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## Treatment of Atherosclerotic Disease at the Cervical Carotid Bifurcation: Current Status and Review of the Literature\*

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Carotid endarterectomy is increasingly used to decrease the risk of stroke associated with cervical atherosclerotic stenosis, and some investigators claim that the results and benefits for carotid stenting are comparable with those of endarterectomy. A review of the literature reveals that there is incomplete knowledge concerning carotid artery atherosclerotic disease, its associated risks, the optimal medical therapy, indications for intervention, and the optimal interventional procedures. No trial has evaluated the currently available “best medical therapy” or compared it with endarterectomy. Current data indicate that carotid endarterectomy as it is presently practiced in the United States bears little relationship to the populations studied, methods used, or results obtained in the North American Symptomatic Carotid Endarterectomy Trial and Asymptomatic Carotid Atherosclerosis Study. There is a high level of interest in carotid stenting, but there is a lack of definitive proof of safety, efficacy, and durability. Carotid stenting can be performed with a reasonable degree of safety, but until it is clinically validated, carotid stenting should be reserved for patients who are at high risk for stroke.

Cervical carotid artery atherosclerotic disease is a correctable cause of stroke, and recent controlled trials of surgical endarterectomy for carotid stenosis have shown its benefit (1–5). Some investigators claim similar morbidity and mortality rates with endovascular treatment, leading to the hope that less invasive therapies will be equally effective for the treatment of carotid stenosis (6–8). The recently published “Carotid Stenting and Angioplasty: A Statement for Healthcare Professionals from the Councils on Cardiovascular Radiology, Stroke, Cardiovascular Surgery, Epidemiology and Prevention, and Clinical Cardiology, American Heart Association” (9) presented several important considerations concerning this developing area of medical

practice. To facilitate optimal patient care in cases of carotid atherosclerosis, a review of the natural history of carotid bifurcation atherosclerotic stenosis, current medical and surgical therapies, and status of carotid stenting has been made.

### Natural History and Treatment of Symptomatic Carotid Atherosclerotic Stenosis

No trial to evaluate the natural history or risk of stroke from extracranial carotid artery stenosis has been performed using presently available best medical therapy (which might include warfarin, dipyridel, aspirin plus another drug such as dipyridamole, etc.). At the time the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was started in 1986, aspirin alone was thought to be optimal and was therefore primarily used as the best medical therapy. Carotid endarterectomy for the prevention of stroke has been extensively studied, and guidelines have been disseminated (1, 10, 11). One arm of the NASCET study was halted in 1991 because of the shown benefit of carotid endarterectomy for patients with stenoses greater than 70% as compared with patients treated with aspirin (1). The cumulative risk of any ipsilateral stroke was found to be 26% at 2 years in aspirin-treated patients and 9% in surgically treated patients. The 30-day perioperative risk for any stroke and death was 5.8%. The incidence of fatal or major ipsilateral stroke in 2 years was reduced from 13.1% in the aspirin group to 2.5% in the surgical group. Higher degrees of stenosis were directly proportional to higher degrees of stroke risk, with endarterectomy thus yielding a higher percentage of absolute risk reduction in these patients.

The recently published final results of the NASCET (2) indicate that there is benefit of surgery over aspirin therapy for carotid stenoses greater than 50% in men, even in patients with higher surgical risk due to comorbidity. For women, the benefits of surgery for stenoses between 50% and 69% do not uniformly outweigh the risks. In this moderate stenosis group, there was an overall perioperative stroke and death rate of 6.8% (2).

