

CAROTID ARTERY STENTING

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of carotid artery stenting for patients with coronary artery stenosis.

BACKGROUND

In the U.S., cerebrovascular disease is currently the third leading cause of death with more than 275,000 stroke-related fatalities per year (American Heart Association, 2004). Annually, there are more than 700,000 strokes and currently there are more than two million stroke survivors with varying degrees of disability (American Heart Association, 2004). 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 (Broderick, 1998).

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) (CAVATAS, 2001). Antiplatelet therapy (e.g., with aspirin) and warfarin have been employed for stroke prevention in patients with carotid stenosis (Ranke, 1993; Chaturvedi, 1998). However, patients with recent symptoms associated with severe carotid stenosis run a $\geq 20\%$ risk of stroke in the following two years if treated medically. Symptomatic is usually defined as patients 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. 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 (ECST, 1991; NASCET, 1991). 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 (ACAS, 1995). Carotid endarterectomy has been shown to normalize impaired cerebral hemodynamics (Markus, 1996).

However, carotid endarterectomy surgery 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 (CAVATAS, 2001). Coexisting medical morbidities greatly influence outcomes of, and therefore decisions to undertake, carotid endarterectomy (Chaturvedi, 1998). 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 (Naylor et al., 1998).

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 (Naylor et al., 1998; Phatouros et al., 2000). Theoretical benefits include reduced morbidity rates, improved long-term patency rates and less anesthetic risks (Jordan et al., 1998).

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 begun. 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 (Evans et al., 1997).

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 (Markus, 1996).

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. (1992) suggested that the risk of major stroke of approximately 1% is less than the approximately 2% stroke rate associated with carotid angiography alone in symptomatic patients.

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. 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.

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 (Bettman et al., 1998). Finally, stent technology is rapidly evolving and the best currently available stent may soon be supplanted (Bettman et al., 1998; Phatouros et al., 2000). Thus, carotid angioplasty/stenting has remained controversial (Beebe et al., 1996; Naylor et al., 1997; Beebe, 1998; Brown, 2001; Bladin, 2001) and many randomized trials have been launched to evaluate it (Sivaguru et al., 1996; Naylor et al., 1998; CAVATAS, 2001).

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

The ACCULINK™ Carotid Stent System and RX ACCULINK™ Carotid Stent System (Guidant Corporation, Santa Clara, CA) received FDA premarket approval on August 30, 2004. These systems are used in conjunction with Guidant carotid embolic protection systems and are indicated for the treatment of patients

at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the following criteria:

1. Patients with neurological symptoms and $\geq 50\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and $\geq 80\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

The ACCUNET™ Embolic Protection System and RX ACCUNET™ Embolic Protection System (Guidant Corporation, Endovascular Solutions, Santa Clara, CA) received FDA 510K clearance on August 31, 2004 as substantially equivalent to predicate devices.

The Xact® Carotid Stent System (Abbott Vascular Devices, Redwood City, CA) received FDA premarket approval on September 6, 2005. The Xact Carotid Stent System, used in conjunction with the Abbott Vascular Devices embolic protection system is indicated for the improvement of the lumen diameter of carotid arteries in patients considered at high risk for adverse events from carotid endarterectomy that require percutaneous carotid angioplasty and stenting for occlusive artery disease and meet the criteria below:

1. Patients with carotid artery stenosis ($\geq 50\%$ for symptomatic patients by ultrasound or angiography or $\geq 80\%$ for asymptomatic patients by ultrasound or angiography), located between the origin of the common carotid artery and the intra-cranial segment of the internal carotid artery, AND
2. Patients must have a reference vessel diameter ranging between 4.8 mm and 9.1 mm at the target lesion.

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 1966 through August 2005. The bibliographies of systematic reviews and key articles were manually searched for additional references. Further 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.

The search identified six published clinical trials that randomized 1,263 patients. Only one of the trials utilized distal embolization protection (SAPPHIRE, 334 patients randomized). Five ongoing clinical trials comparing stents with distal embolization protection to carotid endarterectomy were identified (<http://www.strokecenter.org/trials/>). These five trials plan to randomize 8,840 patients with follow-up ranging from 12 to 60 months. A large number of case series and comparative trials will also be described below.

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 defined (Jordan et al., 1997), although it has been suggested that patients at high risk for surgical complications represent one such subgroup (Yadav et al., 2004).

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 \geq 24 hours. Minor strokes have been defined as those causing minimal neurological deficit yet no loss of the patient’s functional independence (Baker et al, 1988). 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.

Long-term clinical follow-up remains significantly shorter in publications regarding angioplasty/stenting than for endarterectomy (Malek et al., 2000).

Levels of Evidence: 1, 3, 4, 5

TA Criterion 2 is met.

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

Patient Benefits

Carotid Artery Angioplasty for Atherosclerotic Stenosis

Case Series

More than 25 case series of carotid angioplasty for primary atherosclerotic stenosis have been published (Bockenheimer et al., 1983; Vitek et al., 1983; Brown et al., 1990; Bergeron et al., 1996; Kachel et al., 1996; Higashida et al., 1996; Diethrich et al., 1996; Roubin et al., 1996; Theron et al., 1996; Yadav et al., 1996; Crawley et al., 1997; Criado et al., 1997; Vozzi et al., 1997; Wholey et al., 1997; Yadav et al., 1997; Henry et al., 1998; Teitelbaum et al., 1998; Fisher et al., 1998; Schoser et al., 1998; Waigand et al., 1998; Bergeron et al., 1999; Griewing et al., 2000; Crawley et al., 2000; Al-Mubarak et al., 2001; Baudier et al., 2001; Bonaldi et al., 2002; Guimaraens et al., 2002). There have also been several other case series of carotid angioplasty for recurrent stenosis following carotid endarterectomy (Bergeron et al., 1996; Yadav et al., 1996; Lanzino et al., 1999; New et al., 2000).

