CAROTID AND CEREBRAL ANGIOPLASTY AND STENTING FOR ATHEROSCLEROSIS, STROKE AND VASOSPASM

ISSUE

Blue Shield has received requests for coverage of carotid and cerebral artery angioplasty and stenting for patients with atherosclerosis, stroke, and vasospasm. The Medical Policy Committee on Quality and Technology is therefore asked to review the safety and efficacy of this new medical technology in clinical practice.

CURRENT BLUE SHIELD POLICY

Currently, Blue Shield Medical Policy provides coverage for carotid endarterectomy surgery for carotid atherosclerosis, and for tissue plasminogen activator (t-PA) for acute stroke.

BACKGROUND

In the U.S., cerebrovascular disease is currently the third leading cause of death with more than 150,000 stroke-related fatalities per year (Evans et al, 1997). Annually, there are more than 500,000 strokes and currently there are more than 2 million stroke survivors with varying degrees of disability (Wholey et al, 2000). 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 ≥20% risk of stroke in the following two years if treated medically. Currently, carotid endarterectomy is considered standard treatment for severe carotid artery stenosis.
**Carotid Arterial Disease**, continued

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).

**Intracerebral Arterial Vasospasm**

Subarachnoid hemorrhage after rupture of a cerebral aneurysm or arteriovenous malformation often leads to vasospasm of cerebral arteries. Up to one-third of patients with such vasospasm develop an ischemic neurological deficit. Patients with subarachnoid-induced vasospasm are initially treated with standard medical treatment (e.g., hypertensive, hypervolemic, hemodilution therapy) and pharmacological regimens (e.g., calcium channel blockers such as nimodipine). When these methods fail to reverse the vasospasm, intra-arterial infusion of papaverine, a known smooth muscle relaxant, has been utilized. Papaverine has been shown to be efficacious in increasing vessel lumen diameter, decreasing circulation time, increasing cerebral blood flow, and improving ischemic neurological deficits induced by vasospasm (Milburn et al., 1998). However, its effect is often transient, making repeated treatments necessary (ACGME, 2001).
Intracerebral Arterial Vasospasm, continued

Because of this problem, percutaneous balloon angioplasty to mechanically dilate stenotic segments has recently been introduced in certain centers in an attempt to improve clinical outcomes following onset of vasospasm (Eskridge et al, 1999). The effect of balloon angioplasty is essentially permanent; repeated treatments are rarely if ever needed (ACGME, 2001).

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.
**Carotid Artery Angioplasty and Stenting**, continued

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%, 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. 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 several randomized trials were launched to evaluate it (Sivaguru, 1996; Naylor et al, 1998; CAVATAS, 2001).

**Intracerebral Artery Angioplasty**

A variety of balloon angioplasty catheters are available; most centers use compliant balloons, which conform to the shape of the vessel, making overdistension and rupture less likely. This procedure is accomplished with a microballoon catheter via percutaneous transfemoral insertion (Newell et al., 1989).
Intracerebral Artery Angioplasty, continued

Several reviews of devices (Higashida et al., 1990; Terada et al., 1993) and of techniques employed in endovascular treatment of vasospasm following subarachnoid hemorrhage have been published (Grimes, 1991; Higashida et al., 1996; Newell et al., 1999; Barreau et al., 2001).

**TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.**

The balloons used for angioplasty are FDA approved for vascular angioplasty. For angioplasty for vasospasm, the balloons currently used are specifically approved for intracranial use. Currently, there are no FDA-approved stents specifically for use in the carotid arteries, or in the intracranial circulation. However, there are stents that have FDA approval for investigational device exemption (IDE) for carotid and intracranial use (e.g., Guidant Acculink™, Guidant Neurolink™, Medtronic Exponent™) while clinical trials remain open. Other stents (Wallstent®, Palmaz) have FDA PMA approval but are not FDA approved for use in the carotid or cerebral arteries.

TA criterion 1 is met.

