Management of Patients with Carotid Artery Disease is a Team Effort

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"… all the most acute, most powerful, and most deadly diseases, and those which are most difficult to be understood by the inexperienced, fall upon the brain."
–Hippocrates

These words are just as relevant today as they were thousands of years ago, particularly regarding the treatment of patients with carotid artery disease (CAD). The most common form of CAD, atherosclerotic carotid artery occlusion (ACAO), accounts for 10-15% of the approximately 700,000 strokes in the United States each year. Treatment alternatives include surgery, endovascular intervention, or drugs, and although the choice of a management pathway may seem simple, it is actually quite complicated, requiring a delicate balance of science and art to apply evidence-based medicine and clinical experience to each particular patient's unique condition. In the last decade, treatment of patients with CAD has become a contentious issue filled with questions about what is the best treatment and when it should be done.

HOW SHALL WE TREAT PATIENTS WITH CAD?

Carotid Endarterectomy

For both symptomatic and asymptomatic CAD, carotid endarterectomy (CEA) is the most common revascularization technique. Concerns in the 1990s about its safety and efficacy have been resolved since several randomized controlled trials showed it to be highly effective in preventing stroke and improving survival in appropriately selected patients.

But CEA is not for everyone. The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[1], the European Carotid Surgery Trial (ECST)[2], and the Veterans Affairs 309 Trial[3] compared CEA in *symptomatic patients* with medical treatment alone, and concluded that in patients with 70% or greater carotid stenosis, CEA is very beneficial for the first two to three years after surgery.

In patients with 50-69% stenosis, CEA decreases the risk of ipsilateral stroke, but the absolute risk reduction is small in comparison to patients with severe stenosis. Thus, to provide actual benefit to such patients, clinicians must consider the patient's risk factors and the surgeon's skill before offering CEA. The trials also found that in patients with less than 49% stenosis, surgery either had no benefit or actually increased the risk of ipsilateral ischemic stroke.

According to a pooled analysis of the trial data (Table 1), the five-year risk of stroke in patients with more than 70% stenosis is 26%, which surgery lowers to 10.2%. However, in patients with moderate or low-grade stenosis, surgery has a smaller advantage*, and therapeutic decisions must consider the medical and surgical risks in addition to other factors.

The risks of CEA include complications from general anesthesia, cranial or superficial nerve injury, and wound complications. The overall risk of surgery is higher for women than for men. In addition, there is a small but significant risk of stroke and death immediately following the procedure, which decreases with time. Interestingly, in the NASCET trial, the risk of ipsilateral stroke among medically treated patients was greatest during the first two to three years of followup, but decreased to a level similar to that of surgically treated patients after five years.

Despite the reality that CEA has little to no benefit and may even cause harm in some patients with less than 70% stenosis, more than 100,000 carotid endarterectomies are performed each year in the U.S., and not all are appropriate. Wong et al reported that of operated patients with 50-70% stenosis, as many as 20% had CEA inappropriately, and in about 50% the reasons were uncertain[6]. Similarly, Halm et al found that 72.5% of the more than 2100 patients who had CEA were asymptomatic, and nearly 15% of the patients had the procedure for

* *Editors note*: The surgical risk in these pooled data is not only noticeably higher overall than the experience at LGH, but was higher in patients with low or moderate stenosis than in those with severe stenosis – an observation that raises concern about the quality of at least some of the surgery in these trials.

TABLE 1: FIVE YEAR ACTUARIAL RISKS, ABSOLUTE RISK REDUCTION (ARR*) AND RELATIVE RISKS (RR†) OF IPSILATERAL STROKE AND ANY OPERATIVE STROKE OR DEATH, WITH REGARD TO DEGREE OF SYMPTOMATIC INTERNAL CAROTID ARTERY STENOSIS.

Stenosis %	Surgical Risk	Medical Risk	ARR*	RR†
<30	11.8	9.6	−2.2	1.23
30–49	14.6	17.8	3.2	0.82
50–69	13.8	18.4	4.6	0.75
70–99	10.2	26.1	15.9	0.39
Near Occlusion	17.2	15.5	−1.7	1.11

* ARR = Risk of stroke with medical therapy minus risk with surgical therapy.
† RR = Ratio of stroke risk with surgical therapy vs. medical therapy.
Based on the pooled analyses of North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Veterans Administration (VA) Symptomatic Trial (Cooperative Studies Program 309).