Case series are difficult to compare with one another, in part because they have been performed in heterogeneous patient populations, have involved lesions with variable characteristics, have utilized different endovascular techniques and have employed dissimilar outcome measures (Malek et al., 2000). In addition, the lack of control groups precludes comparison of carotid angioplasty with standard carotid endarterectomy.

Wholey and colleagues (2003) reported a survey of 12,392 carotid angioplasty/stenting procedures involving 11,243 patients at 53 centers. There was a technical success rate of 98.9% with 12,254 carotid arteries successfully treated. Overall, there was a 5% complication rate of minor and major stroke and death within 30 days of treatment. Specifically, there was a 3.1% rate of TIAs, a 2.1% rate of minor stroke and a 1.2% rate of major stroke. The within-30-day procedural mortality rate was 0.6%. The overall 30-day stroke plus death rate was 4.8%. However, the rate was significantly lower for procedures using distal embolization protection (2.2% of 4,221 cases) compared with procedures without protection (6.2% of 6,753 cases). Restenosis rates were 2.7% at 12 months and 5.6% at 48 months. Similarly, rates of new ipsilateral neurologic events were 1.2% at 12 months and 4.5% at 48 months.

Nonrandomized, Comparative Trials

Six nonrandomized, comparative trials of carotid angioplasty versus endarterectomy have been published.

a. Primary Carotid Stenosis

In two non-randomized, comparative trials, Jordan and colleagues (1997; 1998) recorded a higher rate of complications associated with carotid angioplasty/stenting compared to carotid endarterectomy. In the 1997 report, they documented a higher rate of non-neurological complications and in the 1998 report, a higher rate of both neurological and non-neurological complications.

In their 1997 report, Jordan and colleagues reported a retrospective analysis comparing elective carotid angioplasty/stenting with endarterectomy: 107 patients underwent angioplasty with stenting and 166 patients had endarterectomy. The indications for treatment included asymptomatic severe stenosis (40.7%), TIA (39.9%), prior stroke (16.8%) and syncope (2.6%). Results showed the following complication rates in angioplasty/stenting patients: minor strokes in 6.6%, major strokes in 1.9% and deaths in 0.9%. In contrast, in endarterectomy patients, there were minor strokes in 0.6%, major strokes in 1.8% and deaths in 2.4%. The total stroke and death rates were 9.3% for the angioplasty/stenting patients and 3.6% for the endarterectomy patients ($p = .088$). Important non-neurological complications, such as femoral hematomas, retroperitoneal hemorrhage, severe bradycardia requiring pacing and respiratory failure, occurred in 5.6% of angioplasty patients versus 1.2% of endarterectomy patients ($p = .06$). At six-month follow-up, the incidence of amaurosis fugax, TIA, minor stroke, major stroke and death was higher in the angioplasty patients than the endarterectomy patients (total: 14% vs. 6%). In addition, carotid stenosis recurred more often in the angioplasty patients than the endarterectomy patients (4.7% vs. 0.6%). The authors concluded that carotid angioplasty/stenting was promising but not safer than endarterectomy and that long-term follow-up was needed to determine the durability of the technique.

In their 1998 report (Jordan et al.), these same authors reported a retrospective chart review comparing elective carotid angioplasty/stenting with endarterectomy, both done under local or regional anesthesia. Patients were separated into two groups: 268 patients underwent angioplasty with stenting and 109 patients underwent carotid endarterectomy. The indications for treatment included asymptomatic severe stenosis (62.8%), TIA (23.1%) and prior stroke (14.1%). Results showed the following complication rates in angioplasty/stenting patients: TIAs in 4.1%, strokes in 8.6% and deaths in 1.1%. In contrast, in endarterectomy patients, there were TIAs in 1.8%, strokes in 0.9% and 0 deaths. The total stroke and death rates were 9.7% for the angioplasty/stenting patients and 0.9% for the endarterectomy patients ($p = .0015$). Cardiopulmonary events such as hypotension and bradycardia that required additional monitoring or

interventions were more often evident after angioplasty/stenting than endarterectomy procedures (32.8% vs. 17.4%, $p = .002$). The authors concluded that, when both procedures were carried out under local or regional anesthesia, carotid angioplasty/stenting carried a higher neurological risk and required more monitoring than endarterectomy. In their view, the proposed use of angioplasty/stenting to avoid the risks of general anesthesia could not be justified when compared with carotid endarterectomy performed under local or regional anesthesia. They wrote, "At times, a 'less invasive' approach may be fraught with a paradoxically higher complication rate than the traditional standard therapy and should not be embraced without extensive scrutiny."

In a third non-randomized, comparative study, Gray et al. (2002) compared in-hospital outcomes of carotid stenting ($n=136$) with carotid endarterectomy ($n=136$). The two groups were similar, though the endarterectomy group had more symptomatic patients than the stent group (42% vs. 31%, respectively, $p = .0004$) and fewer patients with comorbidities meeting exclusion criteria for the NASCET study (35% vs. 68%, respectively, $p < .0001$). Results showed a small, insignificant difference in in-hospital major ipsilateral stroke and death (endarterectomy, 2.9% vs. stent, 0%, $p = \text{N.S.}$). Minor ipsilateral strokes were similar (2.2% vs. 2.9%, $p = \text{N.S.}$). Total adverse outcomes for the two groups were similar (9.6% vs. 6.6%, $p = \text{N.S.}$). The stent group had a six-month angiographic restenosis rate of 3.1%; no comparative data were reported for the endarterectomy group. The stent group had a two-year ipsilateral stroke rate of 0%, but again no data were reported for endarterectomy. The authors concluded that in-hospital outcomes with carotid stenting were similar to those with endarterectomy. Their 2002 report finishes, "As dedicated stent equipment emerges, cerebral embolic devices are added, and operator technique improves, stenting will likely become even more predictable. We await the results of current randomized trials to further define the relationship between endarterectomy and stenting."