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

The indications for carotid or cerebral angioplasty have varied in published reports, as detailed below. Particular patient subgroups for whom angioplasty/stenting might be particularly advantageous have not yet been defined (Jordan et al, 1997).

The major clinical outcomes assessed in the various trials include the occurrence of neurological deficits, in particular, amaurosis fugax (transient visual loss); transient ischemic attack (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 (Ad Hoc Committee, 1988). Major strokes have been defined as deficits that persisted beyond 30 days and that caused a change in the patient’s lifestyle.
TA Criterion 2, continued

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. 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).

As detailed below, there have been at least 12 case reports, 73 case series, 6 non-randomized comparative trials, and 2 randomized comparative trials published concerning these procedures.

TA criterion 2 is met.

Levels of Evidence: 1, 3, 4, 5

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

Patient Benefits

1. Carotid Artery Angioplasty for Atherosclerotic Stenosis

Case Series

TA Criterion 3 (1. Carotid Artery Angioplasty for Atherosclerotic Stenosis – Case Series), continued

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 (2000) reported a survey of 5210 carotid angioplasty/stenting procedures involving 4757 patients at 36 centers. There was a technical success rate of 98.4% with 5129 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 2.8% rate of TIAs, a 2.7% rate of minor stroke, and a 1.5% rate of major stroke. The within-30-day procedural mortality rate was 0.9%. Restenosis rates were 2% at 6 months and 3.5% at 12 months. At 6- to 12-month follow-up, the rate of subsequent neurological events was 1.4%.

Nonrandomized, Comparative Trials

Five nonrandomized, comparative trials of carotid angioplasty vs. 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 (1997) 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%. 
TA Criterion 3 (1. Carotid Artery Angioplasty for Atherosclerotic Stenosis - Nonrandomized, Comparative Trials), continued

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 vs. 1.2% of endarterectomy patients (p=.06). At 6-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, 1999), 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: TIs in 4.1%, strokes in 8.6%, and deaths in 1.1%. In contrast, in endarterectomy patients, there were TIs 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.”
TA Criterion 3  (1. Carotid Artery Angioplasty for Atherosclerotic Stenosis – Nonrandomized, Comparative Trials), continued

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=N.S.). Minor ipsilateral strokes were similar (2.2% vs. 2.9%, p=N.S.). Total adverse outcomes for the two groups were similar (9.6% vs. 6.6%, p=N.S.). The stent group had a 6-month angiographic restenosis rate of 3.1%; no comparative data were reported for the endarterectomy group. The stent group had a 2-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.”

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 7 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 ≥ 50% recurrent restenosis for both groups. Results showed that, overall, angioplasty/stenting had a higher 30-day stroke rate (16%; 3 major and 1 minor stroke) than repeat endarterectomy operations (3.4%; 1 major stroke) (p <.05).
TA Criterion 3  (1. Carotid Artery Angioplasty for Atherosclerotic Stenosis – Nonrandomized, Comparative Trials), continued

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 ≥ 50% restenosis was higher in angioplasty patients (24%) than in endarterectomy patients (0%) (p <.001). Stroke-free survival rates at 6 months and 1, 2, and 3 years for angioplasty were 79%, 79%, 79%, and 79%, respectively, and for endarterectomy patients were 97%, 97%, 94%, and 82%, respectively, versus (p =.059). Freedom from recurrent ≥ 50% restenosis rates at 6 months and 1, 2, and 3 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

The first prospective consecutive randomized trial of carotid angioplasty vs. endarterectomy for symptomatic severe internal carotid artery disease was reported by Naylor and colleagues (1998). 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.
TA Criterion 3  (1. Carotid Artery Angioplasty for Atherosclerotic Stenosis – Randomized Trials), continued

This was because all 10 carotid endarterectomy operations proceeded without complication, but 5 of the 7 patients who underwent angioplasty had a stroke (p=.0034), 3 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, 2001), this was an international, multicenter, unblinded, “exploratory” randomized trial. 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 7 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 vs. endarterectomy: the rates of disabling stroke or death were 6.4% vs. 5.9%, respectively (p=N.S.); the rates of any stroke lasting more than 7 days or death were 10% vs. 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 1 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 3 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 1-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 vs. endarterectomy groups is wide.
TA Criterion 3 (1. Carotid Artery Angioplasty for Atherosclerotic Stenosis – Randomized Trials), continued

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.”

