy.[1] A similar analysis using more recent data from 2005 found that carotid artery stenting was an independent predictor for postoperative stroke (odds ratio [OR], 1.77; 95% confidence interval [CI], 1.5-2.0; $P < .001$), in-hospital mortality (OR, 1.49; 95% CI, 1.2-1.8; $P < .001$) and intracranial hemorrhage (OR, 5.9; 95% CI, 3.1-11.1; $P < .001$) after adjusting for age, gender, symptomatic status, comorbidities, admission, and hospital type.[2] Thus, it is a good time to carefully review the data for the efficacy of carotid artery stenting compared to carotid endarterectomy.

BACKGROUND

In the U.S., cerebrovascular disease is currently the third leading cause of death with more than 143,000 stroke-related fatalities in 2005.[3] Annually, there are almost 800,000 strokes and currently there are more than 6 million stroke survivors with varying degrees of disability.[3] In patients with acute stroke, angiography studies done within six hours of symptom onset have demonstrated that 75-80% of patients with an acute ischemic stroke have an angiographically visible occlusion of an extracranial and/or intracranial artery as its cause.[4]

Carotid Arterial Disease

Atherosclerotic stenosis of the carotid artery close to the carotid bifurcation in the neck causes about 20% of all ischemic strokes and transient ischemic attacks (TIAs).[5, 6] Antiplatelet therapy (e.g., with aspirin and / or clopidogrel) and warfarin have been employed for stroke prevention in patients with carotid stenosis.[7, 8] However, patients with recent symptoms associated with severe carotid stenosis have greater than a 20% risk of stroke in the following two years. Symptomatic patients are usually defined as individuals with transient ischemic attacks, unilateral transient monocular blindness (amaurosis fugax), or non-disabling stroke on the same side as the carotid artery stenosis. Currently, carotid endarterectomy is considered standard treatment for severe carotid artery stenosis.[9] In patients with symptomatic, severe (>70%) internal carotid artery stenosis, two large randomized clinical trials have demonstrated that carotid endarterectomy is more beneficial than medical therapy in reducing the risk of stroke.[10, 11] In addition, the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial demonstrated that carotid endarterectomy is beneficial in reducing the stroke risk for asymptomatic patients with significant carotid artery stenosis.[12] Carotid endarterectomy has been shown to normalize impaired cerebral hemodynamics.[13]

However, carotid endarterectomy surgery usually requires general anesthesia and involves incision of the neck, which can lead to cranial or superficial nerve injury and to wound complications. Carotid endarterectomy also carries a risk of stroke, sometimes disabling or fatal, and of myocardial infarction since many patients with carotid artery stenosis also have coronary artery disease.[5] Coexisting medical morbidities greatly influence outcomes of, and therefore decisions to undertake, carotid endarterectomy.[7] Advances in medical therapy since the ACAS trial, including statins, better blood pressure control, better control of diabetes, and new antiplatelet agents may make medical therapy more effective today than it was in the early 1990's, narrowing the window of benefit for surgical intervention, particularly in asymptomatic patients. Concerns also remain about whether the procedure is cost-effective and whether the results from selected centers and surgeons in the international trials can be generalized to justify its adoption by vascular surgeons in all centers.[14]

Carotid Artery Angioplasty and Stenting

Angioplasty of both coronary and non-coronary arteries was introduced in the 1970's. Initially, many surgeons had avoided carotid and cerebral artery angioplasty because of the potential of procedure-related stroke. Recently, however, angioplasty has been suggested as a safer and more cost-effective alternative to carotid endarterectomy in the management of significant carotid artery stenosis.[14, 15] Theoretical benefits include reduced morbidity rates, improved long-term patency rates and less anesthetic risks. [16]

Percutaneous transluminal angioplasty, also known as endovascular treatment, is an interventional procedure involving balloon dilatation of the atheromatous plaque or vasospasm narrowing the artery. Angioplasty is usually undertaken under local anesthesia, though general anesthesia standby may be needed for patient monitoring or management of complications. For example, angioplasty of the carotid bulb may precipitate symptomatic bradycardia, tachycardia or a profound vagal response. A temporary pacemaker may be needed if temporary complete heart block occurs. Systemic anticoagulation is usually started prior to the procedure and baseline angiography is performed to evaluate the diameter of the affected vessel. An angioplasty catheter is then introduced into the femoral artery in the groin and advanced to the site of arterial stenosis and the balloon inflated across the lesion. After balloon deflation, a second angiogram is then performed to assess residual stenosis. Additional balloon inflations may be needed. Anticoagulation is continued after the procedure.[17]

Recently, angioplasty has been combined with primary stenting of the artery to prevent plaque rupture, arterial dissection and acute occlusion of the blood vessel. In this procedure, a catheter carrying the stent, a tiny wire mesh tube, is inserted with the catheter into the femoral artery. From there, it is carefully threaded to the site of arterial narrowing in the neck or elsewhere. Once in proper position, the stent is mechanically expanded so that it can serve as a scaffold to prop open the artery.

With carotid angioplasty, transcranial Doppler recordings from the ipsilateral middle cerebral artery have shown that blood flow velocity can fall transiently during passage of the balloon catheter through the stenosis or during balloon deflation. However, after the procedure there was a significant improvement in blood flow, resulting in normalization of impaired hemodynamics similar to that seen after carotid endarterectomy.[13]

Carotid angioplasty with balloon dilatation and/or stenting is advantageous because it requires only local anesthetic for insertion of the catheter in the groin and because it avoids the need for surgical incision. While the procedure carries the risk of stroke, an early overview of the published results of carotid angioplasty by Brown et al.[18] suggested that the risk of major stroke approximately was as low as one percent in appropriately selected patients. At that time, he called for randomized trials to better define the risks and benefits of the procedure.

However, unlike carotid endarterectomy, carotid angioplasty/stenting does not remove the atheromatous plaque. Therefore, the long-term efficacy of these techniques in prevention of stroke is unknown. In coronary artery stenting, high in-stent restenosis rates led to the development of drug eluting stents.

Placement of a stent may compress large portions of the plaque against the arterial wall, but multiple small pieces of debris may escape through the stent and cause cerebral emboli. Recognition of the significance of this problem has led to the development of devices to provide distal embolization protection at the time of carotid artery angioplasty and stent deployment, although the value of distal embolization protection remains controversial.[19-26]

In addition, unlike with coronary or iliac artery angioplasty, acute occlusions of the carotid or intracerebral arteries are not amenable to emergency surgical correction. Furthermore, if restenosis occurs after stenting, the standard surgical approach of endarterectomy may be either impossible or substantially more difficult to perform because of the stent.[27] Finally, stent technology is rapidly evolving and the best currently available stent may soon be supplanted.[15, 27-32] Thus, carotid angioplasty/stenting has remained controversial (Beebe et al., 1996; Naylor et al., 1997; Beebe, 1998; Brown, 2001; Bladin, 2001) and many large, randomized trials have been launched to evaluate the procedure.[33-39]

TA Criterion 1: The technology must have the appropriate regulatory approval.

The procedure of Carotid Artery Stenting and Angioplasty does not require FDA clearance. However, the devices used in the procedure do. As of this date there are several manufacturers on carotid artery stents and embolic protection devices that have received FDA pre-market approval (PMA) for their devices.

