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Realizing the Potential of Carotid Artery Stenting: Proposed Paradigms for Patient Selection and Procedural Technique.

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Abstract: Carotid artery stenting, compared with carotid endarterectomy (CEA), is a safe, effective and less invasive method of revascularization for extra-cranial carotid artery stenosis. Carotid stenting is established as the treatment-of-choice for certain high-risk patient subsets, and ongoing clinical trials are evaluating this method across a broader clinical spectrum, including asymptomatic patients. For carotid stenting to reach its full potential, an acceptable risk of peri-procedural complications, particularly in low-risk individuals, must be ensured (the "3% rule"). The present article provides an in-depth review of carotid stenting, with special emphasis on the process of risk stratification pertaining to clinical, anatomic and procedural considerations necessary to optimize procedural safety and patient outcomes.

Introduction

Carotid artery stenting is now widely utilized worldwide as an alternative to carotid endarterectomy (CEA) for the prevention of stroke caused by extracranial carotid atherosclerosis. Compared to CEA, carotid stenting offers the patient a less invasive means of achieving this goal without the operative risks associated with the former procedure. Recent observational and randomized studies have shown that the risk of stroke and death is comparable when skilled operators perform these procedures in well-defined patient subsets. Multiple large-scale, multi-center randomized trials are

in progress to assess the broad-based applicability of carotid stenting to the community at large.

It is noteworthy that the initial studies of carotid stenting leading to device approval by the FDA and limited third party reimbursement in the US focused on patients considered unsuitable for CEA due to high surgical risk. However, the Asymptomatic Carotid Atherosclerosis Study (ACAS)[1] trial in North America and the more recent Asymptomatic Carotid Surgery Trial (ACST)[2] trial in Europe have emphasized the superiority of surgical revascularization over medical therapy in asymptomatic patients with carotid artery stenosis. With the rapid evolution of catheter-based techniques for carotid revascularization, carotid stenting has become feasible in a wide spectrum of patients but appropriate case selection, particularly in the treatment of asymptomatic patients, requires definition. To this end, the "3% Rule" has been coined to ensure case selection resulting in 30-day complication rates of less than 3%. In this article, we focus on patient selection and technical considerations that are prerequisite for procedural safety in carotid stenting, necessary for the next round of randomized clinical trials designed to study this therapeutic modality in asymptomatic patients.

Historical Perspective

Carotid revascularization, initially by CEA, was introduced in early 1950's as a method to prevent atheroembolic stroke due to disease of the carotid bifurcation and internal carotid artery (ICA). At least 4 prospective randomized trials have demonstrated that CEA compared with medical therapy reduces the risk of stroke in patients with carotid artery stenosis,[1-4] with the magnitude of clinical benefit dependent on symptom status, lesion severity and the risk of surgery-related complications. While peri-operative death and stroke rates were low in the highly-selected patients enrolled in these trials, the risk for other complications

causing significant morbidity was not negligible. For example, in NASCET cranial nerve damage was observed in 5.6% of patients and serious medical complications occurred in 8.1%.[5,6]

Effective experimentation with carotid angioplasty began in the mid 1970's[7,8] and rapidly developed during the following 2 decades.[9-13] The contemporary era of carotid stenting began in 1994 when Iyer, Roubin, Vitek and Yadav instigated the first rigorous, prospective study of carotid stenting entailing independent neurological evaluation at baseline and at 30-days post procedure.[14] This study, and as the experience of others,[15] demonstrated that from the outset carotid stenting performed by experienced operators produced excellent outcomes. While stenting compared with balloon angioplasty significantly enhanced the efficacy and safety of percutaneous carotid revascularization, the development of embolic protection methods proved to be a major breakthrough in the field. From Vitek's early description of innominate artery angioplasty with occlusive balloon protection of the common carotid artery (CCA)[16], through pioneering work by Theron's [17] and Henry, [18] distal[19] and proximal[20] anti-embolic protection technology has rapidly developed. The availability of multiple embolic protection systems has been shown in many single and multicenter registries to confer a remarkably low risk of embolic complications following carotid stenting.[21-25] Thus, the feasibility of carotid stenting, its simplicity compared with CEA and the low morbidity afforded by distal protection devices has accelerated the acceptance and utilization of this procedure.