The interim results of the Medical Research Council (MRC) European Carotid Surgery Trial

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(ECST) showed a lower natural incidence of stroke in patients treated with aspirin with 70% to 99% stenoses (approximately 50% to 99% by the NASCET method of measurement) than reported in the NASCET results (16.8% risk of any ipsilateral stroke during a 3-year period compared with 26% in 2 years in the NASCET) (1, 3). The final ECST results indicated that of those patients undergoing endarterectomy, 7.0% had a stroke or died within 30 days of surgery (4) compared with the 5.8% in the NASCET study described previously. During the 3-year follow-up period, the surgical group experienced an additional incidence of stroke of 2.8%, for a total of 9.8%, as compared with the 2.5% additional incidence of ipsilateral stroke in 2 years for the NASCET study, for a total of 8.3%. In agreement with the NASCET, for symptomatic patients with 80% to 99% stenosis, surgical therapy was shown to be beneficial. The ECST showed no clear benefit from endarterectomy for any symptomatic stenoses below 70% to 80% (approximately 50% to 67% by NASCET criteria) because combined neurologic morbidity was equivalent (4). This documents the critical importance of accurate reproducible measurements of the degree of carotid stenosis that is used for patient selection criteria (12). Further analysis of data concerning endarterectomy has also been presented (13–18).

### **Natural History and Treatment of Asymptomatic Carotid Atherosclerotic Stenosis**

The benefits of carotid endarterectomy in the setting of asymptomatic carotid artery disease are not well established. Four trials comparing medical therapy with endarterectomy have been completed (5, 19–21). Three of these four showed no positive benefit for endarterectomy, and all showed commensurately low rates of stroke with medical therapy alone. The Mayo Asymptomatic Carotid Endarterectomy Trial was prematurely terminated because of a significantly higher number of myocardial infarctions and transient ischemic events in the surgical group, even though these were comparable with other surgical series. Only the Asymptomatic Carotid Atherosclerosis Study (ACAS) showed benefit of endarterectomy for asymptomatic carotid stenosis. The ACAS evaluated patients with stenoses of greater than 60% (5). The 5-year natural history risk of ipsilateral stroke was shown to be 11.0% (2.2% annual rate). The total 5-year risk of stroke was reduced by surgical endarterectomy to 5.1% (1.0% annual rate). This, however, was a decrease of only 1% per year, mostly accounted for by a reduction in minor strokes, not major strokes. The ECST Collaborative Group studied 2295 asymptomatic carotid stenoses ranging from 0% to 99% for an average of 4.5 years (22). The 3-year stroke risk in 127 patients with stenoses of 70% to 99% (50% to 99% by NASCET criteria) was 5.7% (1.9% annual rate). Another large series confirmed that the risk of moderate (50% to 79% by NASCET criteria) asymptomatic

stenosis was very low. With life-table analysis, the estimated cumulative risk of ipsilateral stroke was 0.85% in 1 year, 3.6% in 3 years, and 5.4% in 5 years (23). Additional studies have confirmed the low intrinsic risk of asymptomatic carotid stenosis (24–26). Most risk is associated with a stenosis greater than approximately 80%, corresponding to a residual lumen of approximately 1 mm or less (27).

These preliminary data imply that the major risk associated with cervical carotid artery atherosclerotic disease is the presence of symptoms, not necessarily the degree of stenosis. Moderate stenosis seems to be a higher risk for ipsilateral stroke in a symptomatic patient than a more severe stenosis in an asymptomatic patient (1, 3–5, 23).

As opposed to ACAS, which recommended carotid endarterectomy for asymptomatic patients with angiographically proven stenosis of more than 60%, the Canadian Stroke Consortium reached consensus that there was insufficient evidence to endorse this procedure for *any* level of asymptomatic stenosis (28). Reasons cited were lack of proof of reduction of the risk of major disabling stroke, the question of reproducibility of surgical results in the general population, and the unproved long-term benefit of surgical reconstruction. Because of a lack of convincing positive data, others have suggested that further trials to evaluate the efficacy of endarterectomy for asymptomatic carotid artery stenosis be conducted (29).