The CaRESS trial (CaRESS, 2003; CaRESS, 2005) enrolled high-risk patients in a prospective, non-randomized study comparing carotid artery stenting with distal embolization protection to carotid endarterectomy. Two papers have been published describing this double cohort. The first (CaRESS, 2003) summarized the 30 day outcomes and the second (CaRESS, 2005) the one year outcomes. A total of 143 patients received a stent and 254 patients received endarterectomy. Both asymptomatic ($\geq 75\%$ stenosis) and symptomatic ($\geq 50\%$ stenosis) patients were enrolled. Approximately 68% of the enrolled patients were asymptomatic. Patients in the stent arm were much more likely to have had prior endarterectomies or stents ($p < 0.001$). Only 91% in the study had 30 day results available for analysis and the number available for assessment at the one-year follow-up was not reported. The 30 day stroke and death rate was 2% in each arm of the study while the combined stroke, myocardial infarction, and death rate was 2% in the stent arm and 3% in the endarterectomy arm. At one year, the combined stroke, MI, and death rate was 11% in the

stent arm and 14% in the endarterectomy arm. Restenosis rates were higher in the stent arm (6% vs. 4%) as was the revascularization rate (2% vs. 1%). The one year results appear comparable, although the higher rate of restenosis and revascularization in the stent arm suggests that longer term outcomes may be worse in the stent arm. On the other hand, the patients in the stent arm were likely to be at higher risk of restenosis given their much higher rates of prior carotid artery procedures. The questions raised about the impact of differences in baseline characteristics on outcomes in this study highlights the absolute requirement for randomized clinical trials to definitively assess the relative merits of carotid artery stenting and carotid endarterectomy.

b. Recurrent Carotid Stenosis

Hobson and colleagues (1999) reported a non-randomized comparison of angioplasty/stenting (n=15) and repeat carotid endarterectomy (n=16) for patients with recurrent carotid stenosis. In this small series, there were no strokes or deaths within 30 days in either group. Duplex ultrasound scans revealed no restenosis or stent occlusion at a mean seven months of follow-up.

Finally, in a group of 83 patients with recurrent carotid artery stenosis, AbuRahma et al. (2001) conducted a nonrandomized parallel comparison outcomes following percutaneous transluminal angioplasty/stenting (n=25) versus repeat carotid endarterectomy (n=58). Patients were followed at regular intervals with duplex ultrasound scanning. A Kaplan-Meier life table analysis was used to estimate the stroke-free survival rates and freedom from $\geq 50\%$ recurrent restenosis for both groups. Results showed that, overall, angioplasty/stenting had a higher 30-day stroke rate (16%; three major and one minor stroke) than repeat endarterectomy operations (3.4%; one major stroke) ($p < .05$). Cranial nerve injury was noted less often in angioplasty patients (0%) than endarterectomy patients (17%) ($p < .05$). Most of the cranial nerve injuries following reoperation were transient; only 1.7% had permanent injury. However, recurrent $\geq 50\%$ restenosis was higher in angioplasty patients (24%) than in endarterectomy patients (0%) ($p < .001$). Stroke-free survival rates at six months and one, two and three years for angioplasty were 79%, 79%, 79% and 79%, respectively, and for endarterectomy patients were 97%, 97%, 94% and 82%, respectively ($p = .059$). Freedom from recurrent $\geq 50\%$ restenosis rates at six months and one, two and three years were 100%, 94%, 65% and 44%, respectively, for angioplasty and 100%, 100%, 100% and 100%, respectively, for endarterectomy ($p < .0001$). Thus, for recurrent carotid stenosis, carotid angioplasty/stenting had a higher 30-day and subsequent stroke rate and a higher incidence of restenosis, when compared to that of repeat carotid endarterectomy. However, endarterectomy was associated with more cranial nerve injuries.

Thus, two non-randomized, comparative trials of angioplasty/stenting for primary carotid stenosis report a higher rate of complications as compared to carotid endarterectomy and one reports similar complication

rates. In addition, one of the two non-randomized, comparative trials of angioplasty/stenting for recurrent carotid stenosis reported a higher 30-day and subsequent stroke rate and a higher incidence of restenosis, when compared to repeat carotid endarterectomy. The other small report of a total of 31 patients found no strokes or deaths within 30 days in either group. It is hard to draw a definitive conclusion from the non-randomized trials.

Randomized Trials

High quality, randomized controlled trials provide the most reliable data for evaluating the effectiveness of carotid artery stenting. There are no randomized trials comparing stent placement with medical management. Descriptions of the six 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 five ongoing clinical trials. Table 3 summarizes the primary outcomes and Table 4 describes procedural complications.