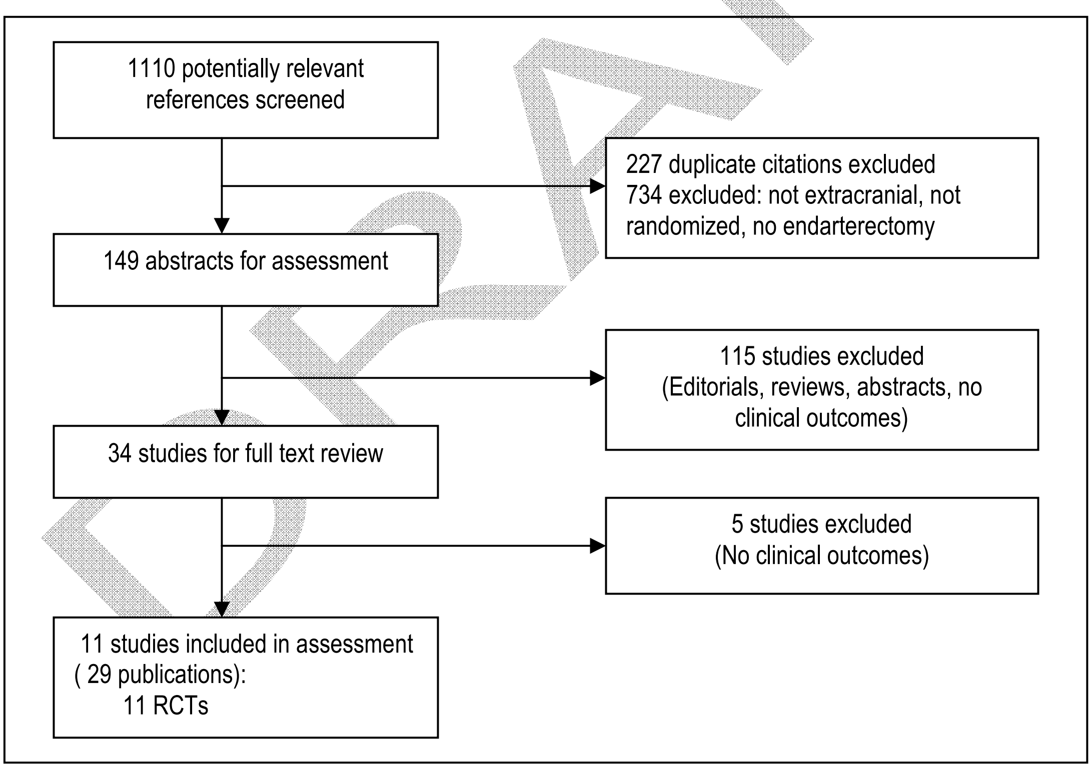
TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “Carotid Stenosis” or “Endarterectomy, Carotid.” These were cross-referenced with the keyword stents. The search was performed for the period from January 2005 through May 2009 to update the prior review. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Full details of the search terms are included in the Appendix. The Figure describes the search results. In brief, a total of 1110 references were reviewed (399 from Embase, 461 from PubMed, and 150 from the combined Cochrane databases). Many case-series and non-randomized trials were evaluated in the prior CTAF review.[40] The results from the large, prospective stent registries[41-59] were also reviewed recently.[60] Because of the strong evidence base for carotid endarterectomy in the treatment of carotid artery stenosis, the improvements in medical and surgical management over the past 20 years, and the sensitivity of procedural outcomes to patient characteristics, cohort studies cannot provide reliably unbiased results. For instance among the stent registries following 7919 patients treated with stents, the 30 day combined stroke, myocardial infarction (MI), and death rate varied from a low of 2.1% in one registry to a high of 8.5% in another.[60] It is difficult to compare such varied results to those of carotid endarterectomy. Thus, we included only randomized trials directly comparing carotid artery stenting to carotid endarterectomy in this review.

Figure: Selection of Studies for Inclusion in Review



The search identified multiple publications from eleven clinical trials that randomized 3,283 patients.[5, 14, 33, 34, 36, 61-78] This represents more than 2000 additional patients randomized since the prior CTAF review of this topic. These trials are summarized in Tables 1 through 4 below. Several of the new trials, though still less than half of the patients randomized used distal embolization protection with stenting. There are at least eight ongoing randomized trials[35, 37-39, 79] (Table 2A) comparing stents with distal embolization protection to carotid endarterectomy (http://www.strokecenter.org/trials/, http://www.ClinicalTrials.gov). These eight trials plan to randomize 15,680 patients with follow-up ranging from 12 to 60 months.

The indications for carotid or cerebral angioplasty have varied in published reports, as detailed below. Particular patient subgroups for which angioplasty/stenting might be particularly advantageous have not yet been fully defined[80], although it has been suggested that patients at high risk for surgical complications represent one such subgroup.[78]

The major clinical outcomes assessed in the various trials include the occurrence of neurological deficits, in particular, amaurosis fugax (transient visual loss), TIA, defined as a neurological deficit persisting <24 hours and stroke, defined as a deficit persisting >24 hours. Minor strokes have been defined as those causing minimal neurological deficit yet no loss of the patient's functional independence.[81] Major strokes have been defined as deficits that persisted beyond 30 days and that caused a change in the patient's lifestyle. Other outcomes include degree of residual stenosis on immediate post-angioplasty angiography, recurrence of carotid stenosis on follow-up Doppler ultrasonography or angiography and occurrence of procedure-related complications such as myocardial infarction, cranial nerve palsies, arrhythmias and bleeding complications. Complications have been defined as events or conditions that led to additional procedures or prolonged hospitalization.

Levels of Evidence: 1, 2

TA Criterion 2 is met.

TA Criterion 3: The technology must improve the net health outcomes.

Randomized Trials

High quality, randomized controlled trials provide the most reliable data for evaluating the effectiveness of carotid artery stenting. There is only one small randomized trial comparing stent placement with medical management.[82] Although it was underpowered, there was no trend towards a reduction in strokes among patients treated with carotid stenting compared with those treated with medical management alone. Descriptions of the eleven randomized trials comparing stent placement with carotid endarterectomy are summarized in Tables 1 through 4. Table 1 summarizes the quality of the trials. Table 2 describes details about the patients enrolled in the trials and includes descriptions of the eight ongoing clinical trials (Table 2A). Table 3 summarizes the primary outcomes and Table 4 describes procedural complications.

The prior CTAF review[40] described the first six trials in detail. Since that review, long-term follow-up of the SAPPHIRE trial was published[33] as were two new, large trials.[34, 61, 62, 74] Three additional small randomized trials have also been published and will be summarized briefly.[69, 71, 77]

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Table 1: Quality of the Randomized Clinical Trials Comparing Carotid Artery Stent Placement to Carotid Endarterectomy for Carotid Artery Stenosis

Study	Randomization	Allocation concealment	Comparable groups at randomization	Loss to follow-up comparable?	Blinded outcome assessment	Patient blinding	Co-interventions equivalent	ITT (lost to follow-up included?)	Overall quality
Naylor 1998 Leicester	Yes	Yes	NR	Yes	No	No	Yes	Yes	Fair
CAVATAS 2001 CAVATAS-CEA	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Fair
Alberts 2001 WALLSTENT	Yes	Yes	Yes CEA 4 years older	NR	NR	No	NR	NR	Poor
Brooks 2001 Kentucky 1 (Symp)	Yes	NR	Yes CEA 3 years older, less CAD (31% vs. 39%)	Yes	NR	No	NR	NR	Fair-poor
Brooks 2004 Kentucky 2 (Asymp)	Yes	NR	No: More CAD in stent group (35% vs. 20%)	NR	No	No	Yes	NR	Fair-poor
Yadav 2004, 2008 SAPPHIRE	Yes Non-inferiority	Yes	No: More CAD and prior PTCA in stent group – p<0.05, >10% absolute difference in prior PTCA, CABG, CAD	Yes for 1 year outcomes, not for 3 year outcomes	Partial Central blinded adjudication, but unblinded event identification	No	No Clopidogrel only in stent group	Yes	Fair Study terminated early due to slowed recruitment
Ling 2006 TESCAS-C	Yes	NR	NR	NR	NR	No	NR	NR	Poor due to limited reporting
Mas 2006, 2008 EVA-3S	Yes Non-inferiority	NR	No: CEA had more prior strokes (20% vs. 13%, P=0.02) and more subjects older than 75 (20% vs. 13%), but fewer contralateral occlusions (1.2% vs. 5%)	Yes	Yes	No	No More anticoagulation and dual antiplatelet therapy in the stent group	Yes in 2008 publication	Fair Terminated early due to excess strokes in stent group
2006; Eckstein 2008 SPACE	Yes Non-inferiority	Yes	Yes	Yes	Partial	No	No 100 mg ASA in both, 75 mg clopidogrel in stent group only	Yes in 2008 publication	Fair
Hoffmann 2008 BACASS	Yes	Yes	No: large differences in % with prior stroke and % with amaurosis fugax	Yes	NR	No	No Clopidogrel only in stent group	Yes	Fair-poor
Steinbauer 2008	Yes	NR	Yes	Yes	NR	No	Yes	Yes	Fair