2. Vertebral and Basilar Artery Angioplasty for Atherosclerotic Stenosis

Case Reports and Case Series

At least 3 individual case reports (Honda et al., 1994; Houdart et al., 1996; de Assis et al., 2002) and 13 case series (Clark et al, 1995; Higashida et al, 1996; Terada et al., 1996; Mori et al, 1997; Mori et al, 1998; Malek et al, 1999; Nomura et al., 1999; Mori et al, 2000; Gomez et al., 2000a; Nahser et al., 2000; Rasmussen et al., 2000; Levy et al., 2001; Jenkins et al, 2001) of angioplasty/stenting in treatment of atherosclerotic vertebral and basilar artery stenosis have been published. In some reports (Clark et al, 1995; Higashida et al, 1996; Mori et al, 1998; Malek et al, 1999; Mori et al, 2000), it is impossible to separate the vertebrobasilar angioplasties from other (anterior circulation) procedures.

There have been no comparative or randomized trials comparing angioplasty to other therapies for atherosclerotic vertebral and basilar artery stenosis.

3. Cerebral Artery Angioplasty for Acute Embolic or Thrombotic Stroke

Case Reports and Case Series

Percutaneous transluminal angioplasty of intracranial arteries has been undertaken in patients with acute stroke. One case report concerned its use for embolic total occlusion of the middle cerebral artery (Mori et al, 1999 Sep). In several cases series, it has been attempted, with some successes, in acute occlusions (Ueda et al, 1997; Nakano et al, 1998; Suh et al, 1999; Ringer et al., 2001), subacute occlusions (Mori, 1997 Jan), and chronic occlusions (Mori et al, 1999 Jan) of the middle cerebral artery.
There have been no comparative or randomized trials comparing cerebral angioplasty to thrombolytic, anticoagulant, or other therapies for stroke.

4. Cerebral Artery Angioplasty for Atherosclerotic Stenosis

**Case Reports and Case Series**

At least 5 case reports (Touho et al., 1995 Jan; Al-Mubarak et al., 1998; Mori et al., 1999 May; Gomez et al., 2000b; Derdeyn et al., 2001) and 17 case series (Smith et al., 1983; Clark et al., 1995; Touho et al., 1995 Jun; McKenzie et al., 1996; Callahan et al., 1997; Mori et al., 1997 Feb; Mori et al., 1998 Sep; Mori et al., 1998; Hacein-Bey et al., 1998; Yokote et al., 1998; Eckard et al., 1999; Marks et al., 1999; Morris et al., 1999; Takis et al., 1999; Mori et al., 2000; Alazzaz et al., 2000; Ramee et al., 2001), have been published of percutaneous transluminal angioplasty for severe atherosclerotic stenosis of the cerebral arteries.

There have been no comparative or randomized trials comparing cerebral angioplasty to other therapies for cerebral artery atherosclerotic stenosis.

5. Cerebral Artery Angioplasty for Vasospasm

**Case Reports and Case Series**

At least 3 case reports of individuals (Barnwell et al., 1989; Konishi et al., 1990; Zubkov et al., 1999) and 12 case series (Zubkov et al., 1984; Newell et al., 1989, Higashida et al., 1989; Terada et al., 1993; Le Roux et al., 1994; Coyne et al., 1994; Honma et al., 1995; Ohkawa et al., 1996; Firlik et al., 1997; Bejjani et al., 1998; Eskridge et al., 1999; Polin et al., 2000), suggest that percutaneous transluminal balloon angioplasty is efficacious in increasing cerebral blood flow, and in improving ischemic neurological deficits induced by vasospasm following subarachnoid hemorrhage.

