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Endovascular treatment of atherosclerotic extracranial cerebrovascular disease: reasonable or irresponsible?

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In recent years, endovascular therapy has expanded from the treatment of coronary and peripheral vascular disease into the more specialized treatment of cerebrovascular (CBV) disease. Almost simultaneously, prospective data have emerged concerning the benefits of surgical carotid endarterectomy in the treatment of disease of the extracranial internal carotid artery. Clinicians and investigators in many subspecialties have begun to "compete" to develop new therapies and this has, in turn, resulted in turf battles in institutions between subspecialty societies and in the literature.[1-4] At present, the endovascular therapy of extracranial CBV disease is not the province of a single subspecialty, but rather is being tackled by vascular surgeons, neurosurgeons,interventional radiologists, neuroradiologists, and interventional cardiologists. Cardiologists, given their acknowledged expertise in caring for very ill patients with cardiovascular disease, their interventional skill in small vessels, and their familiarity with stent technology, have an expanding place in the arena of treating vascular disease outside the heart in general, and in extracranial CBV disease, in particular.

In addition, there exists controversy about how, when, and where, the endovascular treatment of extracranial CBV disease should be applied. Some argue that it should be offered to patients only under strict experimental protocols involving randomized allocation to one or another treatment strategy. Others argue that the current experience with endovascular treatment – in particular, carotid stenting — demonstrates that it can be used as an alternative to standard surgical therapy. In the hope of addressing this dilemma, randomized trials are planned that will allocate patients randomly to surgical endarterectomy or to endovascular stenting. While the goals of this strategy are laudable, it may be premature to compare them to the mature technology of carotid endarterectomy. Clearly, stent technology, stent technique, and operator experience are evolving rapidly. The goal of this review is to convince the potentially skeptical reader that:

- **the available data suggest convincingly that the results are sufficiently similar to those from endarterectomy to justify the availability of a less invasive approach;**
- **it is now reasonable for prudent and experienced centers to develop programs to offer this treatment; and,**
- **the appropriate timing of randomized trials must be considered.**

Background

In treating atherosclerotic CBV disease, the clinician must consider three possible indications: to relieve the subjective symptoms arising from the vascular lesion; to reduce the possibility of future disability, principally from stroke; and lastly, to prolong life. All potential therapies should be judged by their ability to achieve these ends. It is important for cardiologists – as they become more involved in the treatment of cerebrovascular disease – to consider that there is a relative lack of a syndrome in the central nervous system that is comparable with the "supply/demand" effort angina that is familiar

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to many patients with coronary artery disease. Because of the brain's vigorous auto-regulation, it is unusual for atherosclerotic extracranial CBV disease to produce symptoms because of fixed macrovascular obstruction. Thus, periodic hypoperfusion because of increased "demand" (similar to that produced by increased heart rate or blood pressure in the heart) does not generally occur. The production of transient symptoms from CBV disease is usually related to "artery to artery" small emboli, a condition suggesting that CBV transient ischemic attacks (TIAs) and minor strokes are more akin to unstable coronary syndromes than they are to effort angina. In this regard, these symptoms are rarely disabling in and of themselves. Unlike chest discomfort that can limit exertion and activities of daily life, TIAs and minor strokes are usually not effort-related and, compared to episodes of exertional angina, their recurrence is *relatively* infrequent even when untreated. However, TIAs have achieved an important and respected status because they serve as harbingers of stroke and its attendant mortality and morbidity.

Thus, to treat cerebrovascular disease successfully from a patient's standpoint, the proposed therapy must prevent disabling stroke. All other endpoints, no matter how useful as "surrogates," are essentially unimportant to the patient. In planning mechanical treatment therefore, a knowledge of the natural history of cerebrovascular disease is essential.