CEA Carotid endarterectomy
CAD Coronary artery disease
SAPPHIRE Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
PTCA Percutaneous transluminal coronary angioplasty
CABG Coronary artery bypass graft surgery
EVA-3S Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis Trial
SPACE Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy
ASA Aspirin

Table 2: Description of the Procedures and Participants in the Randomized Clinical Trials Comparing Carotid Artery Stent Placement to Carotid Endarterectomy for Carotid Artery Stenosis

Study	Indication	Device DEP?	Co-intervention	N	Follow-up for primary outcome	Age, yrs Sex, %F	Primary outcome	Inclusion criteria	Exclusion criteria	Comment
Naylor 1998 Leicester	Symptomatic	Wallstent No	ASA not stopped	23 Early termination	30 days	67 47%	Stroke + death	70-90% ICA stenosis by U/S	Stroke in evolution Crescendo TIA's Non-hemispheric symptoms	Single center. Mean stenosis 82%. Stopped early due to harm.
CAVATAS 2001 CAVATAS-CEA	Symptomatic (97%)	Angioplasty + 55 stents (Wallstent & Palmaz No	ASA ≥ 150 mg + heparin	504	36 months	67 30%	Ipsilateral disabling stroke + death	"Stenosis requiring intervention amenable to surgery or endovascular…"	Disabling stroke. Thrombus. Severe intracranial arterial stenosis.	Multicenter.
Alberts 2001 WALLSTENT	Symptomatic CAS	Wallstent No	ASA 325 bid Ticlopidine 250 bid For 4 weeks	219 Early termination	12 months	68 36%	Ipsilateral stroke + death	60-99% stenosis by angiogram.	NR	Stopped early for harm. Planned n = 700
Brooks 2001 Kentucky 1 (Symp)	Symptomatic CAS	Wallstent No	ASA 325 + Clopidogrel 75 Heparin in stent arm	104	NR	68 NR	NR	>70% stenosis by NASCET criteria Life expectancy > 5 years	Disabling stroke Recent intracranial hemorrhage	Single center.
Brooks 2004 Kentucky 2 (Asymp)	Asymptomatic CAS	Wallstent or Dynalink No	ASA 325 + Clopidogrel 75 Heparin in stent arm	85 Early termination	48 months	68 NR	NR	>80% stenosis by NASCET criteria Life expectancy > 5 years	Arrhythmia Allergy to ASA, Clopidogrel, heparin	Single center.
Yadav 2004, 2008 SAPPHIRE	Asymptomatic (238/334 = 71%) Symptomatic (96/334 = 29%) "High" risk for surgical complication and Symptomatic > 50% or asymptomatic > 80%	Cordis Precise or Smart stent with Angioguard or Angioguard XP Yes	Clopidogrel 75 starting 24 hours prior to procedure for 2-4 weeks total in stent group. ASA 81 or 325 starting 72 hours prior to procedure in both groups – continued indefinitely. Intraprocedural heparin in both groups.	334 Early termination	12 months	73 33%	Stoke + MI + death	At least one "high risk" factor >18 years old ≥50% stenosis symptomatic or ≥80% stenosis asymptomatic by U/S	CVA in past 48 hours Thrombus present 100% occlusion Unable to use catheter ≥2 stents needed h/o bleeding disorder Surgery planned w/I 30 days Life expectancy < 1 year Osteal lesion	Multicenter <u>"High Risk"</u> Significant CHD Significant pulmonary disease Contralateral carotid occlusion Contralateral recurrent laryngeal nerve palsy Prior radical neck surgery or radiation Prior endarterectomy on this artery Age ≥ 80
Ling 2006 TESCAS-C	Symptomatic + asymptomatic CAS Unknown %	NR	NR	166	6 months	NR	30 day Stoke + MI + death + strokes through 6 months	"Severe" stenosis	NR	Multicenter, China Only abstract translated. Paper is in Chinese.

Study	Indication	Device DEP?	Co-intervention	N	Follow-up for primary outcome	Age, yrs Sex, %F	Primary outcome	Inclusion criteria	Exclusion criteria	Comment
Mas 2006, 2008 EVA-3S	Symptomatic CAS	Multiple Yes (except for 38 subjects = 14%)	100 to 300 mg ASA plus 500 mg ticlopidine or 75 mg clopidogrel 3 days prior to procedure and 1 month after in stent arm only	527 Early termination	48 months	70 25%	Ipsilateral stroke + death	>60% TIA or Ischemic stroke within 4 months	Disabling stroke Non-atherosclerotic carotid disease Severe intracranial carotid stenosis Contraindication to heparin, ticlopidine, or clopidogrel Life expectancy < 2 years	Multicenter, France. Stopped early for harm. Planned n = 900
2006; Eckstein 2008 SPACE	Symptomatic CAS	Multiple Yes (27%) No (73%)	100 mg ASA for all 75 mg/d clopidogrel x 33 days for stent arm	1214 Early termination	24 months	68 28%	Ipsilateral stroke + death	>50% by angiogram or 70% by U/S Age > 50 years	Pregnant Intracranial bleeding within 90 days of randomization Arteriovenous malformation or aneurysm Life expectancy < 2 years Contraindication for heparin, ASA, clopidogrel, or contrast media	Multicenter, Europe. Stopped early for harm \ futility. Planned n = 1900
Hoffmann 2008 BACASS	Symptomatic CAS	Wallstent Yes	ASA + clopidogrel for stents “Antiplatelet therapy” for CEA	20	48 months	70 15%	30 day Stoke + MI + death + strokes through 48 months	> 70% stenosis	Unable to FU for 2 years ICA occlusion Arteriovenous malformation or aneurysm Life expectancy < 2 years Contraindication for heparin, ASA, clopidogrel, or contrast media	Single center Low power
Steinbauer 2008	Symptomatic CAS	Wallstent No	All subjects: 100 mg ASA + 75 mg clopidogrel x 1 month, then 300 mg ASA indefinitely	87	12 months Median 65 months	68 NR	30 day Stoke + MI + death + strokes through 12 months	> 70% stenosis	NR	Single center Low power

CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CAS	Carotid artery stenosis
NR	Not reported
NASCET	North American Symptomatic Endarterectomy Trial
CVA	Cerebral vascular accident
CHD	Coronary heart disease
TESCAS-C	Trial of endarterectomy versus stenting for the treatment of carotid atherosclerotic stenosis in China

Table 2A: Description of the Procedures and Participants in the Ongoing Randomized Clinical Trials Comparing Carotid Artery Stent Placement to Carotid Endarterectomy for Carotid Artery Stenosis

Study Year started	Indication	Device DEP?	Co-intervention	N	Follow-up for primary outcome	Primary outcome	Inclusion criteria	Exclusion criteria	Comment
Ongoing trials									
Link 1999	Symptomatic	Stents		200	?	30 days Stoke + MI + death	> 70% stenosis Ages 40-79 years	> 70% stenosis in contralateral carotid artery	
CREST 2000	Symptomatic (1326) and asymptomatic (1196)	ACCULINK Yes	ASA + clopidogrel + anti-hypertensives	2522	48 months	30 days Stoke + MI + death and stroke through 4 years	>50% by angiogram or 70% by U/S	Comorbidities interfering with evaluation endpoints CEA or CAS contraindicated Life expectancy < 4 years	Mulitcenter, U.S.- NIH funded trial.
ICSS /CAVATAS-2 2001	Symptomatic	Stent Yes		1700	60 months	30 days Stoke + MI + death and stroke through 3 years	≥ 70% Suitable for stenting or endarterectomy, No contraindication to either treatment	Major stroke Thrombus at site Life expectancy < 2 years	Multicenter, international
ACT-1 2005	Asymptomatic	EXACT Stent Yes		1858	12 months	30 days stroke + MI + death and ipsilateral strokes through 1 year	Severe carotid artery disease	Symptoms in the last 180 days High risk for surgery	Multicenter.
ACST-2 2006	Asymptomatic	Stents Yes		5000	12 months	30 days Stoke + MI + death and stroke through 1 year			UK
Comparing Carotid Stenting With Endarterectomy in Severe Asymptomatic Carotid Stenosis 2009	Asymptomatic	Stent Yes		500	24 months	30 days Stoke + MI + death and stroke through 2 years	> 70% stenosis Age 18-79		US
Agostini ?	Symptomatic	Stents		400	24 months	30 days Stoke + MI + death and stroke through 2 years			Italy
TACIT ?	Asymptomatic	Stents Yes	"Best" medical care	3500	60 months	30 days Stoke + MI + death and stroke through 5 years	>60% by U/S Age 18-79	Atrial fibrillation EF < 30%	3 arms: medical care, CEA, stent + DEP. Multicenter, international