**Nonrandomized, Comparative Trials**

An early, small nonrandomized, comparative trial by Terada and colleagues (1997) reported results in a total of 25 patients with symptomatic vasospasm following rupture of a cerebral aneurysm. Patients were treated by percutaneous transluminal angioplasty (PTA) and/or intra-arterial papaverine infusion (IAP).
TA Criterion 3  (5. Cerebral Artery Angioplasty for Vasospasm – Nonrandomized, Comparative Trials), continued

PTA was performed for proximal vasospasm which was located in a main arterial trunk (n = 3), IAP was chosen for distal vasospasm (n = 12), and PTA and/or IAP was performed for diffuse vasospasm which located in proximal and distal arteries (n = 10). Following treatment, on the Glasgow outcome scale, all patients in the proximal vasospasm group were “good” to “moderately disabled.” In the distal vasospasm group, 8 patients were “good” to “moderately disabled,” but 4 patients were “severely disabled.” The authors concluded that balloon angioplasty was effective for proximal vasospasm, but intra-arterial papaverine was not always effective for distal or diffuse vasospasm.

In a larger nonrandomized, comparative trial, Elliott and colleagues (1998) compared balloon angioplasty to intra-arterial papaverine infusion for the treatment of vasospasm following subarachnoid hemorrhage. They compared results obtained in 125 vasospastic distal internal carotid artery or proximal middle cerebral artery vessel segments in 52 patients. Specifically, they reported on mean pre- and post-treatment (24-, 48-hour) blood flow velocities in the involved vessels using transcranial Doppler monitoring after papaverine infusion or balloon angioplasty. Papaverine infusion alone was used in 24 vessel segments in 13 patients and balloon angioplasty alone was performed in 101 vessel segments in 39 patients. Repeated treatment was required following papaverine infusion in 10 vessel segments in 6 patients because of recurrent vasospasm but repeated treatment after balloon angioplasty was needed in only one vessel segment (p < 0.001). Seven vessel segments (29%) with recurrent spasm following papaverine infusion were treated with balloon angioplasty. Papaverine-treated vessel segments demonstrated a 20% mean decrease in blood flow velocity (p < 0.009) at 24 hours post-treatment, but velocities were not significantly lower than pretreatment levels at 48 hours post-treatment (p = 0.133). Balloon angioplasty resulted in a 45% mean decrease in velocity to a normal level following treatment (p < 0.001), a decrease that was sustained. The authors concluded that balloon angioplasty was superior to papaverine infusion for the permanent treatment of vasospasm following subarachnoid hemorrhage.

Katoh et al. (1999) reported a third non-randomized comparison of intra-arterial papaverine infusion versus balloon angioplasty versus standard conservative therapy for the treatment of vasospasm following subarachnoid hemorrhage in 84 patients.
Intra-arterial papaverine infusion was performed for asymptomatic vasospasm in 10 patients and for symptomatic vasospasm in 4 patients. Angioplasty was performed for asymptomatic vasospasm in 18 patients and for symptomatic vasospasm in 12 patients. The other 40 patients were treated with standard medical therapy including hypervolemic and hypertensive hemodilution. The clinical outcomes of these patients were analyzed using the Glasgow Outcome Scale. Results showed better outcomes for patients treated with angioplasty, but not for those treated with papaverine infusion, than for those treated with standard medical therapy. Recurrence of vasospasm occurred more often after papaverine infusion than after angioplasty. Undesirable complications such as abrupt development of unconsciousness were experienced during papaverine infusion but not during angioplasty. The authors concluded that percutaneous transluminal angioplasty is superior to intra-arterial papaverine infusion.

None of these trials was a randomized comparison. However, results of all three were consistent in suggesting that balloon angioplasty was superior to intra-arterial papaverine infusion for treatment of vasospasm following aneurysmal subarachnoid hemorrhage.