Natural history of cerebral ischemia

In order to appreciate the potential for treatment, one needs to consider the natural history of symptomatic CBV disease when conventional medical therapy is used. The results of the recent Dutch TIA trial of over 3000 patients experiencing a TIA randomized to treatment with low- or moderate-dose aspirin are important. After 36 months,the risk of non-fatal stroke,was 5.7% in the low-dose group and 6.9% in the high-dose group. These patients were not anatomically stratified and the results would suggest that the risk of subsequent nonfatal stroke following a symptomatic TIA in patients treated with low-dose aspirin, is between 6 and 7% over 36 months, or approximately 2-3% per year.[5] Interestingly, the majority of morbid events occurring in both patient cohorts were not related to stroke and – as is a theme that emerges in the study of cerebrovascular disease – most of the morbidity and mortality in these patient groups is from coronary disease.

Armed with these and similar data, and concerned by assertions that surgical endarterectomy was overused and ineffective, several randomized trials were organized to address the question of whether endarterectomy offered benefits over medical therapy and, if so, in what patient groups. Though asymptomatic patients have also been studied (with results less clearly demonstrating the effectiveness of surgery), this review focuses on symptomatic patients. In the early 1990s, the European Medical Research Council, European Carotid Surgery Trialists (ECST) study was undertaken. At about the same time, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was begun. The ECST randomized patients with an angiographic 70-99% carotid stenosis, suffering a TIA ipsilateral to the stenosis within 180 days of randomization.[6] The NASCET randomized patients who had a 70-99% stenosis and symptoms within 120 days of randomization.[7] Both trials were angiographically mediated, though the stenosis calculation methods, treatment protocols, and crossover rates differed. Since its publication, the NASCET and its methods have emerged as the "gold standard" in the study of treatment of this patient group.

Table 1: NASCET 30-day follow-up (patients with 70-99% stenosis and symptoms within 120 days.)[5]

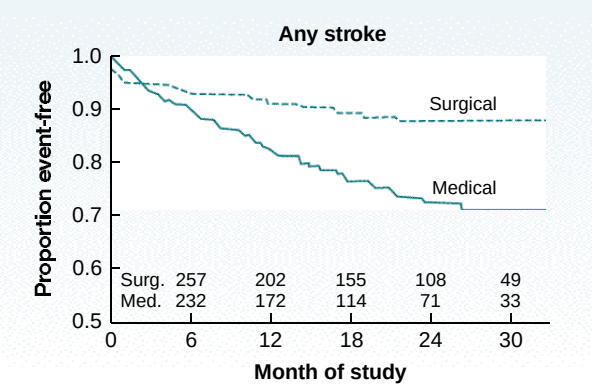
	Surgical (N=328)	Medical (N=331)
All strokes + death	5.8%	3.6%
Major stroke + death	2.1%	0.9%
Death	0.6%	0.3%
All stroke	5.5%	3.3%

Before participating in the trial, institutions were required to show acceptably low rates of complication and stroke (under 5%) in their surgically-treated patients. Patient inclusion criteria consisted of a TIA or non-disabling stroke within 120 days of randomization, and an ipsilateral, angiographically-documented 70-99% carotid stenosis. The patients needed to be surgical candidates and to agree to randomization to surgery or medical therapy. Important exclusion criteria (more about this later) consisted of characteristics associated with a high, non-atherosclerotic embolic stroke risk such as the presence of a prosthetic heart valve or atrial fibrillation, severe symptomatic coronary artery disease, or recent myocardial infarction (MI), past ipsilateral carotid endarterectomy or ipsilateral disabling stroke,and age >79 or life expectancy of < 5years.

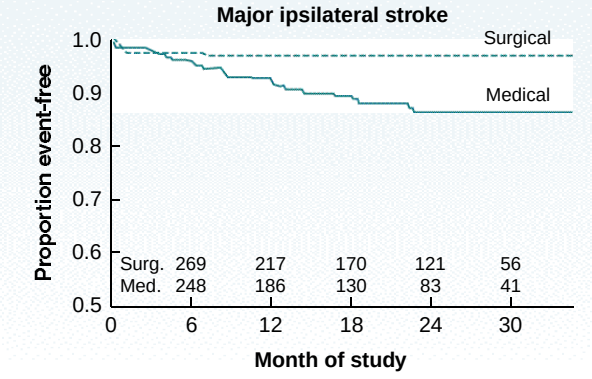
As might be expected, 30-day follow-up (Table 1) showed a "benefit" of medical over surgical therapy.This reflects surgical morbidity concentrated around the time of the operative procedure. 30-day death in both groups was similar. The stroke rate, both major and minor, was greater in the surgical group; however, by 36-months of follow-up, the total number of strokes (9 vs 26%) and major strokes (2.5 vs 13.1%, surgical vs medical, respectively) were less in the surgical group. Interestingly, the rate of death was similar in the surgical and medical treatment groups. Of particular note, as shown in Figure 1A, event-free survival in the surgical group at 30 months was significantly better than in the medical group. An important clue concerning this is shown in Figure 1B; it illustrates that the risk of major ipsilateral stroke following the 30-day surgical period was almost nil in the surgical group. This clearly suggests that successful surgical endarterectomy stabilizes the index lesion and effectively eliminates it as a cause of patient morbidity for at least three years.