### **Unselected Carotid Endarterectomy Experience**

The American Heart Association (AHA) statements concerning indications for endarterectomy for carotid artery disease (10, 11) are organized by patient risk. The NASCET and ACAS were rigorously controlled, only the best operators performed procedures, and only carefully selected patients underwent surgery. Recently, published data indicate a significantly higher perioperative death rate for unselected Medicare patients undergoing carotid endarterectomy at the same institutions participating in the NASCET or ACAS or both than for the original study patients (0.6% for NASCET patients, 0.1% for ACAS patients, but 1.4% for all Medicare patients) (30). The perioperative mortality rate for Medicare patients undergoing carotid endarterectomy at non-study sites was 1.7% for high-volume institutions, 1.9% for average-volume institutions, and 2.5% for low-volume institutions. Thus, the mortality rate was higher at all institutions, including high-volume institutions and original trial sites, when unselected Medicare patients were considered. The patients participating in the NASCET and ACAS were younger and healthier than the typical Medicare patients undergoing endarterectomy at the same or other institutions. Older patients and those with significant comorbidity have been repeatedly shown to be at increased risk for periprocedural morbidity and mortality (16, 30).

The simple presence of carotid artery stenosis was not a clear indication for endarterectomy in either the NASCET or ACAS; comorbidities were taken into account during patient selection. Because the stroke risk in cases of asymptomatic carotid artery stenosis is low, the risk of therapy must be commensurately low for there to be any significant net benefit. Among the ACAS exclusion criteria were cardiac, pulmonary, renal, and neurologic disorders (5, 31). Absence of comorbidity may have had a significant impact on the ACAS results. A comparison of ACAS-eligible patients with ACAS-ineligible patients who underwent surgery at the same institutions revealed that ACAS-ineligible patients had milder stenoses while having exclusionary conditions (32). This was associated with increased postoperative myocardial infarction and mortality rates (32). These data indicate that altered patient selection criteria can increase complications and render this procedure inadvisable.

In short, current data indicate that carotid endarterectomy as it is presently practiced in the United States bears little relationship to the populations studied, methods used, or results obtained in the NASCET and ACAS studies. Patients undergoing endarterectomy in daily practice largely may not qualify for endarterectomy under NASCET or ACAS criteria. There is legitimate disagreement regarding whether asymptomatic carotid atherosclerotic disease should receive invasive treatment at all. At most, carotid endarterectomy for asymptomatic patients should be performed only if the combined perioperative stroke/mortality rate is less than 3% (11). This may be achievable only in relatively healthy patients. Asymptomatic carotid artery stenosis is a relatively benign condition and, like any other condition, should not be treated with a therapy worse than the disease. The symptomatic NASCET-ineligible patients may, however, eventually prove to be the ideal population for carotid stenting. Further study will resolve this issue.

### **Optimal Medical Therapy for Carotid Atherosclerosis**

As noted previously, no controlled trial has examined the risk of stroke from carotid artery disease treated with presently available best medical therapy; only aspirin therapy has been used. In recent years, risk factors for vascular disease have been more clearly defined, and new medical therapies are now available (33–40). Proof of efficacy of carotid endarterectomy was obtained without the benefit of this new knowledge or these recent pharmacologic advances and was therefore not established against contemporary best medical therapy. For example, hyperhomocysteinemia has been shown to be an independent risk factor for vascular disease and stroke and can be effectively identified and treated (33–38). Other medications with beneficial clinical effects on vascular disease that have not been compared with endarterectomy include previously available medications such as dipyrida-

mole and warfarin as well as improved oral antiplatelet agents (eg, ticlopidine, clopidogrel), lipid-lowering HMG-CoA reductase inhibitors (eg, lovastatin, pravastatin), the newer antiplatelet aggregants (GPIIb/IIIa inhibitors such as abciximab, eptifibatide, tirofiban, lamifiban), and oral agents with this same effect (eg, xemilofiban). In addition to favorably influencing coronary and peripheral vascular disease (33–36), some new medications have been shown to effect stroke risk beneficially (37–40). This decreased danger of stroke shifts the entire risk:benefit when comparing optimal medical therapy with endarterectomy or carotid stenting.