Table 3: Outcomes and adverse events in the randomized clinical trials comparing carotid artery stent placement to carotid endarterectomy for carotid artery stenosis

Study	Procedure	N stent / N CEA	30 day			1 year			Restenosis (≥70%)	30 day stroke or death	30d plus 6 month ipsilateral stroke	30d plus 1 year ipsilateral stroke
			Stroke	MI	Death	Stroke	MI	Death				
Naylor 1998	Stent	7	5 (45%)	NR	0 (0%)	NR	NR	NR	NR	45%	NR	NR
Leicester	Endarterectomy	10	0 (0%)	NR	0 (0%)					0%		
CAVATAS 2001	Angioplasty or Stent	251	18 (7.1%)	0 (0%)	7 (2.8%)	NR	NR	NR	14%	10%	11%	12%
CAVATAS-CEA	Endarterectomy	253	21 (8.3%)	3 (1.2%)	4 (1.6%)				4%	10%	11%	12%
Alberts 2001	Stent	107	NR	NR	NR	4%	NR	NR	NR	12%	NR	12%
WALLSTENT	Endarterectomy	112				1%				4.5%		4%
Brooks 2001	Stent	53	0 (0%)	NR	0 (0%)	NR	NR	NR	NR	0%	NR	NR
Kentucky 1 (Symp)	Endarterectomy	51	0 (0%)		1 (2%)					2%		
Brooks 2004	Stent	43	0 (0%)	NR	0 (0%)	NR	NR	NR	NR	0%	NR	NR
Kentucky 2 (Asymp)	Endarterectomy	42	0 (0%)		0 (0%)					0%		
Yadav 2004, 2008	Stent	167	6 (3.6%)	4 (2.4%)	2 (1.2%)	10 (6.2%)	5 (3.0%)	12 (7.4%)	0.6%	5%	NR	12%
SAPPHIRE	Endarterectomy	167	5 (3.1%)	10 (6.1%)	4 (2.5%)	12 (79%)	10 (6.2%)	21 (13.5%)	4.3%	5%		20%**
Ling 2006	Stent	82	NR	NR	NR	NR	NR	NR	NR	NR	10%	NR
TESCAS-C	Endarterectomy	84									12%	
Mas 2006, 2008	Stent	261	23 (8.8%)	1 (0.4%)	2 (0.8%)	NR	NR	NR	NR	9.6%	10%	NR
EVA-3S	Endarterectomy	259	7 (2.7%)	2 (0.8%)	3 (1.2%)					3.9%	4.2%	
2006; Eckstein 2008	Stent	607	44 (7.2%)	NR	6 (1.0%)	NR	NR	NR	11%	6.9%	8.1%	NR
SPACE	Endarterectomy	589	37 (6.3%)		5 (1.0%)				4.6%	6.5%	6.8%	
Hoffmann 2008	Stent	10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	0 (0%)	0%	0%	NR	0%
BACASS	Endarterectomy	10	1 (10%)	0 (0%)	0 (0%)	0 (0%)		1 (10%)	0%	10%		20%
Steinbauer 2008	Stent	43	0 (0%)	NR	NR	1 (2.3%)	0 (0%)	0 (0%)	19%	NR	NR	1 (2.3%)
	Endarterectomy	44	0 (0%)			0 (0%)	1 (2.3%)	0 (0%)	0%			0 (0%)

* Follow-up for primary endpoint

** Includes 30 day MI rate

CREST Carotid Endarterectomy vs. Stent Trial
ICSS International Carotid Stenting Study
ACT-1 Asymptomatic Carotid Stenosis, Stenting versus Endarterectomy Trial
TACIT Transatlantic Asymptomatic Carotid Intervention Trial.
ACST Asymptomatic Carotid Surgery Trial

Table 4: Early Complications in the Randomized Clinical Trials Comparing Carotid Artery Stent Placement to Carotid Endarterectomy for Carotid Artery Stenosis

Study	Procedure	N stent N CEA	Wound infection	Cranial nerve injury	Hematoma or vascular complication	Bradycardia	Hemodynamic instability
Naylor 1998	Stent	11	NR	0 (0%)	NR	NR	NR
Leicester	Endarterectomy	12	NR	0 (0%)	NR	NR	NR
CAVATAS 2001	Stent	251	NR	0 (0%)	3 (1)	NR	NR
CAVATAS-CEA	Endarterectomy	253	NR	22 (8.7%)	17 (7)	NR	NR
Alberts 2001	Stent	107	NR	NR	4%	7%	NR
WALLSTENT	Endarterectomy	112	NR	NR	NR	NR	NR
Brooks 2001	Stent	53	NR	0 (0%)	3 (6)	7 (14)	12 (24)
Kentucky 1 (Symp)	Endarterectomy	51	NR	4 (7.8)	1 (2)	0 (0)	3 (6)
Brooks 2004	Stent	43	NR	0 (0%)	0 (0)	5 (12)	NR
Kentucky 2 (Asymp)	Endarterectomy	42	NR	0 (0%)	0 (0)	0 (0)	NR
Yadav 2004, 2008	Stent	167	NR	0 (0%)	2 (1.2)	NR	NR
SAPPHIRE	Endarterectomy	167	NR	8 (4.8%)	1 (0.6)	NR	NR
Ling 2006	Stent	82	NR	NR	NR	NR	NR
TESCAS-C	Endarterectomy	84	NR	NR	NR	NR	NR
Mas 2006, 2008	Stent	261	1 (0.4%)	3 (1.1%)	9 (3.4%)	0 (0%)	NR
EVA-3S	Endarterectomy	259	1 (0.4%)	20 (7.7%)	2 (0.8%)	11 (4.2%)	NR
2006; Eckstein 2008	Stent	607	NR	NR	NR	NR	NR
SPACE	Endarterectomy	589	NR	NR	NR	NR	NR
Hoffmann 2008	Stent	10	NR	0 (0%)	NR	NR	NR
BACASS	Endarterectomy	10	NR	0 (0%)	NR	NR	NR
Steinbauer 2008	Stent	43	0 (0%)	0 (0%)	1 (2.3%)	NR	NR
	Endarterectomy	44	1 (2.3%)	1 (2.3%)	6 (14%)	NR	NR

SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial[78] was a non-inferiority trial that randomized 334 patients to either carotid endarterectomy or stenting with the Smart or Precise stent in combination with either the Angioguard or Angioguard XP filter for embolization protection. The study randomized both symptomatic patients with at least 50% carotid artery stenosis and asymptomatic patients with at least 80% carotid artery stenosis. All patients were "high risk", defined as having at least one risk factor that was believed to increase the risk for complications with carotid endarterectomy. These high risk conditions included significant coronary heart disease, significant pulmonary disease, 100% occlusion of the contralateral carotid artery, previous radical neck surgery or radiation, prior carotid endarterectomy of the affected artery, laryngeal nerve palsy or age > 80 years. Patients were excluded if they had a stroke in the 48 hours prior to randomization, had thrombus at the site of stenosis, required more than two stents, had a life expectancy less than one year or had other contraindications to either surgery or stenting. All patients received aspirin starting at least 72 hours prior to the procedure and heparin during the procedure. Only patients randomized to the stent arm received clopidogrel starting 24 hours prior to the procedure and continuing for two to four weeks. A central committee blinded to treatment assignment assessed outcomes. The primary outcome was defined as the rate of major cardiovascular events at one year: any stoke, MI or death within 30 days of the procedure plus any subsequent ipsilateral stroke or death. This was the first stroke prevention trial to include MI as part of the primary outcome, but it makes sense when comparing a potentially less stressful procedure to a more invasive one in patients at high risk for vascular events. Unfortunately, enrollment in the study was terminated early because recruitment slowed significantly. The authors wrote that this slowing was due to the opening of multiple stent registries allowing patients to be treated at other sites. The original design planned to enroll as many as 2,400 patients. Planned follow-up included patient examinations at 30 days, six months, 12 months, 24 months and 36 months. The original publication reported on outcomes through one year of follow-up.[78] The three year outcomes were recently published.[68]

A total of 334 patients were randomized (mean age 73, 33% female). An additional 406 patients were considered not to be surgical candidates and were enrolled in a stent registry. The definition of "not a surgical candidate" was left to the discretion of the local surgeon. It is noteworthy that more patients were considered "not surgical candidates" than were randomized in the study. Similarly, seven patients were considered no to be candidates for stent placement and were enrolled in an endarterectomy registry. Of the 167 patients randomized to the stent arm, 159 received the stent as randomized. Similarly, of the 167 patients randomized to endarterectomy, 151 actually had the surgery. Outcomes were analyzed by strict intention-to-treat. The primary outcome (major cardiovascular event) at one year was more common in the endarterectomy arm (20% vs. 12%, p=0.053). Cranial nerve palsy (5% vs. 0%) and target vessel revascularization (4.3% vs. 0.6%) were also more common in the endarterectomy arm. Length of stay (2.8 vs. 1.8 days) and 30-day event rates (10% vs. 5%) also favored the stenting arm. Other adverse events, such as wound infections, bradycardia and hemodynamic instability were not reported.

Among the symptomatic patients there was no difference in the primary outcome at one year of follow-up (16.5% for endarterectomy compared with 16.8% for stenting). Outcomes at 30 days were more common in the endarterectomy arm (9% vs. 2%), but outcomes during subsequent follow-up were less common in the endarterectomy arm (7% vs. 14%). Among the asymptomatic patients, the primary outcome (major cardiovascular event) at one year was more common in the endarterectomy arm (22% vs. 10%) as were events at 30 days (10% vs. 5%). A test for interaction between symptomatic status and randomization status was not significant (p= .55), but the study was not powered to test this potentially very important interaction.

At three years, data were available for 260 patients (86% of patients in the stenting group, 70% of those in the endarterectomy group). The prespecified endpoint for this analysis, 30 day stroke, MI or death plus ipsilateral stroke or death through three years occurred in 41 subjects in the stenting group (cumulative incidence 24.6%) and 45 subjects in the endarterectomy group (cumulative incidence 26.9%, p = 0.71). There were no significant differences between the two groups on any outcome, but the trend favored endarterectomy for total mortality, major ipsilateral and nonipsilateral strokes, MI's, and target vessel revascularization.

The SAPPHIRE trial has several important limitations. The mix of symptomatic and asymptomatic patients with possible important differences in outcomes makes the interpretation and generalizability of the results problematic. If the first year trend in long-term post-procedural outcomes in symptomatic patients continued (7%/year in patients receiving endarterectomy vs. 14%/year in patients receiving stents), stents should not be used in symptomatic patients. The differential loss to follow-up by three years (14% vs. 30%, p = 0.0006) raises the possibility of significant bias in the results, even though Kaplan-Meier analysis was performed. The landmark studies demonstrating benefit to carotid endarterectomy focused on either symptomatic (ECST, NASCET) or asymptomatic patients (ACAS, ACST) and followed a much larger number of patients for three to five years with the benefits of endarterectomy not being evident until at least two years of follow-up. Longer follow-up results in larger groups of patients with more detail on outcomes by symptom status will be essential to have confidence in the benefits of carotid artery stenting in this group of high risk patients. At least one of the high risk criteria, age, has been called into question with subgroup analyses within the SPACE and EVA-3S trials described below. The relatively short follow-up combined with the small samples in each of the symptom groups due to early closure of enrollment leave the SAPPHIRE trial with insufficient power to clearly define the appropriate target group for the use of stents.

A more important criticism is that differential co-interventions may explain the difference in outcomes. Only patients in the stenting arm received clopidogrel and this intervention alone could explain the reduction in peri-operative heart attacks, as well as potentially fewer ischemic events during follow-up. Several randomized clinical trials have suggested that clopidogrel alone or in combination with aspirin is more effective than aspirin alone at preventing strokes and/or myocardial infarctions.[83-88]

EVA-3S: Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis

The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was a non-inferiority trial that randomized 527 symptomatic patients to either carotid artery stenting or carotid endarterectomy.[73, 74] The investigators used a variety of different stents and distal embolization protection devices. The trial stopped recruitment early because of safety and futility. In January 2003, the safety committee recommended the use of cerebral protection devices in all stenting procedures to reduce the risk of periprocedural stroke. Distal protection was used in 227/261 (87%) stenting procedures. The study randomized symptomatic patients with at least 60% carotid artery stenosis. Patients were excluded if they had a prior disabling stroke, prior revascularization, unstable angina, a life expectancy less than two years, or had other contraindications to surgery, stenting, heparin, aspirin, clopidogrel, or ticlopidine. Subjects randomized to the stent arm received aspirin and either clopidogrel or ticlopidine starting three days prior to the procedure and continuing for 30 days after stenting. A central committee blinded to treatment assignment adjudicated outcomes. The primary outcome was any stoke or death within 30 days of the procedure. The original design planned to enroll approximately 900 patients based on an anticipated 30-day incidence of stroke or death of 5.6% after endarterectomy and 4% after stenting.

A total of 527 patients were randomized (mean age 70, 25% female). Three patients randomized to endarterectomy did not undergo surgery: one declined, one had a stroke prior to surgery, and one had a carotid occlusion; two of the three eventually were treated with stents. Similarly, four patients randomized to stenting did not: undergo stenting as one declined, two had stenoses less than 60%, and one had a stroke prior to the procedure; one eventually had an endarterectomy. An additional 13 subjects randomized to stenting were converted to endarterectomy during the procedure. There were some baseline differences between the two groups. The endarterectomy group had more prior strokes (20.1% vs. 12.6%, p=0.02) and a trend towards more men over the age of 75 years (40.5% vs. 32.2%, p=0.06), although their average age was only greater by 1.2 years (p=0.21). Outcomes were analyzed by strict intention-to-treat. The primary outcome (stroke or death at 30 days) was more common in the stenting group (9.6% vs. 3.9%, RR 2.5, 95% CI 1.2-5.1, p=0.01). Bradycardia or hypotension (4.2% vs. 0%, p<0.001) and local complications such as infection, arterial occlusion, and pseudoaneurysm formation (3.1% vs. 1.2%, p NS) were also more common in the stenting group. Cranial nerve palsy (1.1% vs. 7.1%, p < 0.001) and MI's (0.4% vs. 0.8%, p NS) were more common in the endarterectomy arm.

The investigators recently reported outcomes through four years.[74]. Median follow-up was 42 months for the stenting group and 43 months for the endarterectomy group. At that time 29 patients in the stenting group (cumulative incidence 11.1%) and 15 patients in the endarterectomy group (cumulative incidence 6.2%) had an ipsilateral stroke through four years or any stroke or death in the first 30 days (RH 1.97, 95% CI 1.06-3.67). Per protocol analyses and the results for disabling stroke or death were similar. Most of the excess events in the stenting group appeared during the 30 days following the procedure. The 4-year rates of ipsilateral strokes after 30 days (1.26% stenting group vs. 1.97% endarterectomy, RH 0.75, 95% CI 0.17-3.37) and any stroke after 30 days (4.49% stenting group vs. 4.94% endarterectomy, RH 1.02, 95% CI 0.42-2.44) were similar in the two groups. This provides good evidence that the long-term efficacy of stenting is comparable to endarterectomy, though the confidence intervals are wide.