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	Yes	Yes	NR	Yes	No	No	Yes	Yes	Fair
CAVATAS 2001	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Alberts 2001 WALLSTENT	Yes	Yes	Yes CEA 4 years older	NR	NR	No	NR	NR	Poor
Brooks 2001	Yes	Yes	Yes CEA 3 years older, less CAD (31% vs. 39%)	Yes	NR	No	NR	NR	Fair-poor
Brooks 2004	Yes	Yes	Yes More CAD stent group (35% vs. 20%)	NR	No	No	Yes	NR	Fair-poor
Yadav 2004 SAPPHIRE	Yes	Yes	No More CAD and prior PTCA in stent group – p<.05, >10% absolute difference in prior PTCA, CABG, CAD	Yes	Partial Central blinded adjudication, but unblinded event identification	No	No Clopidogrel in stent group only	Yes	Fair Study terminated early due to slowed recruitment

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 (including ongoing trials)

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	Symptomatic	Wallstent No	ASA not stopped	17	30 days	67 47%	Stroke + death	70-90% ICA stenosis by U/S	Stroke in evolution Crescendo TIA's Non-hemispheric symptoms	Mean stenosis 82%. Stopped early due to harm. Single center.
CAVATAS 2001	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	12 months	68 36%	Ipsilateral stroke + death	60-99% stenosis by angiogram.	NR	Stopped early for harm. Planned n = 700
Brooks 2001	Symptomatic CAS	Wallstent No	ASA 325 + Clopidogrel 75	104	NR	68 NR	NR	>70% stenosis by NASCET criteria Life expectancy > 5 years	Disabling stroke Recent intracranial hemorrhage	Single center.
Brooks 2004	Asymptomatic CAS	Wallstent or Dynalink No	ASA 325 + Clopidogrel 75	85	48 months	68 NR	NR	>80% stenosis by NASCET criteria Life expectancy > 5 years	Arrhythmia Allergy to ASA, Clopidogrel, heparin	Single center.
Yadav 2004 SAPPHIRE	"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	12 months	73 33%	Stroke + 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/l 30 days Life expectancy < 1 year Osteal lesion	Multicenter "High Risk" 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

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 (including ongoing trials)

Study	Indication	Device DEP?	Co-intervention	N	Follow-up for primary outcome	Age, yrs Sex, %F	Primary outcome	Inclusion criteria	Exclusion criteria	Comment
Ongoing trials										
CREST	Symptomatic CAS	ACCULINK Yes	ASA + clopidogrel + anti-hypertensives	2500	48 months		Stroke + MI + death	>50% by angiogram or 70% by U/S	Comorbidities interfering with evaluation endpoints CEA or CAS contraindicated Life expectancy < 4 years	Multicenter, U.S.
EVA-3S	Symptomatic CAS	Yes	Ticlopidine or clopidogrel x 1 month in stent arm only	900	48 months		Ipsilateral stroke + death	>60% Ischemic stroke within 4 months	Disabling stroke Non-atherosclerotic carotid disease Severe intracranial carotid stenosis Contraindication to heparin, ticlopidine, or clopidogrel	Multicenter, France.
ICSS CAVATAS-2	Symptomatic CAS	Yes		2000	60 months		Ipsilateral stroke + death	≥ 70% Suitable for stenting or endarterectomy, No contraindication to either treatment	Major stroke Thrombus at site Life expectancy < 2 years	Multicenter.
SPACE	Symptomatic CAS	Yes		1900	24 months		Ipsilateral stroke + death	>50% by angiogram or 70% by U/S	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.
ACT-1	Asymptomatic CAS	Stent Yes		1540	1 year		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.

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	30 day stroke or death	1 year stroke or death
			Stroke	MI	Death	Stroke	MI	Death			
Naylor 1998	Stent	7	5 (71%)	NR	0 (0)	-	-	-			
	Endarterectomy	10	0 (0)	NR	0 (0)						
CAVATAS 2001	Angioplasty or Stent	251	18	0 (0)	7	NR	NR	NR	25 (14%)	10%	12%
	Endarterectomy	253	21	3 (1)	4				7 (4%)	10%	20%
Alberts 2001	Stent	107	NR	NR	NR	4%	NR	NR	NR	12%	12%
WALLSTENT	Endarterectomy	112				1%				4%	4%
Brooks 2001	Stent	53	0 (0)	NR	0 (0)	NR	NR	NR	NR	0%	NR
	Endarterectomy	51	0 (0)		1 (2)					2%	
Brooks 2004	Stent	43	0 (0)	NR	0 (0)	NR	NR	NR	NR	0%	NR
	Endarterectomy	42	0 (0)		0 (0)					0%	
Yadav 2004	Stent	167	6 (3.6%)	4 (2.4%)	2 (1.2%)	10 (6.2%)	5 (3.0%)	12 (7.4%)	1 (0.6%)	5%	12%
SAPPHIRE	Endarterectomy	167	5 (3.1%)	10 (6.1%)	4 (2.5%)	12 (7.9%)	10 (6.2%)	21 (13.5%)	6 (4.3%)	5%	20%

* Follow-up for primary endpoint

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
	Endarterectomy	12	NR	0 (0)	NR	NR	NR
CAVATAS 2001	Stent	251	NR	0 (0)	3 (1)	NR	NR
	Endarterectomy	253	NR	22 (9)	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)
	Endarterectomy	51	NR	4 (8)	1 (2)	0 (0)	3 (6)
Brooks 2004	Stent	43	NR	0 (0)	0 (0)	5 (12)	NR
	Endarterectomy	42	NR	0 (0)	0 (0)	0 (0)	NR
Yadav 2004	Stent	167	NR	0 (0)	2 (1.2)	NR	NR
SAPPHIRE	Endarterectomy	167	NR	8 (5)	1 (0.6)	NR	NR