### **Carotid Angioplasty and Stenting**

In recent years, there has been increasing interest in treating cervical carotid artery bifurcation atherosclerotic disease by endovascular means as an alternative to endarterectomy (6, 7, 41–43). The motivations for this change include perceived improvement in quality of patient care, economic factors, and patient comfort. The increasing use of carotid stenting has caused concern to numerous health care professionals, including the members of the AHA (9), members of the American Society of Neuroradiology (ASNR) (44), and members of the American Society of Interventional and Therapeutic Neuroradiology (ASITN) (45). Controversy in the initial phase of development of a new therapy is common and should not dissuade active pursuit of a potentially valuable technique. Also, in comparing surgical endarterectomy with carotid angioplasty/stenting, it is important to recognize that perioperative complications other than stroke and death are not reported as end points in endarterectomy studies. Some uniquely surgical complications are not considered in the risk:benefit equation, although data indicate that they may be frequent. In the NASCET, for example, reported complication rates were 7.6% for cranial nerve palsies, 5.5% for wound hematoma, 3.4% for wound infection, 0.9% for myocardial infarction, and 3.0% for other cardiac complications (1). These complications are virtually all related to the operative procedure, are not trivial, and are rarely associated with carotid stenting (6, 7, 46, 47).

Angioplasty and stenting are currently used for the treatment of atherosclerotic disease in many vascular locations. This is almost exclusively for improvement in hemodynamic flow rate. This is not the goal with cervical carotid atherosclerotic disease. The overwhelming concern regarding this condition is atherothrombotic intracerebral emboli, not hemodynamic insufficiency. Although probably useful, intravascular stenting has not been proved to benefit this problem directly, particularly when adding procedurally generated emboli to the risk:benefit equation.

It has been shown in vitro, using carotid endarterectomy specimens (48), that emboli of several types are generated to varying degrees in all cases of angioplasty and stenting. Carotid stenting has



resulted in major strokes, and procedural emboli may be the cause, although most of these emboli are apparently insignificant, subclinical, or of minor consequence. The role of emboli in producing non-focal neurologic deficits can be difficult to recognize. For example, cardiopulmonary bypass has been widely practiced for more than 20 years. Although patients began to complain of subtle alterations in mental or neurologic functioning almost immediately, it is only now widely accepted that as many as 30% of patients undergoing surgery requiring systemic cardiopulmonary bypass suffer some degree of permanent brain damage (49, 50). Unrecognized permanent brain damage also has been reported to occur in approximately 15.1% of patients undergoing surgical clipping of unruptured intracranial aneurysms (51). It is unfortunate that these results were overlooked for such a long period, perhaps related to the lack of consistent in-depth pre- and postprocedural neurologic examination in some series. Although careful analysis of possible embolic sequelae of carotid stenting is being proposed, no specific evaluation has ever been performed of potentially subtle neuropsychological changes related to carotid endarterectomy. It must be recognized that the brain's primary function is not simply moving the arms and legs; rather, it is "thinking." In this context, no infarct is truly "asymptomatic," even if unobserved.

The lack of consensus regarding indications for carotid endarterectomy combined with improving medical therapies for vascular disease confound development of unambiguous indications for angioplasty and stenting. Some consider the indications for endovascular treatment to be the same as those presented by the AHA for surgical endarterectomy (10, 11); however, this presupposes procedural morbidity and mortality rates equal to those associated with surgery and a benefit and durability from endovascular treatment equal to that provided by surgery. As yet, there is no proof that this is the case. In general, restenosis rates after stenting in various other vascular locations range from 20% to 40% in as few as 6 months (52–56), although data concerning carotid stenting indicate that it is probably less than 10% (6–8, 42, 47). The rate of restenosis after endarterectomy is estimated to be lower but has not been clearly shown because of inconsistent follow-up (57–59).

