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Advances in Carotid Artery Revascularization

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ABSTRACT

Carotid stenosis is seen in about 10% of patients with ischemic stroke. Many studies have been performed that provide insight into the natural history, diagnosis, and optimal management of carotid disease. Both medical management and surgery have advanced to the point that patients and their providers have many options when considering treatment. Over the last several years, carotid artery stenting has been shown to be a viable treatment choice in selected patients. Both stenting and endarterectomy are superior to medical management alone in stroke prevention when patients are properly selected. In this article we try to review the most recent data regarding the two procedures in the treatment of carotid stenosis and also discuss the controversies in carotid artery revascularization.

►*Implication for health policy/practice/research/medical education:*
This review is intended for those managing patients with carotid disease and aims to provide the recent advances in carotid revascularization.

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1. Epidemiology of Carotid Disease

Like in cardiac and peripheral aterial disease, the primary culprit for carotid disease is atherosclerosis, and accounts for 17% of ipsilateral stroke (1). Carotid artery stenosis is prevalent in the general population with 75% of men and 62% of women older than 65 having a detectable carotid stenosis by Doppler ultrasound. For the most part, this stenosis is benign and not hemodynamically significant. Hemodynamically significant, severe stenosis is much more rare and found in only 2.3% in men and 1.1% in women (2,3). As for the burden of disease created by this stenosis, a US study of a multiethnic cohort (the Northern Manhattan Stroke Study, or NOMASS) found that 9% of all ischemic strokes were attributable to cervical carotid stenosis (1).

Carotid endarterectomy (CEA) is an established treatment in selected patients with symptomatic carotid stenosis of 50% or greater or asymptomatic stenosis of 70% or greater (4,5). However, percutaneous techniques such as carotid artery angioplasty with stenting(CAS) have improved, making them a viable, less invasive option (6). In this article we try to review the most recent data regarding the two procedures in the treatment of carotid stenosis and also discuss the controversies in carotid artery revascularization.

2. Carotid Endarterectomy

2.1. Carotid endarterectomy in patients with recent focal deficits

First described in 1953, carotid endarterectomy is the most widely used invasive treatment for significant carotid stenosis (7). During the 1980s, four major randomized clinical trials, North American Symptomatic Carotid Endarterectomy Trial (NASCET) (8,9), the European Carotid Surgery Trial (ECST) (10-12), the Asymptomatic Carotid Atherosclerosis Study (ACAS), (13), and the Asymptomatic Carotid Surgery Trial (ACST) (14,15) demonstrated the benefit of CEA in symptomatic and

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asymptomatic carotid stenosis. Despite the different methods of estimation of stenosis used in these trials, the conclusions were reasonably consistent (16).

NASCET(North American Symptomatic Carotid Endarterectomy Trial) assigned 2,226 patients with symptomatic stenosis (transient ischemic attack or stroke within the past 180 days) to medical management (which consisted of Aspirin alone) or endarterectomy (8). The NASCET subgroup of severe stenosis (greater than or equal to 70% to 99%) showed a highly significant benefit of carotid endarterectomy (CEA) over medical management(17). Compared to medical management, CEA patients had a risk of ipsilateral stroke at 2 years of 9%, while 26% for the medically managed group had ipsilateral stroke(8, 9). There was a definite but less striking benefit for patients with 50% to 69% stenosis. In this population with moderate disease, the medically managed patients had a 43% risk of stroke or death at 5 years, compared to the CEA patients in whom it occurred in 33%. Finally, in the patients with mild, non-hemodynamically significant stenosis of less than 50%, there was no benefit with CEA over medical management (9).

ECST (the European Carotid Surgery Trial) included a similar population of 3,024 patients. Those with high-grade stenosis of greater than 80% (60% by the NASCET criteria for calculating angiographic stenosis) had significantly better outcomes with endarterectomy, but in those with stenosis less than 70%, surgery was no better than drug therapy. In this study the frequency of major stroke or death at 3 years was 26.5% in the medical management group and 14.9% in the surgery group, an absolute difference of 11.6% (12).