Finally, Johnston (2000), reporting on the effect of endovascular services on cerebral aneurysm treatment outcomes, found that patients treated at institutions that used angioplasty for vasospasm had a 16% reduction in risk of in-hospital death compared with patients treated at other institutions (RR, 0.84; 95%CI, 0.71-0.98; p= 0.03). However, the technique was only performed in 2% of cases, suggesting that it alone could not account for the improved outcomes noted. Rather, the authors surmised that availability of angioplasty was likely be a marker for aggressive and attentive multidisciplinary care or for more skilled narrow interventional radiologists.

**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).
TA Criterion 3  (5. Cerebral Artery Angioplasty for Vasospasm – Patient Risks), continued

Al-Mubarak et al (2000) 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; McCabe 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. (2002) 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 2 large subgroups of patients in the CAVATAS trial did not show any significant difference in neuropsychological sequelae between the two treatments at 6 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).
TA Criterion 3 (5. Cerebral Artery Angioplasty for Vasospasm – Patient Risks), continued

Nonetheless, a major current issue is the need for 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 some 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).

With transluminal angioplasty for vasospasm induced by subarachnoid hemorrhage, there have been reports of fatal rupture of the intracranial carotid artery during the procedure (Linskey et al., 1991; Zubkov et al., 1994).

Other arterial complications: Intracranial percutaneous transluminal angioplasty is associated with risks related to vasospasm, arterial trauma, and compromise of perforating vessels (Takis et al., 1997). Percutaneous transluminal angioplasty of the basilar artery has been complicated by arterial rupture by the guidewire apparatus, leading to massive subarachnoid hemorrhage (Volk et al, 1997). 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).

Cardiac complications: 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 have 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.

Local complications: Femoral hematomas and retroperitoneal hemorrhage have been described (Jordan et al, 1997).
Pending Trials

Several randomized trials of angioplasty/stenting of carotid stenosis are ongoing (Johnston, 2001).

A major NIH-sponsored multicenter randomized trial called the Carotid Endarterectomy vs. Stent Trial (CREST) is currently underway. With a planned enrollment of 2500 patients, the trial compares the efficacy of carotid stenting using a single extending system (ACCULINK, Guidant, Temecula, CA) vs. 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 4 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.

In addition, the FDA has recently approved an Investigational Device Exemption (IDE) for the CARESS study, a trial sponsored by the International Society of Endovascular Specialists (Roubin et al., 2001). This observational trial will enroll patients excluded from the CREST trial, including symptomatic patients with a ≥50% stenosis and asymptomatic patients with a ≥75% stenosis by ultrasound. The primary endpoints are similar to those in CREST. Comparative carotid endarterectomy outcomes will be obtained from a concurrent prospective registry of endarterectomy procedures done at the study sites.

Finally, the NIH is currently funding a randomized trial of angioplasty for vasospasm at the University of California, Davis (PI: Dr. J.P. Muizelaar), comparing early (prophylactic) angioplasty to angioplasty at the time of symptom onset. There is no medical therapy arm in this trial.

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 two randomized trials of carotid angioplasty vs. carotid endarterectomy for primary carotid stenosis.
TA Criterion 3  (5. Cerebral Artery Angioplasty for Vasospasm – Summary), continued

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. Therefore, TA Criterion 3 is not met for carotid angioplasty.

With only case reports and case series and no randomized or non-randomized comparative trials, TA Criterion 3 is not met for vertebral and basilar artery angioplasty for atherosclerotic stenosis, intracerebral artery angioplasty for acute embolic or thrombotic stroke, and intracerebral artery angioplasty for atherosclerotic stenosis.

With three non-randomized comparative trials suggesting that balloon angioplasty was superior to intra-arterial papaverine infusion and one study suggesting a 16% reduction in risk of in-hospital death among patients treated at institutions that used angioplasty for vasospasm, TA Criterion 3 is met for angioplasty for vasospasm of intracerebral arteries following aneurysmal subarachnoid hemorrhage.