Similar findings were generated from the ECST, yielding a risk of 21.9% of stroke in the medically-treated group at 36 months, and 12.3% in the surgically-treated group. As in the NASCET, the 36-month death rate in the surgical group of 9.9% was not different from the rate in the medically-treated group of 12.7%. Of the 455 patients treated surgically, there were 9 who suffered a fatal stroke or surgical death during follow-up, and in the medical group of 323 patients, 10 suffered a fatal stroke or death. Other causes of death were

Figure 1A: The risk of any stroke in NASCET.[5]



1B: The risk of ipsilateral stroke in NASCET.[5]



responsible for 36 and 31 of the remaining fatalities in the surgical and medical groups, respectively; again demonstrating that overall mortality in these patient populations was predominantly related to cardiovascular, than to CBV causes.

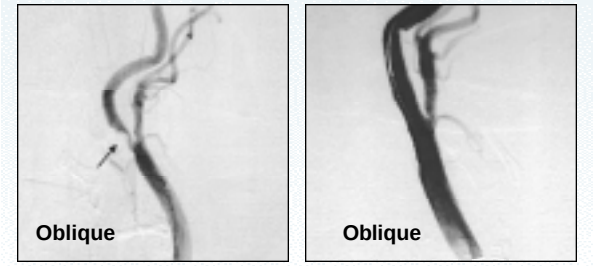
In summary, these randomized trials suggest that carotid endarterectomy increases the *short-term* (30-day) risk, while decreasing the long-term risk of ipsilateral stroke in symptomatic patients with 70-99% stenoses. Endarterectomy has not been demonstrated to prolong life and it must be performed between 6 and 20 times to prevent or defer one stroke for 36 months. Because medically unstable patients and those with a higher risk of "non-carotid" stroke were not included in these trials, endarterectomy has unclear benefit in patients with these characteristics. Finally, endarterectomy is uncomfortable and is associated with minor and moderate complications (eg, a 7% rate of cranial nerve palsy in the NASCET), neck hematomas, and wound infections.

Potential value of endovascular techniques

Now that carotid endarterectomy has been shown to be beneficial when compared to medical therapy in these patient subgroups, is there any room for the application of other new endovascular therapies? Since endarterectomy, when successful, stabilizes the offending stenosis and prevents ipsilateral carotid stroke,could other less invasive methods of plaque stabilization prove equally beneficial? Consider the patient whose initial angiogram is shown in Figure 2A. This individual is a

Figure 2A: Case example – the initial left carotid angiogram in an oblique projection shows severe stenosis at the origin of the internal carotid (arrow).

2B: Case example – the final left carotid angiogram in an oblique projection shows resolution of stenosis after stent deployment.



73-year-old woman who presented with a left ocular TIA. She described the event as a "venetian blind" that lasted 3-5 minutes. It was localized to her left eye and was associated also with scintillating scotomata. She had a past history of hypertension, hypercholesterolemia, hypothyroidism, depression, cataracts,peptic ulcer disease, ongoing angina pectoris, a past MI, and a remote history of polymyalgia rheumatica. Ophthalmologic examination confirmed the presence of a retinal embolus and noninvasive carotid studies showed a severe (70-90%, velocity ratio >7) stenosis. The initial right carotid angiogram showed flow into the external carotid circulation with the right internal carotid completely occluded. The anteroposterior view of the head shows no external to internal carotid collateral filling. The left common carotid angiogram confirmed a severe, short-segment stenosis of the left internal

Figure 3A: Case example – the initial left carotid angiogram (cranial field of view) shows some cross-filling of the anterior cerebral territory but little visualization of the contralateral middle cerebral territory.