Source: Rothwell PM et al. Lancet 2003;361:107; Nguyen-Huynh MN and Johnston SC. *Stroke Rounds* 2004:2(8).[4,5]
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inappropriate reasons.[7,8] Appropriate patient selection is thus critically important, and in light of the risk of vascular events, stroke neurologists tend to wait to recommend surgery until the severity of stenosis exceeds 75%*, unless there are other compelling indications, such as the need for concurrent coronary artery bypass, etc. My own experience supports these findings. On some occasions, when examining patients who were about to have a CEA, I found that the area of their brains affected by the stroke received its blood supply from the vertebral artery, not from the carotid artery, so the CEA would have had no potential to confer a benefit that would outweigh the unavoidable risk of the procedure.

Three major trials *in asymptomatic patients* compared CEA versus medical treatment for carotid disease.[9,10,11] All three studies found that the overall five-year risk of stroke in patients with more than 60% stenosis was significantly reduced (by about half), and the greatest benefit was in patients with at least 70% stenosis. However, in asymptomatic patients, a perioperative stroke and death rate of more than 3%, and inappropriate patient selection, could obviate any benefits from the procedure. A prospective analysis of patients with asymptomatic CAD found that in patients with less than 75% stenosis, the stroke rate is relatively low, so surgery must be clearly justified. The study also could not identify any factor, other than severity of stenosis and presence of ischemic heart disease, that predisposed such patients to an increased risk of stroke (see Table 2).

Carotid Angioplasty and Stenting

Angioplasty with stenting is a good alternative for patients with severe stenosis who have a high surgical risk because of severe cardiac disease or prior CEA with

TABLE 2: ANNUAL PERCENTAGE RATE OF VASCULAR EVENTS IN PATIENTS WITH ASYMPTOMATIC CAROTID STENOSIS.

	Vascular Event			
Percent Stenosis	TIA	Stroke	Cardiac	Vascular Death
<50 (Mild)	1.0	1.3	2.7	1.8
50–75 (Moderate)	3.0	1.3	6.6	3.3
>75 (Severe)	7.2	3.3	8.3	6.5

Period of Follow up: 41 months; TIA = Transient Ischemic Attack; Adapted from: Norris JW et al. *Stroke* 1991:22;1485-90.[12]

* *Editor's note*: This complex topic is further confused by the use of inconsistent boundaries between moderate and severe stenosis. Most surgeons use 70%, since this degree of stenosis has specific hemodynamic implications for flows and gradients, but some reports use 75% as the boundary. The matter is further complicated by the fact that the human eye, reviewing an angiogram, cannot differentiate between 70% and 75% stenosis.

carotid restenosis, or when the surgery is technically difficult because of an unusually high- or low-level lesion. Balloon angioplasty, first performed for CAD in the 1980s, is now used with stenting because it lowers the risk of plaque dislodgement and restenosis. Risks of the procedure itself include embolic stroke, neck or groin hematoma, reperfusion injury, carotid thrombosis, carotid receptor dysfunction, dye-induced renal failure, encephalopathy, and a migraine-like phenomenon that can be mistaken for strokes and TIA.

Angioplasty and stenting are less invasive and can be less expensive than CEA, phenomena that are generally attributable to shorter hospital stays and avoidance of general anesthesia.*

Two of the most frequently cited randomized trials that compared angioplasty and stenting to CEA, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), and the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), showed there was no significant difference in the risk of stroke or death among patients who had stenting compared with surgery.[13,14] Notably, in CAVATAS, in which most of the patients had stenosis of 70% or more, patients treated with endovascular or surgical approaches experienced a 6% total incidence of disabling stroke and stroke with death. This high rate was nearly three times the surgical risk reported in the NASCET and ECST trials. In addition, the rate of restenosis in the endovascular group was twice as high as in the surgery group.