SHORT-TERM OUTCOMES AND THE IMPACT OF EMBOLIC PROTECTION DEVICES

Peri-procedural neurological complications, the major determinant of the risk-benefit ratio of carotid stenting, are due primarily to friable atheromatous material contained within carotid lesions that readily embolizes during angioplasty.[24,26,27] Embolic

protection devices (EPDs) that capture atheromatous debris liberated into the circulation from the angioplasty site have had a significant impact on the safety of carotid stenting. A number of such protection devices have recently been introduced and are under clinical evaluation.[19] Clinical experience indicates that their use is associated with a very low risk of neurological events, particularly major disabling stroke.[18,21,28] Our group's experience in 1,358 carotid stent procedures was recently reported.[29] In a prospective registry, a comparison of carotid stenting procedures with (n=538) vs. without (n=775) utilization of an EPD was associated with significantly lower 30-day rates of any stroke (1.9% vs. 5.8%, respectively, p=0.0003) and stroke or death (2.4% vs. 6.5%, respectively, p=0.001). EPD use was an independent multivariate predictor of freedom from peri-procedural stroke (p=0.0009). The impact of EPD use on stroke risk was most pronounced in patients >80 years old (n=220), in whom the 30-day rates of any stroke (6.6% and 15.4%, p=0.02) or major stroke (0.8% and 2.3%, p<0.001) with were significantly lower with vs. without EPD use, respectively. In asymptomatic, low-risk patients the 30-day rate of any stroke was only 1.1% with EPD use. Similar results were reported from the European Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK, n=1,483) registry,30 in which use of an EPD (n=668) compared with no EPD (n=815) was also associated with significantly lower in-hospital rates of stroke (1.7% vs. 4.1%, p = 0.007) and stroke or death (2.1% versus 4.9%, p = 0.004). The randomized, multicenter Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, comparing CEA with carotid stenting utilizing EPD, enrolled 334 patients at high-risk for surgical intervention due to co-existent vascular disease or nonvascular co-morbidities,[31] has also shown that this percutaneous strategy is safe. Major adverse events rates at 30-days were lower in the carotid stenting compared with the CEA arm (death [0.6% vs. 2%], any

stroke [3.8% vs. 5.3%], major ipsilateral stroke [0.0% vs. 1.3%], p=NS for all comparisons), as was the composite endpoint (4.4% vs. 9.9%, p=0.06). Notably, carotid stenting was entirely devoid of cranial nerve injury, which occurred in 5.3% of the CEA patients. Recent prospective registries of carotid stenting in high-risk patients (reporting 30-day major adverse event rates <8%) support the findings of the SAPPHIRE trial.[32,33] Thus, EPD use should be considered the standard of care in carotid stenting.

Long-term outcomes

Numerous studies have shown that late neurological events and restenosis after carotid stenting are rare. In the SAPPHIRE trial, the 1-year rate of major ipsilateral stroke following carotid stenting was 0.0% (vs. 3.5% with CEA, p=0.02).[31] Roubin et al prospectively followed 528 patients after carotid stenting over a 5-year period.[34] Follow-up, available in 99.6%, ranged from 6 months to 5 years (mean 17-months). Freedom from any ipsilateral stroke was 99% after the first post procedural month. With 30-day events included, long-term freedom from any ipsilateral strokes was 95%. Restenosis requiring re-intevention occurred in only 3% of patients. Importantly, outcomes were independent of symptom status or gender. Gray et al performed serial clinical follow-up and imaging studies in 136 patients after carotid stenting, demonstrating angiographic restenosis in 4 patients (3.1%) at 6-month, an additional 2 cases between 6 and 12 months, with no further restenosis or any major ipsilateral strokes at 2-year follow-up.[35] Although the data await publication, other high-volume centers have also witnessed low rates of late adverse events, with long-term freedom of death or ipsilateral major stroke in excess of 95% and restenosis in <5% (Mathias KD and Wholey M, personal communication). The available data thus demonstrate that in a broad spectrum of patients, carotid stenting is a safe, efficacious and durable procedure.