Of note, NASCET and ECST criteria for estimating the degree of stenosis in the carotid artery are different. NASCET used the ratio of the luminal diameter of the narrowest segment of the diseased portion of the artery to the normal distal luminal diameter of the internal carotid artery (beyond any poststenotic dilatation segment). ECST used the ratio of the residual lumen in the zone of stenosis to the estimated diameter of the carotid bulb. As a result, a 70% stenosis by the ECST criteria might only equal a 40% stenosis by the NASCET criteria(18). The NASCET criteria are preferred for decision making in the present.

The US Veterans Affairs trial of CEA, or Veterans Affairs Cooperative Study Program (VA CSP), was stopped after 189 patients with symptomatic high degree stenosis had been randomly allocated to surgery plus medication therapy versus medical management alone. The rate of death, stroke or transient ischemic attack (TIA) was 7.7% in patients assigned to surgical treatment as compared with 19.4% in those on medical management alone. The results are consistent with those of NASCET and provide a robust indication for surgery in patients with high-degree, symptomatic carotid stenosis (19).

A pooled analysis of NASCET/ECST/VA CSP was performed that corrected for measurement inconsistencies by reanalyzing the source angiograms from ECST and applying the NASCET criteria. Interestingly, this analysis found that in patient who underwent CEA, those with moderate stenosis had a greater 30-day mortality and stroke rate (8.4%) than those with severe stenosis (6.2%). As NASCET showed independently, this analysis confirmed that patients with greater than or equal to 70% stenosis have a highly significant reduction in stroke and death within 1 year which persisted for the duration of follow-up (20). One important exception is near occlusion. In this group, the medically treated patients fared better likely because intracranial collaterals had already compensated for the diseased arteries insufficient flow and surgery simply exposed the patients to a risk of atheroembolism (18). In subgroup analysis, the groups that fare the best include the elderly (patients aged 75 years or more), patients with ulcerated plaques, and patients with acute focal deficits that completely resolve (TIA) (21).

NASCET and ECST demonstrated that endarterectomy is clearly superior to medical therapy in patients with severe symptomatic carotid disease. However, both trials excluded patients at high surgical risk; for example, those with severe coronary artery disease, kidney disease, or heart failure. Additionally, by today's standards, medical management in the above mentioned studies was not aggressive in terms of control of blood pressure and control of hyperlipidemia, and this could have skewed the results in favor of carotid endarterectomy (6).

2.2. Elective Carotid endarterectomy

The first major trial of CEA in asymptomatic patients was conducted in 10 US Veterans Affairs (VA CPS) medical centers to test the hypothesis that surgery in combination with aspirin and risk factor modification would result in fewer TIAs, strokes, and deaths than medical management alone. Of note, the surgical risk of stroke or death in this population was lower than in the symptomatic population and was 4.3% at 30days. Also, this study compared the outcomes of medical management to surgery over a longer time frame of 5-years and found that the primary outcome of stroke, TIA, and death was 10% in the surgical group versus 20% in the medical management group (22). The inclusion of TIA as a part of the combined primary endpoint was controversial because of the low morbidity of TIA and the relative difficulty in accurately diagnosing TIA.

Similarly to the VA CSP, the Asymptomatic Carotid Atherosclerosis Study (ACAS) (1995) was designed with stroke and death as the primary outcome, and excluded TIA. As with the VA study, the 30-day stroke and mortality rate was low at 2.3%. The primary outcome at 5 years was 5.1% for CEA and 11% for medical management, a relative risk reduction of 53% (13).