The investigators also performed subgroup analyses to try to identify patients who might benefit more from one or the other of the procedures. Men (HR ~3, p for interaction 0.03), patients 70 years and older (HR ~3, p for interaction 0.08), patients with prior strokes (HR ~5.2, p 0.12), and patients with time from qualifying event to treatment less than two weeks (HR ~6.5, p 0.40) seemed to have better results with carotid endarterectomy. Women and patients presenting with ocular symptoms were the only subgroups with hazard ratios favoring stenting and both were very close to one. These analyses were exploratory and the results should be considered preliminary and in need of validation in other trials.

There were several issues with the EVA-3S study. First, the inconsistent use for distal embolization protection makes it difficult to generalize the results. The investigators did briefly report subgroup analyses with and without use of protection. The 30-day stroke or death rate was lower when using distal embolization protection (18/227 = 7.9% versus 5/20 = 25%, p=0.03). However, the relative number of events occurring in the endarterectomy group also decreased after distal embolization protection was recommended. Prior to requiring protection the relative risk of stroke or death for stenting relative to endarterectomy was 2.0, 95% CI 0.8 to 5.0) and after protection was required the relative risk was 3.4, 95%

CI 1.1 to 10.0). The baseline imbalances in prior strokes and age potentially biased the results against endarterectomy, though the ultimate findings favored endarterectomy. Finally, terminating a trial early because of harm usually exaggerates the true magnitude of harm. Given those caveats, the authors still conclude that endarterectomy results in lower rates of stroke and death at 30 days than stenting for patients with symptomatic carotid artery stenosis.

SPACE: Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial is the largest (n=1214) of the published randomized trials of carotid artery stenting.[34, 62] It was also designed as a non-inferiority trial. The investigators in this trial also used variety of different stents and distal embolization protection devices. Distal embolization protection was used for 151 patients (27%) treated with stenting.

The study randomized symptomatic patients over the age of 50 years who had at least 70% carotid artery stenosis. Patients were excluded if they had a prior revascularization, planned surgery, a life expectancy less than two years, or had other contraindications to surgery, stenting, heparin, aspirin, or clopidogrel. Subjects randomized to the stent arm received aspirin and either clopidogrel or ticlopidine starting three days prior to the procedure and continuing for 30 days after stenting. A central committee that may have been blinded to treatment assignment adjudicated outcomes, though this was not explicitly stated. The primary outcome was any ipsilateral stoke or death within 30 days of the procedure. The trial stopped recruitment early because of futility and limited funding when it was determined that a total of approximately 2500 patients would need to be randomized to prove noninferiority.

A total of 1214 patients were randomized (mean age 68, 28% female). Eighteen patients withdrew consent between randomization and treatment (six in stenting group, 12 in endarterectomy group). These patients were excluded from the intention to treat analyses. The investigators also classified an additional 60 patients with severe protocol violations; they were included in intention-to-treat analyses, but excluded from per-protocol analyses. In the stenting group, 34 subjects had severe protocol violations including one with an event prior to surgery, one treated by a non-certified provider, 13 receiving therapy outside the trial, and at least 14 treated with endarterectomy. Similarly, in the endarterectomy group, 26 subjects had severe protocol violations including three with events prior to surgery, 19 receiving therapy outside the trial, and at least six treated with stenting.

There were no important differences between the groups at randomization. The primary outcomes (ipsilateral stroke or death at 30 days, intention to treat analysis) were similar in the two groups (6.9% vs. 6.5%, RR 1.07, 95% CI 0.70-1.63). Similar results were found for with non-significant trends in favor of endarterectomy for all combinations of ipsilateral stroke, any stroke, and death. The per protocol analyses found larger differences in favor of endarterectomy. Ipsilateral cerebral bleeding was less common in the stenting group (0.3% vs. 1%, p NS). Other outcomes, such as procedural complications were not reported.

The investigators recently reported outcomes through two years[34]. Two year visit data was complete for 89% of patients in both groups. The Kaplan-Meier estimates for 30 day events plus ipsilateral strokes through two years did not differ (9.5% versus 8.8%, HR 1.10, 95% CI 0.75-1.61, p=0.62) with the per protocol analysis even more strongly favoring the endarterectomy group. A series of secondary clinical outcomes were analyzed, including ipsilateral strokes between days 31 and two years (excluding peri-procedural events), and all favored endarterectomy, though none of the differences were statistically significant. Of note, the rate of recurrent stenosis greater than 70% was significantly greater in the stenting group at two years (10.7% versus 4.6%, p=0.0009). Only two of the recurrent stenoses led to symptoms, but raise concerns about the long-term efficacy of stenting compared with endarterectomy.

The SPACE investigators also performed subgroup analyses to try to identify patients who might benefit more from one or the other of the procedures. The only significant interaction was with age at randomization: patients 68 years and older had significantly worse outcomes with stenting (HR for older subjects 1.80; for younger subjects 0.54, p for interaction 0.004). This confirms the similar observation in the EVA-3S study: that older patients seem to do worse with stenting. Several of the other potential subgroup interactions seen in the EVA-3S study (sex, prior strokes, ocular symptoms) trended in the opposite direction in the SPACE study highlighting the uncertainties inherent in post-hoc analyses.

Once again, the inconsistent use of distal embolization protection makes it difficult to generalize the results of the SPACE study. No subgroup analyses based on distal embolization protection were reported. And, as in the EVA-3S trial, early termination may have exaggerated the true magnitude of harm. However, in this largest of the randomized trials of carotid artery stenting, the investigators failed to prove the non-inferiority of stenting to endarterectomy. Moreover, restenosis rates at two years were clearly greater in the stenting group.

Small trials

The remaining three trials were all small trials in symptomatic patients and were incompletely reported. The Chinese trial (TESCAS-C) was published in Chinese, with only the abstract translated into English.[71] Trial methodology and details of the interventions were unavailable. They reported that the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the surgical intervention, or death or ipsilateral stroke between 31 days and six months was 9.8% in the stenting group and 11.9% in the endarterectomy group (p NR). However, their secondary end point (complications of either intervention or severe restenosis at six months) was more common in the stenting group (cumulative incidence, 22.0 percent versus 19.1 percent, p NR). The BACASS trial only randomized 20 patients, but reported no outcomes in the stenting group and two outcomes after four years of follow-up in the endarterectomy group (20%, p NS).[69] No significant restenoses was reported in either arm during the four years. Finally, Steinbauer et al. reported the results of a single center trial of stenting without distal embolization protection that had a median of 65 months of follow-up.[77] Outcomes at one year were low in both groups (2.3% stenting versus 0% endarterectomy for all 30 day results plus one year ipsilateral strokes). However, over the full follow-up period, restenosis rates were much higher in the stenting group (19% vs. 0%, p=0.023) as was the rate of re-intervention (16% versus 0%, p=0.027) and ipsilateral stroke (10% versus 0%, p=0.041). Taken together, data from these trials are inconsistent, but the long-term follow-up data continue to raise concerns about higher rates of restenosis in the stenting groups.

Pending Trials

As noted under TA criterion 2 and described in Table 2A, there are at least eight pending randomized trials of stenting for carotid artery disease. The studies plan to randomize over 15,000 patients in these trials, several of which have completed recruitment. Three of the trials are enrolling patients with symptomatic carotid artery stenosis, four are enrolling asymptomatic patients, and one is enrolling both. At least six of the trials are using stents in combination with distal embolization protection devices. Planned follow-up in the trials ranges between one and five years.

A major NIH-sponsored multicenter randomized trial called the Carotid Revascularization Endarterectomy versus Stent Trial (CREST) has randomized 2522 patients. The trial compares the efficacy of carotid stenting using a single extending system (ACCULINK, Guidant, Temecula, CA) versus endarterectomy in symptomatic patients with carotid stenosis.[89-91] Primary outcome measures are stroke, myocardial infarction, or death during a 30-day peri-procedural period, or ipsilateral stroke over a follow-up period extending up to four years. The primary eligibility criterion is a significant carotid artery stenosis (≥70% by ultrasound or ≥50% by angiography) in patients with TIA or ipsilateral nondisabling stroke within the prior 180 days. Patients with medical conditions likely to limit their participation during the follow-up or to interfere with outcome evaluation will be excluded.