The SAPPHIRE trial, the first to compare CEA with current techniques for carotid stenting in which an embolic protection device was used, found that stenting with a protection device was not inferior in selected patients.[15] This study also had its shortcomings, however, because 55% of the patients were poor candidates for surgery and were excluded from randomization, and more than 20% of patients in each group had restenosis following prior CEA, which made them incontrovertibly better suited for endovascular treatment.

Also, more recently the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study concluded that in patients with symptomatic carotid stenosis of 60% or greater, the rates of stroke and death were significantly lower after surgical endarterectomy than after stenting.[16]

Despite the promising results of CAVATAS and SAPPHIRE, more investigation is needed to evaluate the effectiveness of angioplasty and stenting. Several ongoing clinical trials, including CAVATAS-2 and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) by the National Institutes of Health, may provide more information. In addition, several trials are investigating the use of different distal embolic protection devices, including filtration devices. Some clinicians have even projected that as new types of stents become available, stenting and angioplasty may be preferred over surgery in the future.**

MEDICAL TREATMENT

Treatment of Risk Factors

All patients should have their associated risk factors treated with high-dose statins, angiotensin-converting enzyme (ACE) inhibitors, or ACE receptor blockers (ARB). In addition to direct effects on blood lipid and blood pressure, these drugs may exert a plaque-remodeling effect as an added benefit.

Antiplatelet Therapy

In patients with CAD and less than 50% stenosis, and in patients who have had a previous stroke or TIA, antiplatelet agents are prescribed for secondary stroke prevention. Although at one time aspirin was the standard first line treatment, it is unsuitable for certain patients because it increases the risk of major bleeding, and clopidogrel alone may be preferred in aspirin intolerant patients.

* *Editor's note:* Many surgeons at LGH perform CEA under regional anesthesia with the patient in a sedated but responsive state which permits the patient's neurological status to be continuously monitored, a particularly valuable indicator while the carotid artery is clamped. For some surgeons this technique has resulted in an incidence of perioperative stroke well below the national averages. It can also accelerate discharge from the hospital – usually on the first postoperative day in uncomplicated cases.

** *Editor's note:* It is important to point out that in all these trials of angioplasty, the physicians performing the intervention are experienced with the technique. If angioplasty becomes more widespread, there will be an inevitable learning curve during which complication rates will likely be higher than in these trials, and there will be turf battles for control of these patients.

Clopidogrel, dipyridamole, and ticlopidine, have all been shown to be effective in preventing strokes, either alone or in combination with aspirin. One of the most notable randomized trials, the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH),[17] compared aspirin and clopidogrel with clopidogrel alone, and found no significant difference between the two regimens in the prevention of vascular events. Although several studies of short-acting dipyridamole and aspirin found the combination did not significantly reduce the risk of stroke, one study has shown that extended-release dipyridamole may be more effective.

Anticoagulation

Anticoagulation with heparin or coumadin is appropriate in certain patients with symptomatic CAD (e.g. mobile thrombus, crescendo TIA, and preocclusive disease).

Withal, it must be emphasized that stroke has many causes in addition to carotid disease. Thus far, no study has assessed the effectiveness of antiplatelet or anticoagulant therapy in a cohort of stroke patients confined to those with carotid disease. Several ongoing trials will provide more information,[18] but in the meantime, selection of the best agent(s) requires not only clinical *findings*, but clinical *judgment*, all based on experience and interest in this complicated and rapidly evolving field.

Important Considerations for Therapeutic Decisions

The information and guidelines provided by randomized controlled trials only provide part of the story for decisions about appropriate management of CAD. In order to apply the guidelines in an optimal manner for each patient, a clinician not only needs comprehensive knowledge of current medical literature and proficient clinical skills, but also creativity. As discussed further below, any intervention in the patient with CAD, whether medical, surgical, or endovascular, requires thoughtful evaluation of various clinical factors and the cerebrovascular anatomy. The surgical complication rate of the clinician's hospital also plays an important role. Lancaster General Hospital, designated a Primary Stroke Center by the Joint Commission on Accreditation of Healthcare Organizations, has been recognized by the commission as a center that makes exceptional efforts to foster better outcomes for stroke care. Surgical results are regularly analyzed and discussed. Since they inevitably vary among surgeons, they are not the subject of this report by a stroke neurologist.