Like NASCET, the medical management in ACAS was less aggressive than today's standards. To address this, a follow-up study was done that was very similar in design to ACAS, called ACST (The Asymptomatic Carotid Surgery Trial). Performed in 2004, this was the largest study to compare carotid endarterectomy with drug therapy for asymptomatic stenosis. In it, 3120 patients were randomized to surgery or drug therapy. The outcomes remained very similar to ACAS. The net 5-year risk of stroke was 6.4% with endarterectomy and 11.8% with drug therapy ($P < 0.0001$). The rate of fatal stroke was also lower with endarterectomy: 2.1% vs 4.2% ($P = 0.006$) (15).

Athough the relative risk reduction in both studies was about 50%, the absolute risk reduction is rather small for patients with asymptomatic carotid stenosis, compared to those with symptomatic stenosis. Because of this differential, much care and attention must be given to discussing treatment options and the timing of surgery in an asymptomatic patient. Since the benefit of this procedure is realized at 5 years, most patients with a shorter life expectancy than 5 years should be advised to continue medical management. Also, the operator's complication rate is highly significant. A surgeon with a complication rate of less than or equal to 3% should be used for patients with asymptomatic disease (18). Given the advances in medical therapy, the annual rate of stroke in medically treated patients with ACS has fallen from 2.5 to 1%. Current estimates suggest that only 5% of patients with ACS stand to benefit from CEA in the era of modern medical therapy with antiplatelets, statins, and angiotensin-converting enzyme inhibitors. Further selection of patients can be enhanced by using advanced imaging of plaque morphology and content and assessment of cerebral vasomotor reactivity and reserve by Transcranial Doppler (TCD) (23). Two recent studies suggest that the use of TCD to detect embolic signals might be particularly useful in stratifying patients with ACS who would benefit from surgery. (24,25)In the asymptomatic carotid emboli study (ACES), only 16% of patients with ACS had embolic signals on baseline transcranial Doppler, and only 13% of them had ipsilateral strokes during a 2-year follow-up period.(24) Although these results are promising, further larger-scale studies are needed before emboli monitoring can be recommended for clinical decision making (23).

The American Heart Association and the American Stroke Association have, on the basis of these trials, recommended carotid endarterectomy in patients with:

Ipsilateral, symptomatic carotid artery stenosis of 70% to 99% (class I, level of evidence A)

Symptomatic stenosis of 50% to 69%, depending on patient-specific factors such as age, sex, and comorbidities.

High-grade asymptomatic carotid stenosis, if the patients are carefully selected and the surgery is performed by surgeons with procedural morbidity and mortality rates of less than 3% (class I, level of evidence A).

In all cases, treatment should be individualized according to the patient's comorbid conditions and preferences, with a thorough discussion of risks and benefits (4,5,26).

2.3. Selecting the right patient for surgery

Based on subgroup analyses, the elderly stand to benefit more than any other group from endarterectomy. Unfortunately, many large trials exclude patients more than 70 years of age, and thus robust data in this population is still needed. Nonetheless, a clinician should consider CEA in elderly patients with carotid disease, and it will become increasingly necessary to treat this population as life expectancy improves and comorbid conditions are better controlled to provide for longer life expectancy. Age is a well established risk for stroke, and with increasing age, the risk of stroke increases. On the other hand, the risks of perioperative stroke and death from CEA in the elderly are similar to all other age groups (27).

Controversies still exist regarding women and endarterectomy. In general, the large studies above have shown significantly less benefit, if any, for women with carotid disease. The major cause of this gender discrepancy is the increased perioperative complication rate in women and the relatively better response to medical management in women. Further studies are needed to define the cause of the increase perioperative stroke risk in women and to better understand and assist in patient selection.

As discussed above, patients who are symptomatic experience greater benefit from CEA, but also have a higher risk of perioperative complication.(28, 29)One of the most common debates in clinical practice is when to time surgery. The impulse to delay surgery in a stable patient is futile. Once stabilized, surgery should be considered emergent and does not confer a higher risk than delayed surgery (29).