Indications

Candidates for carotid revascularization include patients with symptoms attributable to an ipsilateral carotid lesion and asymptomatic patients, usually diagnosed as the result of a screening procedure. In general, the indications for carotid revascularization relating to symptomatic status and lesion severity are similar for the endovascular and surgical strategies (Table 1).[36-39]

With experience in the field of carotid revascularization increasing it is becoming evident that carotid stenting is particularly suitable for certain patient subsets characterized by specific clinical and/or anatomical features. Patients who have serious co-morbid medical and/or anatomical conditions that increase the risk from an open surgical approach or general anesthesia should be primary candidates for carotid stenting.[31] These conditions include advanced age, significant cardiac and pulmonary disease, prior neck irradiation or radical surgery, restenosis following endarterectomy, contralateral carotid occlusion, high lesions behind the mandible and low lesions that would require thoracic exposure. Trials comparing carotid stenting and CEA in patients at low risk for either procedure are in progress.

Carotid stenting has a number of notable relative contraindications. Patients who are intolerant to antiplatelet agents are more safely managed with endarterectomy. Similarly, if the patient has a compelling reason to undergo a major surgical procedure within 3 to 4 weeks that will require the cessation of anti-platelet therapy, CEA may be a better option. While contrast nephropathy is an important consideration in patients undergoing carotid stenting, this seldom represents a contraindication since experienced operators should rarely require more than 75 cc of contrast material complete the procedure and since gadolinium-based contrast can also be used. Several important anatomical conditions represent relative contraindications to carotid stenting. These consist of: 1) tortuosity of the aortic arch, brachiocephalic vessels, or carotid bifurcation that make access and device delivery to the ICA risky, technically challenging, and occasionally impossible; and 2) heavy,

concentric calcification. The presence of a mobile thrombus should be also ruled out before carotid stenting. Intracranial arterial stenoses, arteriovenous malformations or stable aneurysms are not necessarily contraindications for CAS. However, in the latter case, stringent control of blood pressure and careful modulation of anticoagulation is mandatory.

Patient Selection

The clinical advantages afforded by any therapeutic intervention are obviously dependent upon the natural history of the untreated condition, the clinical course following a successful intervention and the risks inherent to the procedure itself. The risk of peri-procedural complications following CEA appears to be largely independent of symptoms and the degree of the stenosis[4] and the available data suggest that the same holds true for carotid stenting, even before the widespread implementation of embolic protection (unless the lesion contains a large thrombus load).[34,40]

Symptomatic patients. Given the demonstrated benefit of revascularization compared with medical therapy in the management of symptomatic lesions that are severely stenotic (70-99% diameter stenosis by the North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria[38,41,42]), CEA in these patients has been considered indicated when the periprocedural risk of death or stroke is <6%.[37] The same is applicable to carotid stenting. Accumulating data demonstrate that the rates of peri-procedural death or disabling stroke following carotid stenting are below 6%, even without the universal use of EPDs[34,43] and in high risk patients.[31]

The risk of recurrent ipsilateral neurological events with conservative medical management is much lower for moderate (50-69% by the NASCET criteria) compared with severe carotid lesions.[4] Thus, the potential benefit of any

revascularization procedure is inversely related to angiographic lesion severity,[39] and in patients with lesions of moderate or borderline severity the risk-benefit ratio of carotid stenting should weighed accordingly.

Asymptomatic patients. Stroke prevention in asymptomatic patients requires special consideration. The risk of stroke in the territory of an asymptomatic carotid artery has been shown to be strongly dependent on angiographic lesion severity[44] (although the same may not apply when lesion severity is assessed by ultrasound[2]). In the European Carotid Surgery Trial (ECST), the 3-year rates of ipsilateral strokes were approximately 2% and 5.7% for lesions less or greater than 70%, respectively[44] (in this respect, it is noteworthy that the methods for the measurement of the degree of carotid stenosis varied among trials, so that application of the ECST compared with the NASCET methodology results in greater degrees of stenosis for a given lesion[38,42]).