3B: Case example – the left carotid angiogram after stent deployment (cranial field of view) shows continued cross-filling of the anterior cerebral, and much improved cross visualization of the middle cerebral territory.

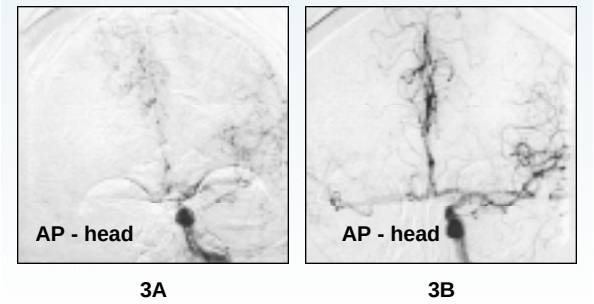


Table 2: UAB-LHH 30-day carotid stent outcomes.[7]

	Patients 409	Vessels 450
Deaths		
Procedure-related (neuro)	3 (0.7%)	
Procedure-related (non-neuro)	1 (0.2%)	
Non-procedure related	4 (1.0%)	
Major strokes		
Procedure-related		2 (0.4)%
Non-procedure-related		2 (0.4)%
Minor strokes		
>NIH Stroke Scale 2-3		11 (2.6%)
>NIH Stroke Scale ≤1		11 (2.6%)
Cranial nerve palsy	0	0
Q-wave MI	0	0

carotid artery. The intracranial view (Figure 3A) shows cross-filling of the anterior cerebral circulation on the right and some faint opacification of the middle cerebral territory. Following pre-dilatation, a single 8 mm x 20 mm Wallstent was placed and post-dilated, yielding the result shown in Figure 2B. Follow-up injection of the left common carotid (Figure 3B) shows vigorous cross-filling of both the anterior and middle cerebral territories. This patient was discharged the day following her procedure and maintained on aspirin and clopidogrel, and has been asymptomatic since.

Critics of carotid stenting have also suggested that early-published data suggest a high rate of procedural complications. Table 2 shows the complications of TIA, stroke, MI, and death reported by Roubin, et al in their series of patients treated with carotid stenting.[8,9] The aggregate total 6% rate of all strokes by 30-days post-procedure may suggest that this technique results in an excess of procedural events. Interestingly, this rate compares favorably with the overall rate of stroke and death at 30 days of 5.8% in the surgically-treated group in the NASCET – nearly a numerical identical risk. Of particular note is the "learning curve" that is apparent in the

Figure 4: The evolution of technique in carotid stenting.[7]

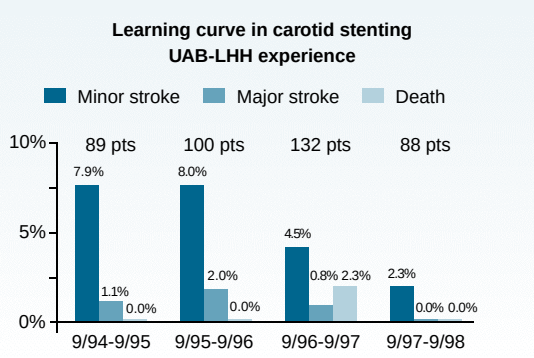


Table 3: NASCET carotid endarterectomy compared to stenting: 30-day follow-up.[5,7]

	NASCET		Stent
	Surgical (N=328)	Medical (N=331)	UAB-LHH (N=405)
All strokes + death	5.8%	3.6%	7.9%
Major stroke + death	2.1%	0.9%	2.8%
Death	0.6%	0.3%	1.9%
Minor stroke	3.7%	2.7%	5.2%
All stroke	5.5%	3.3%	6.0%

application of this technology. Figure 4 illustrates this point: patients treated in the earliest period suffered a 7-8% procedural minor stroke. This fell to 4.5% and, possibly emboldened by their earlier success, the operators began to tackle more difficult lesions,perhaps increasing the procedural death rate in the third period. With increased experience and a more sanguine approach (in particular, not tackling total occlusions), the minor and major stroke rates and death have been reduced quite substantially in the most recent group.