* Follow-up for primary endpoint

Naylor and colleagues (1998) reported the first randomized trial of carotid angioplasty versus endarterectomy for symptomatic severe internal carotid artery disease. The study population consisted of 23 patients with focal carotid territory symptoms and severe (>70%) internal carotid artery stenosis who were randomized to either angioplasty with stenting (n=11) or endarterectomy with patching (n=12). Patients with asymptomatic disease, symptomatic <70% stenosis, crescendo TIAs or stroke in evolution and vertebrobasilar or non-hemispheric symptoms were excluded. The main outcome measures were death or disabling or nondisabling stroke within 30 days. The trial was suspended prematurely when only 17 patients had received their allocated treatment. This was because all ten carotid endarterectomy operations proceeded without complication, but five of the seven patients who underwent angioplasty had a stroke ($p = .0034$), three of which were disabling at 30 days. The median number of cerebral emboli detected during the procedures differed significantly: 12 (range, 0 to 26) for carotid endarterectomy versus 284 (range, 151 to 279) for carotid angioplasty ($p = .0015$). There were no deaths in either group. None of the patients with a stroke had any obvious abnormality of the stented internal carotid artery on duplex ultrasound scanning. The investigators concluded that the trial should be stopped--and not restarted even in an amended fashion--because of problems posed for informed consent. They also concluded that, if future trials did suggest a selected role for carotid angioplasty, it would be essential that both patient inclusion and exclusion criteria be completely documented.

More recently, results have been reported from a second randomized trial. Known as the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), this was an international, multicenter, unblinded, "exploratory" randomized trial (CAVATAS, 2001). One of its aims was to determine the risks and benefits of carotid artery angioplasty with or without stenting and to compare these with carotid endarterectomy (Sivaguru et al., 1996). The CAVATAS investigators randomly assigned 504 patients with carotid stenosis to angioplasty (n=251) or endarterectomy (n=253). Most (96-97%) patients in both groups were symptomatic with amaurosis fugax, TIA, retinal infarct or hemispheric stroke. Patients were randomly assigned only if their carotid stenosis was suitable for both endovascular and surgical treatment. Patients were excluded if thought to be unsuitable for surgery because of medical or surgical risk factors, if they had thrombosis in the carotid artery or severe intracranial carotid artery stenosis beyond the skull base, or if they had had a disabling stroke in the territory supplied by the treatable carotid artery. For endovascular patients treated successfully, the investigators used balloon angioplasty alone in 74% and with stents in 26%. All angioplasty/stenting procedures were performed under local anesthesia; most (93%) carotid endarterectomy procedures were done using general anesthesia. The primary outcome was disabling stroke or death and secondary analyses examined for any ipsilateral stroke lasting more than seven days. Patients were followed up to 36 months by an independent neurologist. The study employed an intention-to-treat analysis.

Results demonstrated that outcomes within 30 days of treatment did not differ significantly between angioplasty with or without stenting versus endarterectomy: the rates of disabling stroke or death were 6.4% versus 5.9%, respectively (p=N.S.); the rates of any stroke lasting more than seven days or death were 10% versus 9.9% (p=N.S.). Cranial neuropathy occurred in none of those undergoing endovascular treatment but in 8.7% of endarterectomy patients (p< .0001). Major groin or neck hematomas occurred less often after endovascular treatment than after endarterectomy (1.2% vs. 6.7%, p< .0015). However, at one year after treatment, severe (70-99%) ipsilateral carotid stenosis was found more often after endovascular treatment than after endarterectomy (14% vs. 4%, p< .001). There were also somewhat more carotid occlusions in the endovascular group than in the surgery group (4% vs. 1%, p=N.S.). Nonetheless, with survival analysis up to three years, no substantial difference in the rate of ipsilateral stroke was noted (adjusted hazard ratio=1.04, 95% CI, 0.63-1.70, p=N.S.). The authors concluded that angioplasty with or without stenting had similar major risks and similar effectiveness in stroke prevention, compared with carotid endarterectomy. Endovascular treatment had the advantage of avoiding minor complications. However, the durability of the procedure is uncertain; at one-year follow-up, recurrent or residual carotid stenosis was found significantly more often after angioplasty than after endarterectomy.

The CAVATAS trial had several limitations. First, in contrast to other trials such as the NASCET trial, the exclusion criteria were few and not standardized; patient selection was left to the discretion of the participating centers (Naylor et al., 1998). Perhaps because of this fact, the risk of stroke and death within 30 days of treatment was higher in both CAVATAS groups than reported in the two much larger randomized trials of carotid endarterectomy, the ECST and NASCET (ECST, 1991; NASCET, 1991). In particular, the perioperative rate of stroke and death in the CAVATAS endarterectomy group was greater than the rates achievable in other centers (Naylor, 2000; CAVATAS, 2001). Second, bradycardia and hemodynamic instability are known common complications of endovascular therapy (Qureshi et al., 1999) and yet their occurrence is not reported in the CAVATAS trial (Johnston, 2001). Finally, the authors note that the 95% confidence interval surrounding the 9.9% risk of any stroke within 30 days of treatment in the endovascular versus endarterectomy groups is wide. Indeed, results could be consistent with a 47% reduction or a 64% increase in the hazard with endovascular treatment compared with endarterectomy (Johnston, 2001). Therefore, the authors appropriately conclude that, "There is an important need to establish the efficacy and safety of carotid stenting by comparison with surgery, before the technique is widely introduced without adequate trial-based evidence."