Difficult to access lesions, such as below the clavicle or above the mandible require a great degree of retraction and increase the risk of cranial nerve injury. Also, in patients with prior neck irradiation or prior neck surgery, a CEA can be daunting; in these patients the risk of cranial neuropathy should be weighed against the risk of stroke with the alternative procedure of stenting (18).

2.4. Post operative outcomes

While preventing stroke and death remain the primary goals of CEA, other outcomes are worth noting. Neuropathy to the cranial and cervical nerves commonly occur after CEA. Permanent injury, however, is observed rarely in 1% to 2% of cases (30,31). As with any surgery, wound infections and hematomas occur and in 4.3% of patients in NASCET these complications prolonged a hospital stay (17). The risk of myocardial infarction looms large over CEA and if defined narrowly as elevation in serum markers plus either symptoms or ECG changes, then in the recent CREST trial, 2.3% of CEA patients experience perioperative myocardial infarction (32).

3. Carotid Artery Stenting

Carotid endarterectomy is superior to medical management alone in certain patient subsets; however, studies favoring surgery over medical therapy have been criticized for exclusion of patients with significant comorbidities. Also, carotid endarterectomy has been associated with significant cardiovascular events, wound complications, and cranial nerve damage, and additionally requires general anesthesia in most cases. These factors encouraged the development of non-surgical approaches for patients with substantial comorbidities (6).

Carotid artery stenting(CAS) is a relatively new procedure compared to CEA, and it originally emerged as an alternative to CEA for patients with high surgical risk. In the late 1970s, CAS was described in isolated case reports. This was followed by larger case series and independent trials (16). The potential of CAS has been challenged in both the earlier controlled studies and the more recent non-randomized multicenter and industry postmarketing registries. Major concerns regarding CAS were raised

mainly related to high periprocedural stroke rates for patients with high surgical risk. However, methodological deficiencies in the studies were evident.

Aspirin (81 mg to 325 mg daily) combined with clopidogrel (75 mg daily) must be started prior to the procedure. An alternative could be ticlopidine (250 mg twice daily) for patients who are not able to tolerate Clopidogrel. Patients with a contraindication for aggressive antithrombotic therapy, comorbid renal insufficiency and extensive peripheral atherosclerotic disease (which might complicate catheter access) might not be appropriate candidates for CAS and further evaluation need to be done prior to CAS.

Initial attempts at angioplasty without distal protection were not very successful. With improvements in technology, routine use of embolic protection devices(EPD), more experience, and better selection of patients, the outcome of carotid stenting has improved. In fact, a meta-analysis comparing stenting without an embolic protection device (26 trials with 2,357 patients) versus stenting with an embolic protection device (11 trials with 839 patients) showed that embolic protection led to significantly better outcomes with fewer strokes—outcomes arguably similar to those of carotid endarterectomy (33-35). While traditional EPDs are placed distal to the stenotic lesion, typically forming an umbrella-like filter device to capture the debris dislodged during angioplasty and stenting (18), a newer generation of proximal EPD that has two catheter-mounted balloons, avoids the need to cross the stenotic lesion prior to deployment. The distal balloon is inflated in the ECA and the proximal balloon is inflated in the CCA, after which the stent-assisted angioplasty of the lesion is performed. The proximal balloon temporarily arrests flow during the CAS, which minimizes antegrade flow of debris during the intervention. The ARMOUR trial evaluated the safety and efficacy of this "endovascular clamping" device and showed a very low 30-day stroke rate of 0.9% as compared to previous studies using distal EPDs (33).

3.1. Periprocedural Outcome

The baroreceptors are receptors mostly present in the carotid bulb that are sensitive to changes in blood pressure, modulating the sympathetic and parasympathetic activity. With stretching of the baroreceptors by angioplasty or stent placement, and increment of vagal parasympathetic tone bradycardia and hypotension may develop in 5% to 10% of patients. Hypotension that either did not require treatment or required atropine was observed in less than 3% of patients in the CREST (versus less than 0.5% in the CEA group) (18).