For clinical benefit to be derived by patients with a significant but asymptomatic stenosis, the composite 30-day rates of death or stroke following the procedure must be ≤3%. Due to the very low event rates in patients with asymptomatic lesions of moderate severity, it is unknown whether currently available interventional techniques can improve long-term outcomes over those achievable with optimal medical management.

The 3% Rule

In determining the risk of death or stroke associated with carotid stenting it is crucial to recognize 4 factors that have been associated with increased procedural complications following carotid stenting (Table 2). In the multicenter Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) registry, the risk of 30-day stroke or death was directly related to age (<60 years: 1.7%; 60-69 years: 1.3%; 70-79: 5.3%; and >80 years: 12.1%, p=0.006). The risk attributable to

advanced age in this preliminary analysis appeared to be independent of other clinical (e.g., gender, symptom status), anatomic (e.g., lesion severity, the presence of distal arterial tortuosity), or procedural (e.g., use of distal protection devices) factors.[45] Decreased cerebral reserve is another important clinical factor when considering the risk of carotid stenting. Carotid revascularization (carotid stenting or CEA) is usually associated with some element of particulate embolization and interruption of cerebral blood flow. Patients with good cerebral reserve generally tolerate this well but patients with prior strokes, lacunar infarcts, microangiopathy or dementia of varying stages are much more likely to experience neurological deficits even after carotid stenting. The presence of an isolated hemisphere with lack of good collateral support will amplify the effects.

While some lesion characteristics (e.g., degree of stenosis, complexity, length) indicate potential technical difficulties, the two most important anatomic findings indicating increased procedural risk in carotid stenting are tortuosity and heavy concentric calcification. Excessive tortuosity is defined as ≥2 bend points exceeding 90°, within 5 cm of the lesion, including the take off of the ICA from the CCA (Figure 1). Excessive tortuosity is problematic since it increases the difficulty of CCA access, does not permit easy delivery of devices across the lesion, and may prevent distal positioning of a EPD with a sufficient "landing zone" for stent placement. The multiple factors expose the patient to the risks of emboli from arch atheromata, air embolism, excessive use of contrast, bifurcation plaque disruption and ICA dissection. These risks are markedly higher if the external carotid artery (ECA) is occluded or if plaque extends into the bifurcation and distal CCA. Importantly, tortuosity cannot be fully assessed until the sheath (or guide catheter) has been placed in the CCA since force by the catheter directed cephalad, towards the unyielding base of the cranium, tend to exaggerate ICA tortuosity (Figure 2).

Finally, heavy calcification is an important predictor of complications. This is defined as concentric calcification, ≥3 mm in width and deemed by at least 2 orthogonal views to be circumferentially situated around lesion (Figure 3). Heavy calcification, especially in combination with arterial tortuosity, causes difficulties in tracking devices, lesion dilation, stent positioning, and achieving adequate stent dilatation. In our experience in over 1500 cases, the presence of 2 or more of the risk factors listed in Table 2 is an important prognosticator in patients being considered for carotid stenting. Although special techniques generally result in a satisfactory angiographic outcome, the risk of neurological adverse events is in excess of the "3% Rule" and thus prohibitive.

Clinical decision-making incorporating these principles in the selection of patients for carotid revascularization is depicted in Figure 4.

Procedural Considerations

The protocol for carotid stenting has been described in detail previously.[46] The following technical and procedural factors have proved important in ensuring a facile and complication-free carotid stenting procedure.