Brooks et al. (2001) published a third randomized trial comparing outcomes following carotid angioplasty and stenting versus carotid endarterectomy in 104 patients with symptomatic carotid stenosis of >70%. Patients who had cerebrovascular ischemia (TIAs or stroke) ipsilateral to the carotid stenosis were selected

randomly for carotid stenting (n=53) or endarterectomy (n=51) and then followed for two years. Results showed that stenosis decreased to an average of 5% after angioplasty and stenting; data was not given for endarterectomy. The patency of the reconstructed artery as determined by sequential ultrasound remained satisfactory with both techniques to ≥ 24 months. Post-operatively, no one in either group sustained a stroke but one TIA occurred in the angioplasty group. In terms of other complications, in the endarterectomy group, one patient died from a myocardial infarction; four patients had transient peripheral or cranial neuropathies; and one had a wound hematoma requiring exploration. In the angioplasty group, one patient sustained a popliteal artery thrombosis necessitating a below-the-knee amputation; three patients suffered retroperitoneal hemorrhage, seven patients suffered bradycardia requiring temporary pacing and 12 patients had hypotension requiring treatment. MRI scans at six and 12 months showed no subclinical focal ischemia in the distribution of the treated vessel in either group. Procedural pain/discomfort was similar in both groups. Hospital stay was similar (mean = 1.8 days for angioplasty vs. 2.7 days for endarterectomy, p=? [not reported]). However, complications associated with angioplasty prolonged hospitalization more than those related to endarterectomy (mean = 5.6 days vs. 3.8 days, p=?). Return to full activity occurred within one week in 80% of the angioplasty group and 67% of the endarterectomy patients and within two weeks in 100% in both groups.

The authors noted that this trial was limited to a single institution and a “select” team with experience in cerebral vascular disease and endovascular techniques, thus could not advocate that carotid artery angioplasty/stenting replace carotid endarterectomy as a primary revascularization procedure in patients with symptomatic carotid stenosis. However, they concluded that carotid angioplasty/stenting is equivalent to endarterectomy in reducing carotid stenosis without increased risk for major complications of death or major or minor stroke.

Similar concerns apply to the study of the same design by the same investigators (Brooks et al., 2004), which randomized 85 asymptomatic patients with at least 80% carotid artery stenosis to stenting or carotid endarterectomy. There were no deaths or perioperative strokes in either arm of this small, single institution study.

The WALLSTENT trial has only been published in abstract form (Alberts, 2001). Because it represents almost 20% (n=219: 107 to stenting, 112 to endarterectomy) of the patients in randomized trials, the study was included for completeness. It is unfortunate that the full details of the trial have never been published more than four years after their presentation at a national meeting and more than six years after the trial was halted after analyses demonstrated that endarterectomy was more effective than stenting. The study was originally designed to randomize 700 symptomatic patients with 60-99% stenosis of the carotid artery

ipsilateral to symptoms. The primary outcome was the rate of ipsilateral stroke and death during the year following randomization. All patients received 325 mg of aspirin and 250 mg of ticlopidine, twice daily for at least four weeks. The 30-day rate of any stroke or death was 12.1% for stents and 4.5% for carotid endarterectomy (p=0.049). The two-day peri-procedure rate was 7.5% for stents and 1.8% for endarterectomy (p=0.055). Stenting was also associated with severe bradycardia (7%) and groin hematoma (4%).

It is important to note at this point that none of the randomized trials described above used distal embolization protection. The recently published SAPPHERE trial (Yadav et al., 2004) 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. Thus, this is the only published randomized study to date that directly compares stenting as practiced today to carotid endarterectomy. The study randomized both symptomatic patients with at least 50% carotid artery stenosis or 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 surgical complications. These 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 stroke, heart attack or death within 30 days of the procedure plus and subsequent ipsilateral stroke or death. 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 published data report results through one year of follow-up.

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 – no further descriptions of these patients or outcomes in this group have been published. The definition of “not a surgical candidate” was not defined other than that it was the opinion 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 not 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.

The SAPHIRE 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. Indeed, if the trend in long-term post-procedural outcomes in symptomatic patients continues (7%/year in patients receiving endarterectomy vs. 14%/year in patients receiving stents), stents should not be used in symptomatic patients. 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. In fact, the benefits of endarterectomy in these trials were not seen until at least two to three years of follow-up. Longer follow-up results with more detail on outcomes by symptom status will be essential to have confidence in the benefits of carotid artery stenting. The relatively short follow-up combined with the small samples in each of the symptom groups due to early closure of enrollment leave the SAPHIRE trial with insufficient power to clearly define the appropriate target group for the use of stents.

The primary endpoint in the trial included peri-operative heart attacks, an outcome not traditionally included in studies of stroke prevention with endarterectomy. Indeed, the major difference in 30 day and one-year outcomes is in the number of heart attacks in the first 30 days. However, as the authors argue, including myocardial infarction as a major adverse outcome was reasonable as it has more important long term health

implications that a peri-operative TIA. The authors did report an analysis of the data using the conventional endpoint without heart attacks and there was no longer a significant difference between the two arms of the study, although the trend still favored stenting (8.4% vs. 5.5%, $p=0.36$).

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 (Harker, 1999; Markus 2005; McKevitt, 2005; Payne, 2004; Sabatine, 2005; Yusuf, 2003).

Patient Risks

Stroke: Qureshi and colleagues observed relatively high rates of thromboembolic events (TIAs and strokes) with carotid balloon angioplasty alone (5.9%) (Qureshi et al., 2002) and with carotid angioplasty and stent placement (8.8%) (Qureshi et al., 2000). Most strokes after carotid angioplasty result from plaque fracture in the carotid artery at the time of balloon inflation, with subsequent thrombosis and embolism (CAVATAS, 2001). Al-Mubarak et al. (2001) reported a greater likelihood of embolic event during carotid angioplasty/stenting in patients who are older than age 80 or who have tortuosity of the aortic arch or carotid artery.