**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%) (McCrory 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. One of the two randomized comparative trials was suspended prematurely because of a much higher incidence of stroke in the angioplasty group than in the endarterectomy group (Naylor et al, 1998). The other randomized comparative trial documented that angioplasty with or without stenting had similar major risks and similar effectiveness in stroke prevention compared with carotid endarterectomy.
TA Criterion 4, continued

Residual or recurrent carotid stenosis has been noted after both carotid endarterectomy and angioplasty. In the Asymptomatic Carotid Atherosclerosis Study (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).

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 for this indication.

For acute ischemic stroke, the established alternative to intracerebral angioplasty is thrombolytic therapy (Broderick, 1998). The NINDS t-PA Stroke Study demonstrated that recanalization of occluded brain arteries can successfully salvage ischemic brain if intravenous tissue plasminogen activator (t-PA) is initiated within 3 hours of stroke onset (NINDS, 1995). Intraarterial thrombolytic therapy has yet to be proven effective and safe in improving long-term outcome of ischemic stroke patients. Mechanical lysis of clots, perhaps in combination with pharmacological therapies, will require advances in catheter technology (Broderick, 1998). However, published studies do not compare cerebral artery angioplasty to the established alternative of thrombolytic therapy with t-PA. Because of this, it is impossible to conclude that intracerebral angioplasty/stenting improves the net health outcomes as much as or more than the established alternative of thrombolytic therapy. TA Criterion 4 is not met for this indication.

For intracranial atherosclerotic stenosis, the established alternative to intracerebral angioplasty is anticoagulation (warfarin or aspirin) and antilipidemic therapy (e.g., statin drugs). However, published studies do not compare cerebral artery angioplasty to these established alternatives.
TA Criterion 4, continued

Because of this, it is impossible to conclude that intracerebral angioplasty/stenting improves the net health outcomes as much as or more than these established alternatives. TA Criterion 4 is not met for this indication.

For cerebral vasospasm following subarachnoid hemorrhage, the established alternatives are conventional medical therapy with calcium channel blockers and hypertensive, hypervolemic, hemodilution therapy; and papaverine infusion. However, in three nonrandomized comparative trials conducted in patients refractory to conventional medical therapy, balloon angioplasty was superior to papaverine infusion. TA Criterion 4 is met for this indication.

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

Carotid, vertebrobasilar and cerebral angioplasty/stenting have been performed in multiple centers in the U.S., Europe, Australia, Canada (CAVATAS, 2001) and Japan. Centers performing the technique must have available one or more interventional radiologists who have received specific training in and who have experience with neuroradiology and angioplasty/stenting techniques. These procedures are technically demanding and patients must be carefully selected. Nonetheless, provided that physicians are experienced with the technique, results similar to those in the published trials summarized above should be attainable when used to treat individuals with in the community setting under conditions of usual medical practice. TA Criterion 5 is met.
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association

The Blue Cross Blue Shield Association Medical Policy Reference Manual statement of 07/10/98 states that, “Carotid angioplasty with or without associated stenting is considered investigational.”

Society for Vascular Surgery and the International Society for Cardiovascular Surgery, North American Chapter

A 1996 statement reads, “The Society for Vascular Surgery and the International Society for Cardiovascular Surgery, North American Chapter support the investigation, evaluation, and development of new and promising treatment methods for patients who have carotid artery disease. The safety of any new therapy, however, must be clearly established in controlled and adequately monitored clinical trials under Institutional Review Board and Food and Drug Administration guidelines for such therapy.

When such clinical trials can demonstrate that carotid angioplasty and stenting procedures have a treatment-related risk that is comparable with that of carotid endarterectomy, a prospective randomized trial should be conducted to determine the relative efficacy of the two treatment methods. Until the safety and efficacy of carotid angioplasty and stenting can be proved, the widespread clinical application of this technology is not justified.” (Joint Council, 1996)