Peri-procedural monitoring and management. With respect to pre-procedural therapy, adequately dosed dual anti-platelet therapy is key. Patients must receive either a combination of clopidogrel 75 mg and aspirin 325 mg for 5 days prior to carotid stenting, or alternatively, loading doses of clopidogrel (600 mg) and aspirin (650 mg) at least 4 hours prior to the procedure. On the day of the procedure oral anti-hypertensive therapy is withheld and adequate volume status is ensured. Mild sedation may be offered to anxious patients but for the vast majority reassurance and adequate local anesthesia are all that is necessary. Avoiding sedatives enhances neurological monitoring and limits hypotension. Continuous monitoring of pulse oximetry, intra-arterial pressure, and heart rhythm is essential as is meticulous

control of hemodynamics. Intravenous atropine (0.6-1.0 mg) should be administered following placement of the sheath in the CCA to suppress bradycardic responses to balloon inflation and stent implantation. Hypotension is invariably noted after balloon dilatation of the stent, particularly in elderly patients with heavily calcified stenoses. This hypotension is generally benign. However, in some patients aggressive volume expansion, intravenous phenylephrine and occasionally dopamine infusions are necessary. Blood pressure elevation after the relief of the stenosis can also occur and should be treated using intravenous nitroglycerine, nitroprusside or labetalol. If distal protection is with an occlusion-aspiration system, blood pressure should be lowered *before* deflating the occlusive balloon. Anticoagulation therapy with carotid stenting is vital, but it is equally important to note that modest anticoagulation levels should be targeted. Either heparin (70 IU/Kg initial bolus, targeting an activated clotting time of 200-250 sec) or bivalirudin (0.75 $mg \cdot kg^{-1}$ bolus, followed by a maintenance infusion of 1.75 $mg \cdot kg^{-1} \cdot hr^{-1}$) are administered immediately with sheath insertion. Prolonged infusion of anticoagulant drugs is unnecessary and these are stopped immediately following stent deployment. Glycoprotein IIb/IIIa antagonists are not routinely used.[47]

The use of 6Fr femoral sheaths and arteriotomy closure devices allows for early ambulation. This counteracts the bradycardia and hypotension commonly associated with carotid stenting. Post procedural intensive care monitoring is unnecessary although patients should be followed in a monitored environment by staff familiar with the post procedural course and groin access site management. Remaining sheaths should be removed as early as possible, once the activated clotting time has fallen below 150 sec. Hypotension should be treated aggressively and causes unrelated to baroreceptor resposes (e.g., retroperitoneal hemorrhage) should be considered and managed promptly.

Procedural stages. The extent of diagnostic angiography is determined by the anatomic information obtained by pre-procedural non-invasive studies, but should at the very least include an accurate evaluation of lesion severity; the carotid bifurcation, ipsilateral intracranial anatomy, and the anatomy of the CCA. If a balloon-occlusive EPD is to be used, it is mandatory to ensure adequate collateral flow from the contralateral carotid or posterior circulations. For diagnostic angiography, a double-curved 5Fr catheter (VTK, Cook Inc.) and a 0.038-inch angled-tip hydrophilic coated wire are used.[48] In >98% of patients this system enables safe selective catheterization of the CCA, ICA and ECA, both subclavian arteries and at least one vertebral artery. The same catheterization technique is used to introduce a 6F 90 cm sheath (Shuttle, Cook Inc.) into the CCA, generally delivered over a soft-tipped, stiff 0.035-inch guide wire (e.g., Supracore, Guidant Inc.) positioned in the ECA. The tip of the sheath is positioned in the distal CCA. "Guiding-shots" of the lesion immediately following sheath placement are performed, since ICA tortuosity might be more pronounced by the sheath. Next, the lesion is crossed with a 0.014-inch guide wire, usually that of the EPD. The EPD is deployed in a distal segment of the cervical ICA. Next, the lesion is dilated with an undersized coronary balloon ("pre-dilatation). The stent is the deployed and subsequently "post-dilated" with a conservatively sized, low profile balloon. Finally, the EPD is removed and final angiography is performed. Using contemporary rapid exchange ("monorail") systems the entire process should take as little as 10 to 15 minutes.

Special considerations. *Catheter placement.* Modifications of the catheter placement technique may be required when the lesion is located in the distal segments of the CCA or if the ECA cannot be catheterized. In these cases, the tip of the 5Fr catheter and guide wire (Amplatz Super Stiff J-wire, MediTech) assembly over which the 6Fr sheath is placed in the CCA is kept below the lesion or bifurcation. In cases of