Proper timing of the intervention is naturally also essential. Although conventional wisdom recommends waiting 4-6 weeks after an event before proceeding to revascularization, decisions to proceed earlier can be made on a case-specific basis. Some stroke neurologists would like to have surgery performed as soon as possible after a stroke, but in my experience minor symptoms and subtle clinical findings may conceal a substantial territorial stroke that can be seen on a brain MRI, and precludes early revascularization. Even if symptoms have subsided after a substantial stroke, it is necessary to consider complications such as reperfusion injury, cerebral hemorrhage, and disruption of auto-regulation, before deciding upon early revascularization. In sum, there is no cookbook recipe on how to approach the patient with an acute stroke. In my opinion, waiting to revascularize may be wiser unless there are compelling reasons to intervene early.

HOW SHOULD PATIENTS BE EVALUATED?

Because many patients are completely asymptomatic, with disease discovered only incidentally on a physical examination or during a screening procedure, proper evaluation therefore requires consideration of not only the patient's age, general medical condition, and disease presentation, but also the degree of stenosis, any other cerebrovascular disease, and any co-morbid conditions. Both tandem occlusive lesions and bilateral carotid artery disease are associated with a higher incidence of neurovascular and cardiovascular events, as well as a higher incidence of fatal ischemic strokes. The prudent use of neuro-imaging is crucial to choosing the proper method for revascularization.

Several non-invasive modalities – each with its own strengths – are now widely used, including computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and neurovascular ultrasound, which includes carotid ultrasound and Transcranial Doppler (TCD). MRA and CTA allow the identification and assessment of the vessel walls; carotid ultrasound provides invaluable information regarding plaque morphology, the degree of stenosis, and the volume flow rates; gray scale imaging evaluates plaque quality.

Transcranial Doppler tests vasomotor reactivity and allows the practitioner to identify collaterals and cerebral vascular reserve in patients with asymptomatic CAD. Micro-embolic signals can also be identified by

Transcranial Doppler and this can be applied to assess both medical and surgical interventions.

Still, none of these non-invasive modalities alone can substitute for digital subtraction angiography, which – though invasive, and associated with a stroke risk of 1% -remains the gold standard for imaging cerebral and cervical vessels. Regardless of who treats the patient with CAD, all clinicians should be responsible for management of complications related to invasive angiography.

WHO SHOULD TREAT PATIENTS THAT NEED CAROTID INTERVENTION?

Further complicating the management of CAD is the need to choose from among the many interventionalists – radiologists, cardiologists, cardiothoracic surgeons, vascular surgeons, and neurosurgeons – who all have a vested interest in providing their own approach. In no other medical field are so many qualified specialties vying for patients.

Certainly, the importance of these specialists should not be minimized, as they know the strengths and limitations of their individual approaches in dealing with specific cases. But with so many therapeutic options available, I believe that a neutral party who is not an interventionalist – the stroke neurologist – is needed to decide on the best course of management for a patient. In addition, the stroke neurologist can provide long-term followup and handle the consequences of procedure-related complications such as thrombosis, embolic strokes, carotid dissection, reperfusion cerebral injury, and intracranial hemorrhage. The neurologist can also continue to manage the patient's risk factors, such as smoking, diabetes, hypertension, and hypercholesterolemia.

SUMMARY

Treatment of patients with CAD follows a complicated algorithm that requires knowledge, skill, and creativity to sift through the wealth of evidence, apply the evidence to a specific patient, and choose the optimal treatment pathway. For patients with CAD there is no single across-the-board criterion that identifies whom to treat and how to treat. Adding to the complexity of management decisions is the variety of interventionalists vying for the opportunity to treat the patient. A stroke neurologist is an unbiased clinician who can assess the patient's condition, help the patient choose the best treatment regimen, and even help select the best interventionalist to perform the specific intervention. In my opinion, neurologists should not be sidelined in patient care, but should be an integral part of the treatment plan. Together with cardiologists, surgeons, radiologists, and other clinicians, neurologists can work to seek the best balance of science and art to provide the highest quality of care for the patient.

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