Several series of carotid angioplasty/stenting for cervical carotid stenosis have been reported (6–8, 43, 46, 47, 60). Only one has yielded a periprocedural complication rate approaching the low risk of asymptomatic carotid artery atherosclerotic disease (6). No large controlled carotid stent series has shown a resultant decrease in stroke rate to the already low level of asymptomatic carotid stenosis, and the issue of restenosis after stenting for asymptomatic disease has not been resolved. In addition, two recent reports have indicated an unacceptable complication rate from carotid stenting (61, 62). One large retrospective comparison of carotid stenting and endarterectomy reported a periproce-

dural stroke and death rate of 9.7% for stenting and 0.9% for endarterectomy (61). Until these issues are clarified, carotid stenting should consequently be restricted to high-surgical-risk, symptomatic patients. An asymptomatic lesion should be presently considered an "unacceptable" indication, except under certain circumstances, possibly including high surgical risk patients with preocclusive states and contralateral occlusions. With continuing development of equipment and technical advancement and, as more data are gathered, carotid stenting may prove beneficial for a broad range of patients in addition to high-risk symptomatic surgical candidates (eg, older than 75 years with contralateral carotid artery occlusion, history of congestive heart failure, recurrent carotid artery stenosis, or other comorbidity) (47, 63, 64).

Endovascular treatment of atherosclerotic disease at the carotid bifurcation is neither technically simple nor without serious implications. It must be remembered that the target of therapy is the brain, not the neck, and the physiologic consequences of complications can be profound and grave (7, 8, 41–47, 52–56, 60). The primary complication of this procedure is atherothrombotic intracerebral embolization, which must be managed immediately by appropriate means that might include direct intracranial endovascular rescue. There are still relatively few individuals who are expert in all facets of the carotid stenting procedure; a team is usually necessary. There are, however, experts in brain imaging, cerebral hemodynamics, brachiocephalic catheterization technique, microcatheter manipulation, and the treatment of acute stroke and procedurally related intracranial emboli. Use of all available expertise in investigational protocols concerning new techniques and, in particular, this procedure, is warranted.

### Optimal Performance of Carotid Stenting

Angioplasty and stenting at the cervical carotid bifurcation is not a mature technology. Procedural success and safety need to be optimized using all available approaches. Potential areas of optimization include preprocedural evaluation and patient selection, procedural technique and equipment, and pharmacologic aids. The ability to prevent, detect, and treat complications is extremely important. An example of optimization of technique that may be of benefit is cerebrovascular hemodynamic protection (6). Early data emphasize the need for this protection, and elimination of all embolic consequences of carotid stenting should be the goal of technical progress (48).

Hemodynamic management of cerebrovascular insults is very different from that of cardiovascular insults; these differences may be more familiar to physicians experienced in the neurosciences. Pharmacologic aids (neuroprotectants) to reduce the effects of temporary ischemic complications (due to emboli) need to be evaluated. Furthermore, treatment for restenosis after carotid stenting is not

“standard surgical therapy;” repeated angioplasty is preferred for this problem because of its simplicity and effectiveness (47). Other treatments for restenosis already exist and may yield great hope, including brachytherapy (65–68) and drug therapy (eg, probucol [Lorelco, Hoechst, Marion, Roussel]) (69).

There is presently a lack of definitive knowledge concerning the specifics of this procedure. Nonetheless, the task to be accomplished, the goals to be met, and the necessary resources and expertise can be delineated. A wide scope of clinical and technical expertise is needed for optimal performance of this procedure, typically mandating a team approach. Clinical and technical abilities are critical, rather than specific training disciplines. As in any therapeutic regimen, the ability to manage technical procedural difficulties and treat complications is vitally important.

These concerns mandate addressing the following issues in a protocol investigating this new therapy:

1. Pre- and postoperative clinical neurologic evaluation
  - Reason: proper patient selection and accurate initial and follow-up (outcome) evaluation
2. Pre- and postoperative intracranial cross-sectional imaging, preferably MR imaging
  - Reason: for precise pre- and postprocedural evaluation, diagnosis of concurrent lesions or diseases, and detection of other, occasionally subclinical, previous or subsequent events.