What then are the current best estimates of the procedural morbidity and mortality of carotid stenting? Table 3 combines and compares data from the NASCET and from the University of Alabama/Lenox Hill Hospital experience and, though statistical comparisons are not possible, the overall surgical stroke rate of 5.5% and stenting stroke rate of 6% appear equivalent. Note that the major stroke and death rates of 2.1% and 2.8% are nearly numerically identical. The most common procedural morbidity of stenting is the minor stroke, an event that clears completely within 7 days and does not produce long-term patient morbidity.

If one believes that short-term surgical and endovascular morbidities may be equivalent, what then of the late outcomes? Data from the combined University of Alabama and Lenox Hill Hospital experiences (Table 4), indicate that in 225 patients, including 266 vessels, at a mean follow-up of over 13 months, no patient suffered a major stroke after their initial successful and uncomplicated procedure. The minor stroke rate was 1.7% and one patient died from a non-cerebrovascular cause. If one compares the NASCET data with these as shown in Table 5, one can take the overall 36-month NASCET results and "subtract" those events occurring in the periprocedural period. This yields an overall follow-up stroke rate 4.5%,the majority of which were minor. Sim-

Table 4: Late outcomes of stenting (UAB-LHH patients having initially successful procedures).[7]

Patients/vessels	225/266
Mean F/U (range)	13±9 (6-29) months
Major stroke	0 (0%)
Minor stroke	4 (1.7%)
Death	1 (0.4%)

Table 5: NASCET 36-month follow-up compared with stenting (UAB-LHH follow-up mean 12.9 months).[5,7]

	NASCET			Stent
	30 day	36 mo. (N=328)	ΔF/U*	UAB-LHH (N=225)
All strokes	5.5%	9.0%	4.5%	1.7%
Major or fatal stroke	2.1%	2.5%	0.4%	0%
Minor stroke	3.7%	6.5%	2.8%	1.7%
Death	0.6%	4.6%	4.0%	0.4%

*Difference between 30-day and 36 month rates

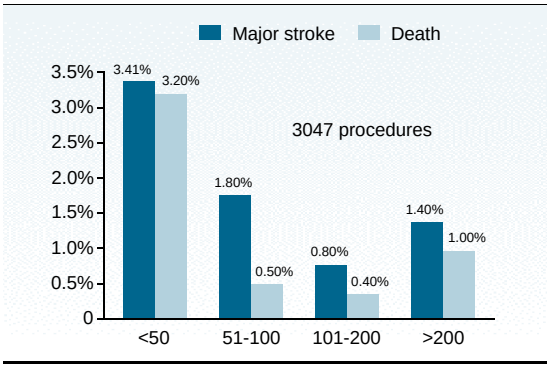
ilarly, the overall stroke rate in the post-procedure University of Alabama/Lenox Hill Hospital follow-up group was 1.7%, all of which were minor. These data are not taken from comparable patient groups (the majority of the stented patients would have been excluded from NASCET) and they cannot be rigorously compared. However, they do suggest that once one has had a successful reconstructive procedure, be it surgical or endovascular, the follow-up incidence of ipsilateral stroke is very small.

Endarterectomy in practice

Despite the encouraging data from the NASCET and the other randomized trials, carotid endarterectomy is not performed simply on patients who meet the inclusion criteria for these studies under conditions that duplicate them. An analysis of the variation in carotid endarterectomy mortality in the Medicare population was performed by Wennburg, et al in 1998. Interestingly, this analysis indicated that the 30-day mortality was 1.44% in hospitals that participated in the NASCET or ACAS versus an average of 1.77% in hospitals that did not participate. Hospital volume was divided into terciles and the highest mortality was 2.5% in hospitals that were in the lowest volume group.[14] Of interest is that the mortality of 1.44% in the trial hospitals' Medicare population contrasts with the lower reported rate of 0.6% reported by these same institutions in the NASCET – suggesting that the results of endarterectomy in practice cannot be generalized from the select NASCET population. Further, Cebul, et al, found that 90% of endarterectomies performed in the United States were performed by surgeons who performed less than 20 per year, and 80% of endarterectomies were performed in low-volume hospitals.[15]