The other uncommon periprocedural complications includes carotid dissection, 3.6% in an early reported series from 1996 (36), benign and transient Vasospasm , benign external carotid stenosis (due to the straightening and dilation of the ICA with the stent deployment), deployment failure (37) (less than 1% of cases) and stent migration (only a few cases reported).(38) Angiograms might also become complicated by access-site injury, site infections (less than 0.5%) (39), self-limited groin hematomas (0.5% to 4.8%) (39,40) and pseudoaneurysms or arteriovenous fistulas at puncture site (which might require surgery in 1.5% of cases) (39). Other complications include retroperitoneal hematoma (less than 0.5%) (32) and contrast-induced renal dysfunction (less than 1%) (40).

Factors that might increase the risk of stent thrombosis include long stent length, small minimum luminal stent diameter, persistent dissection, and multivessel intervention (41).

4. Carotid Endarterectomy versus Carotid Artery Stenting

Several tries have compared stenting to endarterectomy in various clinical settings. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized patients with at least one high-risk factor and either greater than 50% symptomatic carotid stenosis or greater than 80% asymptomatic carotid stenosis to receive either CAS or CEA. The goal was to assess whether CAS was not inferior to CEA in high-risk patients with carotid artery stenosis and with at least one comorbid condition that would have excluded them from the early endarterectomy trials. SAPPHIRE was the only completed trial until CREST that compared carotid artery stenting with distal protection against surgery. The 3-year results demonstrated no significant differences between the two procedures in the major outcome measures (accurate subgroup analysis of symptomatic and asymptomatic patients was not possible because of the small sample) (42). On the basis of these data, stenting with distal protection for high-risk patients was approved in the US (6).

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) study was designed to compare CEA and CAS using distal emboli protection devices in a nonrandomized fashion, where patients' and treating physicians' preferences would determine which would be the more appropriate approach. All the patients in this study had at least 50% symptomatic stenosis or 75% asymptomatic carotid stenosis. At 30 days, 7 (2.4%) of 254 patients in the endarterectomy group had strokes and 1 of the 7 patients with stroke died, so the combined rate of stroke or death (the primary end point) was 2.4%. In the stenting group, 3 (2.1%) of 143 patients had strokes and no patients died. Overall, there was no significant difference in the composite of death, stroke, or myocardial infarction: 3% for CEA and 2% for CAS patients (43). The goal was to reflect the population of patients with carotid disease who undergo treatment in real practice, since the early evidence evaluating CAS focused on high-risk patients which is not considered to accurately (18).

SPACE (The Stent-Protected Angioplasty versus Carotid Endarterectomy in Symptomatic Patients trial), conducted in Germany, included 1,214 patients with symptomatic stenosis of at least 50%. Results were similar in terms of the combined primary end point of stroke or death at 30 days. The study failed to prove the non-inferiority of CAS compared with CEA for the periprocedural complication rate (44).

EVA-3S (the Endarterectomy Versus Stenting in Patients With Symptomatic Severe Carotid Stenosis trial), in

France, evaluated 527 patients with symptomatic carotid disease (stenosis ≥ 60%), but was terminated early due to significantly higher rates of death or stroke at 30 days in the stenting group. The 30-day incidence of any stroke or death was higher in the stenting group (9.6% vs. 3.9%). The 30-day incidence of disabling stroke or death was also higher in the stenting group (3.4% vs. 1.5%). At 6 months, the incidence of any stroke or death was 6.1% after CEA and 11.7% after stenting (P = 0.02). There was a trend toward more major local complications after stenting and systemic complications after endarterectomy. (39)EVA-3S and SPACE both have been widely criticized for the fact that EPD use was limited, double antithrombotic treatment was not mandated in EVA-3S, and the CAS arm had more patients with contralateral occlusion (3.8% higher absolute frequency)in EVA-3S. Questions were also raised about the experience level of operators who performed the carotid stenting: up to 40 % of the primary operators involved in stent placement were trainees. This results magnified the need of appropriate training prerequisites for centers and operators enrolling patients in the stenting trials (45).