In addition, just as occurs with carotid endarterectomy, delayed intracranial hemorrhage due to a "hyperperfusion syndrome" is known to be a complication of carotid angioplasty/stenting (McCabe et al., 1999; Meyers et al., 2000; Morrish et al., 2000; Ho et al., 2000; Masuo et al., 2000; Pfefferkorn et al., 2001; Nikolsky et al., 2002; Phatouros et al., 2002). Abnormal leptomeningeal enhancement has been detected by MRI after carotid stenting (Wilkinson et al., 2000). In two published series, Meyers et al. (2000) reported a 5.0% incidence of cerebral hyperperfusion among 140 patients who underwent angioplasty/stenting of the craniocervical arteries and Morrish et al. (2000) reported a 3.8% incidence in 90 patients undergoing angioplasty/stenting of the carotid arteries. These rates appear to be higher than the 0.3-1.2% incidence reported in the literature after carotid endarterectomy. Mathur and colleagues (1998) have identified a higher risk to carotid angioplasty/stenting in patients with advanced age, long or multiple stenosis and severe lesions.

With carotid angioplasty, there is concern about the incidence and clinical consequences of distal embolization. Transcranial Doppler monitoring has demonstrated that embolic signals occur commonly during and immediately after the procedure, but these emboli are usually asymptomatic (Markus et al.,

1994). Findings from transcranial Doppler monitoring of subgroups of patients randomly assigned in the CAVATAS trial show that substantially more microscopic emboli to the brain occur after carotid angioplasty than after endarterectomy (mean 202 ± 119 vs. 52 ± 64 ; $p = .001$) (Crawley et al., 1997; Crawley et al., 2000). However, extensive neuropsychological tests in two large subgroups of patients in the CAVATAS trial did not show any significant difference in neuropsychological sequelae between the two treatments at six months (Sivaguru et al., 1999). In addition, substantial reduction in the middle cerebral artery blood flow occurred significantly more often during endarterectomy than angioplasty (Crawley et al., 1997; Crawley et al., 2000).

Nonetheless, most current practitioners use some form of cerebral protection from embolization of thrombus and atherosclerotic debris during angioplasty and stent placement. The use of embolic protection devices to protect the distal cerebral circulation was first described by Theron et al. (1996) and is now becoming routine in most centers (Albuquerque et al., 2000; Jaeger et al., 2001; Martin et al., 2001; Reimers et al., 2001). Both occlusive balloon and filter designs have been developed. Such protection devices need to be streamlined in design in order not to dislodge plaque, result in spasm of the arterial wall or cause other iatrogenic complications (Wholey et al., 2000).

Carotid bulb manipulation during the angioplasty balloon inflation can cause bradycardia with or without hypotension (Qureshi et al., 1999). In some reports, bradycardia is common, though symptoms less common. In the report by Jordan et al. (1997), 71% of patients had bradycardia, but only 24.3% developed symptoms of severe bradycardia or hypotension requiring treatment. Both transient and permanent cardiac pacing has been required in some patients. The hypotension, transient and sustained, reported following carotid artery stenting (Mendelsohn et al., 1998; Al-Mubarak et al., 1999; Dangas et al., 2000) may be related to the carotid sinus reflex arc. The long-term effects of carotid bulb manipulation are unknown.

Femoral hematomas and retroperitoneal hemorrhage have been described (Jordan et al., 1997). Additionally, surgical intervention may be required because of either acute complications (e.g., carotid artery thrombosis and rupture) or to correct subsequent critical restenosis (Owens et al., 2002).

Pending Trials

At least five randomized trials of angioplasty/stenting for carotid stenosis are ongoing (Johnston, 2001; www.strokecenter.org/trials/). The study designs intend to randomize over 9,000 patients in these trials. Four of the ongoing trials are enrolling patients with symptomatic carotid artery stenosis, while the fifth is enrolling asymptomatic patients. All five trials are using stents in combination with distal embolization

protection devices. Planned follow-up in the two largest trials ranges between four and five years. Descriptions of the trials are summarized in Table 2. The largest is described in detail below.

A major NIH-sponsored multicenter randomized trial called the Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is currently underway. With a planned enrollment of 2,500 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 (Hobson, 2000; Roubin et al., 2001). 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 ($\geq 70\%$ by ultrasound or $\geq 50\%$ by angiography) in patients with TIA or ipsilateral non-disabling 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

For primary carotid stenosis, there were higher rates of complications in two of three non-randomized trials comparing carotid angioplasty compared to endarterectomy and conflicting results from six randomized trials of carotid stenting versus carotid endarterectomy for primary carotid stenosis. The most recent randomized trial (SAPPHIRE, Yadav, 2004) used distal embolization protection and provided evidence for better outcomes of stenting compared with carotid endarterectomy after one year follow-up in high-risk patients. However, most of the benefit was a reduction in perioperative heart attacks in asymptomatic patients, the number of patients was low and follow-up was short. For recurrent carotid stenosis, there were more complications and a higher incidence of recurrent stenosis with angioplasty in one of two non-randomized comparative trials.

TA Criterion 3 is not met.

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

Carotid endarterectomy is the major established alternative to carotid angioplasty/stenting for treatment of high-grade stenosis of extracranial carotid arteries. Two analyses of published endarterectomy series have identified a significantly higher combined risk of stroke and death in symptomatic patients (5.18-9.5%) than in asymptomatic patients (2.7-3.35%) (McCrorry et al., 1993; Rothwell et al., 1996). In the two nonrandomized comparative trials described above (Jordan et al., 1997; 1998), there were higher rates of

complications associated with carotid angioplasty/stenting compared to carotid endarterectomy. In the 1997 report, they documented a higher rate of non-neurological complications and in the 1998 report, a higher rate of both neurological and non-neurological complications. Four randomized comparative trials documented that angioplasty with stenting had similar major risks and similar effectiveness in stroke prevention compared with carotid endarterectomy (CAVATAS, 2001; Brooks et al., 2001; Brooks et al., 2004; Yadav et al., 2004). However, two other randomized comparative trials were suspended prematurely because of a much higher incidence of stroke in the angioplasty group than in the endarterectomy group (Naylor et al., 1998; Alberts, 2001).