In addition, endarterectomy, even in practiced hands, is not without complications that may be quite distressing. In the NASCET, the rate of cranial nerve palsy postoperatively was 7.6%, neck wound hematomas occurred in 5.5%, and a wound infection occurred in 3.4%. Most cardiac complications were uncommon, with MIs occurring in 0.9%, and worsening heart failure in 0.6%.[7]

Figure 5: ISCAT Survey – complication rate according to number of procedures performed at individual centers.[15]



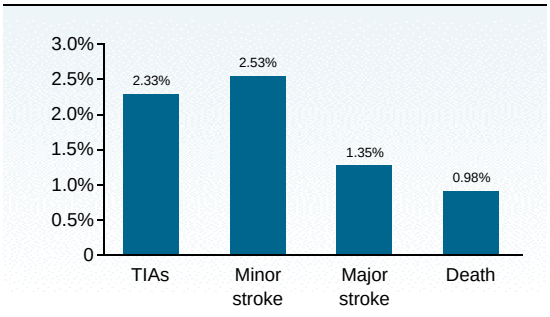
Carotid stenting in daily practice

While not yet subjected to a head-to-head randomized trial against surgery, there are accumulating data available on the "general" practice of carotid stenting. The International Society for Carotid Artery Treatment (ISCAT) has compiled an ongoing registry of procedures performed.[16,17] Procedural complications versus the number of procedures performed at each registry center are shown in Figure 5. A clear "learning" or "experience" curve is demonstrated, with the highest rates of major stroke and death (approximately 3% each) occurring in centers that have performed less than 50 patients. Overall, however, in this patient group (Figure 6), the reported rates of TIA and minor stroke are under 3%, major stroke 1.35%,and death <1%. All of these are self-reported registry data and not independently collected or prospective randomized studies; however, these data clearly support the notion that carotid stenting,while still an immature technology subject to developing experience, can likely provide benefits of the same order of magnitude as carotid endarterectomy.

Conclusions

Carotid stenting is a relatively new technique that is undergoing continual refinement. To date, data have been collected using the first generation of devices adopted for

Figure 6: ISCAT Survey – complications and 30-day procedure-related deaths in 3047 carotid stent cases.[15]



this procedure. As technology matures, future operators will likely improve on the results obtained thus far. Nevertheless, at present, carotid stenting carries with it similar short-term risk as endarterectomy. Endarterectomy, though successful and valuable in many patient populations, carries with it complications such as neck wound discomfort and cranial nerve palsies that are avoided with endovascular techniques. Once stenting or endarterectomy is successfully accomplished, the risk of subsequent stroke related to the treated vascular segment is very low.

The "best practice" of carotid stenting is rapidly changing and maturing. In the future,the use of distal embolization protection devices, refinement of antiplatelet therapy, the development plaque characterization methods and better risk stratification will undoubtedly change the practice of stenting. Calls for a randomized trial are understandable given the emotional climate surrounding this procedure and everyone's desire to settle the issue of which therapy is "better." However, given the very rapidly evolving technique of stenting versus the relatively mature status of endarterectomy, it is unlikely that clinical practice will stand still during the years it will take to conduct and analyze contemporary trials. As a consequence, though very useful data will be produced, it may not be possible to resolve the controversy. Years of study and debate will be required before catheter-based therapy can be summarily accepted or rejected as an alternative to more traditional surgical or medical therapy.

For the present, carotid endarterectomy is still the "gold standard" for revascularization of the extracranial cervical carotid. However, despite the recently proven benefits of surgery in preventing stroke in some patient subsets, it is certainly not irresponsible to offer selected patients endovascular repair. It may be beneficial to consider stenting in patients with increased surgical risk because of restenosis, high anatomic location, contralateral carotid occlusion, concomitant common carotid disease, or cardiopulmonary illness.

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