American Association of Neurological Surgeons

A 1997 statement reads in part, “Preliminary reports suggest that carotid angioplasty and stenting can be performed with low risk and excellent angiographic results. These retrospective analyses were characterized by a lack of data concerning presenting symptoms, role of other neuroimaging procedures, and detailed pre- and post-treatment neurological examinations. In addition, long-term follow-up data for these patients are not yet available and the risk of subsequent stenosis this procedure is as yet unknown…the long-term effects of placing a stent in the carotid artery are unknown. The number of additional critical questions regarding carotid angioplasty and stenting remain unanswered. These and other equally important questions can be answered only by rigorous scientific study and analysis and the application of this technology to testing by randomized prospective controlled trials… At present, the application of carotid angioplasty and stenting should be restricted to patients enrolled in an institutional review board-approved and carefully monitored registry” (Joint Officers, 1997).
American Heart Association

The Councils on Cardiovascular Radiology, Stroke, Cardio-thoracic and Vascular Surgery, Epidemiology and Prevention, and Clinical Cardiology of the American Heart Association issued a position statement on carotid stenting and angioplasty in 1998. It reads, in part, “At a minimum, the equivalence of percutaneous approaches to surgical carotid endarterectomy must therefore be established in sufficiently powered, prospective randomized trials…At this point, carotid angioplasty and carotid stenting, with rare and infrequent exceptions, should be undertaken only as part of a prospective, randomized trial with independent, dispassionate oversight” (Bettman et al, 1998)

Consensus Conference Statement

Veith et al (2001) published results of a 1999 consensus conference involving 17 experts in interventional radiology, vascular surgery, interventional cardiology, and neurosurgery. Consensus conference conclusions included: “Carotid bifurcation angioplasty and stenting (CBAS) should not currently undergo widespread practice, which should await results” of randomized trials. CBAS is currently appropriate treatment for patients at high risk in experienced centers. CBAS is not generally appropriate for patients at low risk. Neurorescue skills should be available if CBAS is performed. When cerebral protection devices are available, they should be used for CBAS. Adequate stents and technology for performing CBAS currently exist.” There were divergent opinions regarding the proportions of patients presently acceptable for CBAS treatment (varying from <5% to 100%) and best treated by CBAS (varying from <3% to 100%).

Society of Cardiovascular and Interventional Radiology (SCVIR)
American Society of Interventional and Therapeutic Neuroradiology (ASITN)
American Society of Neuroradiology (ASNR)

On March 25, 2002, Blue Shield received a position statement and detailed letter with references from all 3 societies, which reads in part: “We recommend that Blue Shield cover intracranial angioplasty and stenting for atherosclerosis and for vasospasm and join with the Centers for Medicare and Medicaid Services (CMS) in coverage of carotid angioplasty and stenting when provided as part of an approved investigational device (IDE) clinical trial.”
California Association of Neurosurgeons (CANS)
Association of California Neurologists (ACN)

The executive boards of CANS and CAN have both adopted a position statement prepared by Dr. Neil Martin, which reads, in part:

“Carotid angioplasty/stenting is NOT indicated for routine atherosclerotic carotid stenosis at the carotid bulb – standard management is carotid endarterectomy. Angioplasty/stenting, while not standard, is being appropriately studied for this application in a prospective randomized trial.

Carotid angioplasty/stenting is an acceptable alternative for types of symptomatic carotid stenosis treated by conventional endarterectomy: post-surgical re-stenosis, post-radiation stenosis, fibromuscular dysplasia, and high inaccessible cervical carotid lesions.

Intracranial angioplasty with or without stenting is an acceptable alternative for patients with symptomatic severe intracranial carotid, vertebral, basilar or branch vessel (eg MCA) stenosis, who have continued to have ischemic symptoms (TIAs or stroke) despite maximal medical therapy (anti-thrombotic therapy, plus aggressive anti-atherosclerosis treatment).

Intracranial angioplasty is an acceptable alternative for patients with severe symptomatic cerebral arterial spasm after subarachnoid hemorrhage, when the ischemic neurologic deficit fails to respond to, or occurs despite maximal medical therapy (nimodipine, induced arterial hypertension, hypervolemia, hemodilution, optimization of cardiac output).