Although this form of evaluation has not been performed regarding endarterectomy, a thorough contemporary trial of either carotid stenting or endarterectomy should include this form of procedural assessment.
3. Preoperative brachiocephalic and intracranial anatomic and hemodynamic evaluation (ie, a true cerebral angiogram, not a cervical carotid “neck only” angiogram)
  - Reason: for evaluation of correct indications, establishing baseline vascular status (should a later intracranial complication require evaluation of acute change) and to rule out associated additional (possibly intracranial) pathologic abnormalities
4. Technical capability to select the appropriate target vessel and perform the angioplasty/stent procedure safely
  - Reason: to complete the mechanics of the procedure safely
5. Ability to manage potential hemodynamic abnormalities associated with procedures involving the cervical carotid bifurcation
  - Reason: this is one of the predictable potential complications of manipulation of the carotid bulb
6. Intra- and postprocedural extra- and intracranial angiographic hemodynamic evaluation

- Reason: to recognize any cerebrovascular abnormality or hemodynamic change
7. Ability to perform intracerebral rescue
    - Reason: intracerebral embolus is the most serious and potentially life-threatening complication of this procedure

### **Future Direction for the Treatment of Carotid Stenosis**

There is incomplete knowledge concerning carotid artery atherosclerotic disease, its specific risk characteristics, the current optimal medical therapy, indications for intervention, and the optimal means of intervention. There are different types of carotid stenosis (eg, calcified, ulcerated, acutely hemorrhagic, “sonolucent”) with unique risk patterns independent of the degree of stenosis (48, 70–77). Newer imaging and evaluation techniques will further refine estimates of the intrinsic risk of this disease. Therefore, it may be found that certain carotid atherosclerotic stenoses can be adequately treated by modern medications whereas others may require more urgent intervention. Specific types of stenosis in specific patients may be found to require specific forms of therapy. Not only has optimal medical therapy undergone significant recent change but the results of endarterectomy as currently practiced do not seem to be consistent with previous trial results. Furthermore, the optimal endovascular technique and equipment have not yet been determined, and advances are continually being made. Clinical follow-up needs to be sufficient to determine short-term morbidity and mortality, to determine the durability of the repair, and to document a long-term decrease in the incidence of stroke with any form of therapy.

With the goal of comparing the safety and efficacy of carotid stenting to endarterectomy, a multicenter multidisciplinary trial is being organized: the Carotid Revascularization: Endarterectomy versus Stent Trial (CREST) (78). The CREST will use qualified, selected, and trained operators and will randomize 2500 symptomatic patients with greater than 50% angiographically proven or 80% carotid Doppler-proven stenosis to either carotid stenting or endarterectomy. The CREST was designed with great care by a multispecialty team of experts to attempt to make an accurate comparison of these two procedures. Further efforts to study carotid atherosclerotic stenosis, endarterectomy, and carotid stenting scientifically are to be commended and supported.

### **Conclusion**

Carotid endarterectomy has not been proven to be safer and more effective than currently available medical therapy for a large percentage of patients actually undergoing endarterectomy, and results of endarterectomy as currently practiced do not match the NASCET or ACAS results. There is a high level of interest in carotid stenting but a lack of defin-

itive proof of safety, efficacy, and durability. The relatively good results attained performing this procedure at certain institutions are commendable and encouraging; however, it must be appreciated that these results have generally been achieved by use of numerous physical resources and the involvement of skilled personnel from many disciplines. Until clinically validated, carotid artery angioplasty and stenting should be reserved for those patients who are at high risk for stroke, the best candidates being high-surgical-risk, symptomatic patients with significant comorbidity, and should be performed by a qualified team or individual with appropriate training and expertise. Carotid stenting under these circumstances may offer a less invasive means than endarterectomy for favorably influencing the risk of stroke and can be viewed as "acceptable, but not yet proven" (10, 11). Further research to clarify the roles of endarterectomy and carotid stenting is needed and encouraged and should be supported by all health care professionals interested in the advancement of patient care.

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