Summary

The two largest randomized trials of carotid stenting in symptomatic patients failed to prove non-inferiority of carotid stenting compared to endarterectomy.[34, 36, 62, 74] Both had trends towards better outcomes with endarterectomy and in one of the two, the differences were statistically significant. The SAPPHIRE trial was smaller and randomized both symptomatic and asymptomatic patients at high risk for surgical complications.[78] The investigators used distal embolization protection for all patients. This study provided evidence for better outcomes with stenting compared with carotid endarterectomy after one year follow-up in high-risk patients. Most of the benefit was due to a reduction in perioperative heart attacks in asymptomatic patients. The results appeared stable for three years, although there was differential loss to follow-up between the two treatment groups.[68] A major concern is that the rates of significant restenosis (≥70%) has been higher in the stenting groups in several of the clinical trials, including the largest.[34, 67, 77]

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Carotid endarterectomy is the established alternative to carotid angioplasty/stenting for treatment of high-grade stenosis of extracranial carotid arteries. The strongest evidence for benefit for the treatment of symptomatic patients; carotid endarterectomy also has been shown to reduce the risk of stroke in asymptomatic patients with significant carotid artery stenoses, but the net benefit is smaller and is dependant upon low perioperative complication rates.

In comparative trials, Crawley et al.[92, 93] found that there were significantly more microembolic signals during carotid angioplasty than during endarterectomy, though there was no correlation with peri-procedural stroke[93] or neuropsychological outcomes.[92] The current standard is to use distal embolization protection when performing angioplasty/stenting. However, there is still controversy about the best way to minimize embolization and evidence of greater microembolization with stenting and embolization protection compared to carotid endarterectomy.[19, 21, 94-96] Using such devices makes the procedure more technically demanding and there is conflicting clinical trial literature on the clinical benefits. For instance, in the EVA-3S trial, which started requiring use of the distal embolization protection partway through the trial, the 30-day incidence of stroke or death was higher in procedures not using the device compared to procedures with the device (25% vs. 7.9%, p=0.03). However, the relative risk for 30-day stroke or death compared with endarterectomy was higher after distal embolization protection was recommended (3.4, 99% CI 1.1 - 10) compared to the prior period (relative risk (RR) 2.0, 95% CI 0.8 – 5.0).[73]

The most recent Cochrane meta-analysis[97] summarized the results of ten randomized trials comparing carotid stenting to endarterectomy. They found that the rate of cranial neuropathy was significantly lower with stenting (OR 0.16, 95% CI 0.09-0.28) and that there was a potentially important trend towards fewer myocardial infarctions (OR 0.24, 95% CI 0.05-1.04). However, the stroke and mortality outcomes all favored carotid endarterectomy. The rate of ipsilateral strokes at six months plus 30-day stroke and mortality rate was significantly higher for patients treated with stenting (OR 1.53, 95% CI 1.14-2.05). The 30-day perioperative rates for death (OR 1.14, 95% CI 0.54-2.40), stroke or death (OR 1.53, 95% CI 0.89-2.62), disabling stroke or death (OR 1.30, 95% CI 0.87-1.96), and stroke, MI or death (OR 1.37, 95% CI 0.91-2.08) all favored carotid endarterectomy, although none achieved statistical significance. The authors concluded that the evidence does not support changing clinical practice from carotid endarterectomy as the treatment of choice for carotid artery stenosis.

The majority of randomized patients included in the meta-analysis were symptomatic, so the results apply primarily to that patient group. Only one small randomized trial (n=85) studied exclusively asymptomatic patients and there were no events in that trial.[66] In addition, the SAPPHIRE trial randomized predominantly asymptomatic patients (238/334, 71%), but there was insufficient power to determine if differences in outcomes between symptomatic and asymptomatic patients was real (p for interaction 0.55).

In summary, for symptomatic patients, the comparative trials suggest that carotid artery stenting increases the risk for death or stroke. When perioperative MIs are included, there was a non-significant trend for 37% more events in the study subjects randomized to stents. There is some data suggesting a higher rate of restenosis in the stenting groups, but ipsilateral stroke rates appear to be similar in the two groups for two to four years after the perioperative period. There are too few data to draw any firm conclusions about asymptomatic patients. One trial found carotid artery stenting to be equivalent to endarterectomy in "high risk" patients, but the definition of high risk needs further refinement. Based on these findings, it is impossible to conclude that carotid angioplasty/stenting improves the net health outcomes as much as or more than the established alternatives of carotid endarterectomy, either for symptomatic or asymptomatic patients.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

Carotid angioplasty/stenting have been performed in multiple centers in the U.S., Europe, Australia, Canada and Japan. Centers performing the technique must have available one or more physicians who have received significant specific training in and who have experience with neuroradiology and angioplasty/stenting techniques. Complication rates must be kept low if carotid artery stenting is to achieve net clinical outcomes that are not inferior to carotid endarterectomy. These procedures are technically demanding and patients must be carefully selected.

However, given that no improvement has clearly been demonstrated in the investigational setting for the use of carotid angioplasty/stenting for either symptomatic or asymptomatic carotid artery stenosis, no conclusions can be drawn regarding its effectiveness in the community setting.

TA Criterion 5 is not met.

CONCLUSION

The published literature regarding carotid angioplasty/stenting for atherosclerotic primary and recurrent stenosis includes many case series, nonrandomized comparative trials and eleven randomized comparative trials. However, much of the early literature evaluates angioplasty/stenting without distal embolization protection, a procedure that has fallen out of favor. Both the non-randomized, comparative trials and the randomized trials report conflicting results regarding complications associated with carotid angioplasty/stenting compared with carotid endarterectomy. In particular, four of the eleven randomized trials were suspended prematurely because of a higher incidence of stroke in the angioplasty/stenting group than in the endarterectomy group. A fifth trial (SPACE), the largest, was terminated early because it was determined that it would have insufficient power to demonstrate the non-inferiority of carotid stenting to endarterectomy. Summary odds ratios from meta-analyses of the completed trials demonstrate that stenting reduces the risk for cranial nerve palsy and probably peri-operative MI's compared to endarterectomy, but at a cost of an increased risk of stroke and death. Improvements in stent design, embolization protection, catheter technique and more judicious patient selection may reverse the trend towards net harm with stents. Eight large, ongoing multicenter trials will randomize over 15,000 patients and follow them for up to five years. These trials should clarify the relative risks and benefits of stenting and endarterectomy. Several of the trials have already completed recruitment and should report early results in the next year.

Data from the SAPPHIRE trial support the non-inferiority of stent placement with distal embolization protection compared to carotid endarterectomy for up to three years in patients at high risk for complications from endarterectomy. Many people are advocating the use of stenting in symptomatic, high-risk patients based on this trial. However, the SAPPHIRE trial only randomized 95 symptomatic patients. One-year results for the primary outcome were similar in the two groups (16.5% stent vs. 16.8% endarterectomy) and there were more events in the stent arm from 30 days to one year (14% stent vs. 7% endarterectomy, p not reported). Furthermore, the early benefit in the stent arm (primarily a reduction in myocardial infarctions) may be due to the use of clopidogrel in the peri-operative period in the stent arm but not in the endarterectomy arm of the trial. Hence, it appears premature to recommend the use of stents over carotid endarterectomy in symptomatic high-risk patients.

Based on currently available publications, it is impossible to conclude that the carotid angioplasty with stenting improves the net health outcomes as much as or more than the established alternative of carotid endarterectomy for atherosclerotic carotid stenosis.

DRAFT RECOMMENDATION

It is recommended that carotid artery angioplasty with stenting does not meet California Technology Assessment Forum TA Criterion 3 through 5 for improvement in health outcomes.