It should be pointed out that these are unusual clinical situations, representing a small number of patients in each category. Because of this, it is highly unlikely that prospective randomized trials will ever be done to address use of angioplasty for these specific indications. We therefore have to rely on case series (generally Class III evidence), which support these indications.”
CONCLUSION

The published literature regarding carotid angioplasty/stenting for atherosclerotic primary and recurrent stenosis includes a host of case series, five nonrandomized comparative trials and two randomized comparative trials. Unfortunately, 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, one of the two randomized comparative trials was suspended prematurely because of a much higher incidence of major stroke in the angioplasty group than in the endarterectomy group. The other randomized trial comparing angioplasty with or without stenting and endarterectomy found similar major risks and similar effectiveness in stroke prevention. Two large multicenter trials are still in progress, one of which is a randomized comparison of carotid angioplasty/stenting to endarterectomy.

The published literature regarding vertebrobasilar angioplasty/stenting for atherosclerotic stenosis and regarding cerebral artery angioplasty for acute embolic or thrombotic stroke and atherosclerotic stenosis, consists only of case reports and small case series. No randomized comparative trials are available.

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.

Based on currently available publications, it is impossible to conclude that the new technology of carotid or cerebral angioplasty/stenting improves the net health outcomes as much as or more than the established alternatives of carotid endarterectomy for atherosclerotic carotid stenosis, intravenous t-PA for stroke, or anticoagulation (aspirin or warfarin) and antilipidemic therapy for atherosclerotic cerebral artery stenosis.

TA Criteria 3-4 are not met for these indications.

However, in 3 non-randomized, comparative trials, cerebral artery angioplasty for treatment of cerebral vasospasm induced by subarachnoid hemorrhage appears to be superior to intra-arterial papaverine in having a more sustained effect on the vessels. In addition, patients treated at institutions offering angioplasty for vasospasm appear to have a significant reduction in risk of in-hospital death compared with patients treated at other institutions. A randomized trial evaluating early (prophylactic) vs. late (symptomatic) intracerebral angioplasty for vasospasm is ongoing.

TA Criteria 1-5 are met for this indication.
RECOMMENDATION

It is recommended that carotid artery angioplasty with or without stenting does not meet Blue Shield TA criteria.

It is recommended that vertebobasilar artery angioplasty with or without stenting for atherosclerosis and stroke does not meet Blue Shield TA criteria.

It is recommended that intracerebral artery angioplasty with or without stenting for atherosclerosis and stroke does not meet Blue Shield TA criteria.

It is recommended that intracerebral artery angioplasty for vasospasm induced by subarachnoid hemorrhage meets Blue Shield TA criteria for patients in whom standard medical and pharmacological therapy has failed.

June 12, 2002

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ADDENDUM:

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

6. Carotid Artery Angioplasty for Atherosclerotic Stenosis

Randomized trials

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...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 1 TIA occurred in the angioplasty group. In terms of other complications, in the endarterectomy group, 1 patient died from a myocardial infarction; 4 patients had transient peripheral or cranial neuropathies; and 1 had a wound hematoma requiring reexploration. In the angioplasty group, 1 patient sustained a popliteal artery thrombosis necessitating a below-the-knee amputation; 3 patients suffered retroperitoneal hemorrhage, 7 patients suffered bradycardia requiring temporary pacing, and 12 patients had hypotension requiring treatment. MRI scans at 6 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 1 week in 80% of the angioplasty group and 67% of the endarterectomy patients, and within 2 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.
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 three randomized trials of carotid angioplasty vs. carotid endarterectomy for primary carotid stenosis...

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

Carotid endarterectomy is the major established alternative to carotid angioplasty and 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%) (McCrory 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 and 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. Two randomized comparative trials documented that angioplasty with or without stenting had similar major risks and similar effectiveness in stroke prevention compared with carotid endarterectomy (CAVATAS, 2001; Brooks et al, 2001). However, a third randomized comparative trial was suspended prematurely because of a much higher incidence of stroke in the angioplasty group than in the endarterectomy group (Naylor et al, 1998).

Reference