The interim results of International Carotid Stenting Study (ICSS) trial which enrolled 1713 symptomatic patients showed that the 30-day and also 120-day risk of stroke, death, or myocardial infarction was significantly higher after stenting than after CEA (7.4% vs. 4.0%; P = 0.003 and 8.5% vs. 5.2%; P = 0.006) (46). In addition, in a subgroup of 231 patients who underwent diffusion-weighted magnetic resonance imaging (MRI) both before and after carotid intervention, new ischemic brain lesions were found much more in the stenting group than in the CEA group (50% vs. 17%; adjusted odds ratio 5.2; 95% CI 2.8-9.8; P < 0.0001) (47). Two centers had an unacceptably high risk of CAS complications and this might have affected the results and highlight the need for appropriate operator selection. Additionally, double antiplatelet therapy was only recommended (not mandated), and the data regarding their use were not reported in the interim analysis. Long-term data are awaited (18).

The highly anticipated (CREST) (32) study was methodologically rigorous. There were strict requirements for operator and center participation (minimum experience with CAS and use of EPDs), with a maximum 30-day stroke or death rate of 6% to 8% (48). What was unique about CREST was the implementation of a lead-in phase prior to the randomization to ensure that the interventionalists had enough experience and acceptable complication rates. Additionally, stringent angiographic exclusion criteria were applied (severe tortuosity, intraluminal thrombi, large or bulky plaques), which contributed to better CAS selection and improved outcomes (49).

The CREST trial included symptomatic patients (events within 180 days) with greater than or equal to 50% stenosis on angiography, greater than or equal to 70% stenosis on ultrasonography, or greater than or equal to 70% stenosis on CTA or MRA if the stenosis on ultrasonography was 50% to 69%. It also enrolled asymptomatic patients with greater than or equal to 60% stenosis on angiography, greater than or equal to 70% stenosis on ultrasonography, or greater than or equal to 80% stenosis on CTA or MRA if the stenosis on ultrasonography was 50% to 69%. Two thousand five hundred patients were followed over a median of 2.5 years. No significant difference was found in the rates of the primary end point (composite of any stroke, myocardial infarction, or death), between the CAS and CEA groups in the periprocedural period (5.2% versus 4.5%, respectively) and in the estimated 4-year outcomes (7.2% and 6.8%, respectively). The periprocedural rates of individual components of the end point in the CAS and the CEA groups were 0.7% versus 0.3% for death, 4.1% versus 2.3% for stroke, and 1.1% versus 2.3% for myocardial infarction, respectively. Elderly patients seemed to have better outcomes with CEA. Even though the relative increased risk of nonfatal stroke with CAS was statistically counterbalanced by an increased risk of nonfatal myocardial infarction with CEA, the quality of life after stroke appeared to be worse than after myocardial infarction (32). Although the CREST data is valid because of the methodological rigor, additional data for long-term results are still warranted.

Recent data, including the randomized data from CREST, suggest that age of greater than 70 years poses a higher risk for CAS compared to CEA. This is contrary to the traditional practice of stenting older patients. The arch anatomy is often unfavorable and the carotid arteries are more tortuous in the elderly population, increasing the complexity of navigating endovascular devices through the lesions (18).

AHA/American Stroke Association (ASA) now recommends patients with average or low surgical risk who experience an ischemic stroke or TIA within 6 months, to undergo CEA if greater than 70% stenosis is present by noninvasive imaging or greater than 50% stenosis is present by catheter angiography and the rate of perioperative stroke or mortality is less than 6%. CEA and CAS are not recommended for patients with severe disability, including those with disabling strokes as index events. CAS is recommended as an alternative to CEA under the same criteria. Intervention within 2 weeks of the event is reasonable and is preferred to delaying the procedure. Revascularization is contraindicated for patients with total occlusion (50).

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