Residual or recurrent carotid stenosis has been noted after both carotid endarterectomy and angioplasty. In the ACAS trial, the risk of late restenosis was 1.9% to 4.9% (Moore et al., 1998). Use of patch angioplasty closure following endarterectomy has been shown in randomized trials to reduce the risk of such restenosis (Ranaboldo et al., 1993). In one Jordan angioplasty trial (1997), the 4.7% rate of late restenosis was roughly comparable.

In comparative trials, Crawley et al. (1997, 2000) found that there were significantly more microembolic signals during carotid angioplasty than during endarterectomy, though there was no correlation with peri-procedural stroke (Crawley et al., 1997) or neuropsychological outcomes (Sivaguru et al., 1999; Crawley et al., 2000). The current standard is to use distal embolization protection when performing angioplasty/stenting. Using such devices makes the procedure more technically demanding and there is only one comparative trial in the literature using such devices. Unfortunately, recruitment in the trial was terminated early and follow-up was only one year, so the study was underpowered to provide definitive answers to the relative merits of carotid artery stenting in either symptomatic or asymptomatic patients.

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.

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, five nonrandomized comparative trials and six randomized comparative trials. However, most of the literature evaluates angioplasty/stenting without distal embolization protection, a procedure that has fallen out of favor. Only the SAPPHIRE trial directly compares stenting with distal embolization protection to carotid endarterectomy. Both the non-randomized, comparative trials and the randomized trials report conflicting results regarding complications associated with carotid angioplasty/stenting compared with carotid endarterectomy. Specifically, two of the six randomized trials were suspended prematurely because of a much higher incidence of major stroke in the angioplasty group than in the endarterectomy group. The other randomized trials comparing angioplasty /stenting and endarterectomy found similar major risks and similar effectiveness in stroke prevention. However, follow-up was very short in these trials. The randomized trials that demonstrated the effectiveness of carotid endarterectomy required three to five years of follow-up for the benefits to emerge. Five large, multicenter trials are still in progress, which will randomized over 9,000 patients and follow them for up to five years. These trials should clarify the relative risks and benefits of stenting and endarterectomy.

While preliminary results are promising, the long-term patency rates for stents must still be determined and long-term durability of published results must be established. Stent technology is evolving, and the best currently available stents may soon be supplanted. In particular, all of the recent trials of carotid artery stenting use distal embolization technology to decrease the high rate of early strokes seen in the earlier trials.

Data from the SAPPHIRE trial support the non-inferiority of stent placement with distal embolization protection compared to carotid endarterectomy after one year of follow-up 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), but there were more events in the stent arm from 30 days to one year (14% stent vs. 7% endarterectomy, p not reported). If this trend continues, three to five year outcomes may be worse in the stent arm. 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 new technology of carotid angioplasty/stenting improves the net health outcomes as much as or more than the established alternative of carotid endarterectomy for atherosclerotic carotid stenosis.

RECOMMENDATION

It is recommended that carotid artery angioplasty with stenting with or without embolic protection does not meet California Technology Assessment Forum TA Criterion 3 and 4.

The California Technology Assessment Forum panel voted to accept the recommendation as written.

October 19, 2005

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center Medical Advisory Panel reviewed this topic in October 2004 and determined that the use of carotid artery angioplasty and stenting with or without distal embolic protection of the cerebral circulation for patients with carotid artery stenosis does not meet TEC criteria.

Centers for Medicare and Medicaid Services (CMS)

On March 17, 2005 the CMS announced expanding coverage of Percutaneous Transluminal Angioplasty (PTA) of the carotid artery concurrent with stent placement to patients who are at high risk for carotid surgery – also known as carotid endarterectomy or CEA.

American College of Cardiology, California Chapter (ACCCA)

The ACCCA provided an opinion statement in support of the use of this technology in the patient population approved by CMS. A representative was not available to provide testimony at the meeting.

American Society of Interventional & Therapeutic Neuroradiology (ASITN)

A representative of ASITN attended the meeting and provided testimony in support of the use of CAS similar to that of CMS for high-risk symptomatic patients.

Society of Interventional Radiology (SIR)

The SIR provided an opinion statement in support of the use of this technology in certain patients. A SIR representative was not available to provide testimony at the meeting.

Society for Vascular Surgery (SVS)

The SVS provided an opinion statement supporting the use of this technology when used for high-risk patients such as recommended by CMS and stressed the need for appropriate training and outcomes monitoring. A representative of SVS was not available to provide testimony at the meeting.

Association of California Neurologists (ACN)

The ACN provided an opinion statement in support of the use of this technology, but was not able to attend the meeting.

California Association of Neurological Surgeons (CANS)

The CANS was invited to provide a position statement and testimony at the meeting.

American Heart Association (AHA)

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

ABBREVIATIONS USED IN THIS ASSESSMENT:

TIA: Transient Ischemic Attack

ACAS: Asymptomatic Carotid Atherosclerosis Study

CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study

CREST: Carotid Endarterectomy vs. Stent Trial

CAS: Carotid Artery Stenosis

NASCET: North American Symptomatic Carotid Endarterectomy Trial

ASA: Aspirin

WALLSTENT

DEP: Distal Embolization Protection

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

U/S: Ultrasound

NR: Not reported

EVA-3S: Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis Trial

CEA: Carotid Endarterectomy

ICSS: International Carotid Stenting Study

MI: Myocardial Infarction

SPACE: Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy

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