June 17, 2009

This topic was last reviewed by the California Technology Assessment Forum in 2005

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center Medical Advisory Panel reviewed this topic in June 2007 and determined that the use of angioplasty and stenting of the cervical carotid artery with embolic protection of the cerebral circulation does not meet TEC criteria.

Centers for Medicare and Medicaid Services (CMS)

Effective October 14, 2008 the CMS released a National Coverage Decision for Percutaneous Transluminal Angioplasty which allow for use of this technology for specific conditions including:

- Concurrent with carotid stent placement in FDA-approved category B Investigational Device Exemption (IDE) Clinical Trials
- Concurrent with carotid stent placement in FDA-approved post approval studies
- Concurrent with Carotid stent placement in patients at high-risk fro carotid endarterectomy

American College of Cardiology, California Chapter (ACCCA)

The ACCCA has been invited to provide a position statement and testimony at the meeting.

Society for Cardiovascular and Angiography Interventions (SCAI)

The SCAI has been invited to provide a position statement and testimony at the meeting.

American Society of Neuroradiology (ASN)

The ASM has been invited to provide a position statement and testimony at the meeting.

Society of Neurointerventional Surgery (SNIS)

The SNIS has been invited to provide a position statement and testimony at the meeting.

Society for Vascular Surgery (SVS)

The SVS has been invited to provide a position statement and testimony at the meeting

American Heart Association (AHA)

The AHA has been invited to provide a position statement and testimony at the meeting

Association of California Neurologists (ACN)

The ACN has been invited to provide a position statement and testimony at the meeting

ABBREVIATIONS USED IN THIS ASSESSMENT:

OR	Odds ratio	IDE – Investigational Device Exemption
CI	Confidence interval	
TIA	Transient Ischemic Attack	
ACAS	Asymptomatic Carotid Atherosclerosis Study	
FDA	Food and Drug Administration	
PMA	Pre-market Approval	
DARE	Database of Abstracts of Reviews of Effects	
MI	Myocardial infarction	
CEA	Carotid Endarterectomy	
CAD	Coronary artery disease	
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy	
PTCA	Percutaneous transluminal coronary angioplasty	
CABG	Coronary artery bypass graft surgery	
EVA-3S	Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis Trial	
SPACE	Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy	
ASA	Aspirin	
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study	
CAS	Carotid Artery Stenosis	
NR	Not reported	
NASCET	North American Symptomatic Carotid Endarterectomy Trial	
CVA	Cerebral vascular accident	
CHD	Coronary heart disease	
TESCAS	Trial of endarterectomy versus stenting for the treatment of carotid atherosclerotic stenosis in China	
CREST	Carotid Endarterectomy vs. Stent Trial	
ICSS	International Carotid Stenting Study	
ACT	Asymptomatic Carotid Stenosis, Stenting versus Endarterectomy Trial	
TACIT	Transatlantic Asymptomatic Carotid Intervention Trial	
EF	Ejection fraction	
DEP	Distal embolization protection	
ECST	European Carotid Surgery Trial	
ACST	Asymptomatic Carotid Surgery Trial	
RR	Relative risk	

Appendix: Search strategy

PubMed:

Search	Most Recent Queries	Time	Result
#19	Search **#17 NOT #18**	14:27:45	461
#18	Search **#17 AND Animals, English**	14:18:04	20
#17	Search **#9 OR #14** Limits: **Publication Date from 2004 to 2009, English**	14:17:42	481
#16	Search **#9 OR #14** Limits: **English**	14:17:25	702
#15	Search **#9 OR #14**	14:17:14	770
#14	Search **#11 OR #12 OR #13**	14:16:57	146
#13	Search **#10 AND (RANDOM* OR CONTROLLED) AND (IN PROCESS[SB] OR PUBLISHER[SB] OR PUBMEDNOTMEDLINE[SB])**	14:16:38	32
#12	Search **#10 AND SYSTEMATIC REVIEW***	14:16:12	23
#11	Search **#10** Limits: **Meta-Analysis, Randomized Controlled Trial, Controlled Clinical Trial**	14:16:00	99
#10	Search **CAROTID AND STENT***	14:15:35	3514
#9	Search **#4 OR #5 OR #6 OR #7 OR #8**	14:15:24	716
#8	Search **#3 AND TREATMENT OUTCOME[MH] AND (CLINICAL TRIAL[PT] OR MULTICENTER STUDY[PT] OR VALIDATION STUDIES[PT] OR EVALUATION STUDIES[PT] OR LONGITUDINAL STUDIES[MH] OR FOLLOW-UP STUDIES[MH] OR COMPARATIVE STUDY[PT])**	14:15:11	392
#7	Search **#3 AND SYSTEMATIC REVIEW***	14:14:40	16
#6	Search **#3 AND OBSERVATIONAL[TIAB]**	14:14:30	14
#5	Search **#3 AND (RANDOMIZED CONTROLLED TRIALS AS TOPIC[MH] OR CONTROLLED CLINICAL TRIALS AS TOPIC[MH] OR RANDOM ALLOCATION[MH])**	14:14:19	187
#4	Search **#3** Limits: **Meta-Analysis, Randomized Controlled Trial, Controlled Clinical Trial, Research Support, N I H, Extramural, Research Support, N I H, Intramural, Research Support, Non U S Gov't, Research Support, U S Gov't, Non P H S, Research Support, U S Gov't, P H S**	14:13:49	255
#3	Search **#1 AND #2**	14:13:15	2194
#2	Search **STENT***	14:13:10	46825
#1	Search **CAROTID STENOSIS/SURGERY OR CAROTID STENOSIS/THERAPY[MH:NOEXP] OR CAROTID STENOSIS[MAJR] OR CAROTID ARTERIES/SURGERY[MAJR:NOEXP] OR CEREBROVASCULAR DISORDERS/SURGERY [MAJR:NOEXP] OR CEREBROVASCULAR DISORDERS/THERAPY[MAJR:NOEXP] OR CAROTID ARTERY DISEASES/SURGERY[MAJR:NOEXP] OR CAROTID ARTERY DISEASES/THERAPY[MAJR:NOEXP]**	14:13:00	14204

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No.	Query	Results	Date
#1	**'carotid artery obstruction'**/exp	17,307	06 May 2009
#2	**'stent'**/de OR **'coronary stent'**/de OR **'drug eluting stent'**/de OR **'bare metal stent'**/de OR **stent***:ti	49,455	06 May 2009
#3	**'carotid artery obstruction'**/exp/mj	8,924	06 May 2009
#4	**'stent'**/mj OR **'coronary stent'**/mj OR **'drug eluting stent'**/mj OR **'bare metal stent'**/mj OR **stent***:ti	29,653	06 May 2009
#5	**#1** AND **#4**	1,595	06 May 2009
#6	**#2** AND **#3**	1,415	06 May 2009
#7	**#5** OR **#6**	1,946	06 May 2009
#8	**#7** AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	237	06 May 2009
#9	**#7** AND (**'controlled study'** OR **'controlled clinical trial'**/exp OR **'observational study'**/de OR **'randomization'**/de)	427	06 May 2009
#10	**carotid**:ti AND **stent***:ti	2,138	06 May 2009
#11	**carotid**:ti AND **stent***:ti AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	194	06 May 2009
#12	(**#3** OR **#10**) AND **'treatment outcome'**/exp AND **'multicenter study'**/exp	48	06 May 2009
#13	**#8** OR **#9** OR **#11** OR **#12**	618	06 May 2009
#14	**#8** OR **#9** OR **#11** OR **#12** AND [english]/lim	533	06 May 2009
#15	**#8** OR **#9** OR **#11** OR **#12** AND [english]/lim AND [2004-2009]/py	403	06 May 2009
#16	**#8** OR **#9** OR **#11** OR **#12** AND [english]/lim AND [animals]/lim AND [2004-2009]/py	4	06 May 2009
#17	**#15** NOT **#16**	399	06 May 2009

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ID	Search	Hits	Edit	Delete
#1	(carotid) and (stent*)	235	edit	delete
#2	(carotid) and (stent*), from 2004 to 2009	150	edit	delete

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