Published in final edited form as:

Curr Neurol Neurosci Rep. 2011 February ; 11(1): 61–66. doi:10.1007/s11910-010-0153-z.

Treatment of Carotid Artery Disease: Endarterectomy or Angioplasty?

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Abstract

The management of carotid stenosis has enjoyed renewed interest in the neurological community in recent years due to the advent of endovascular approaches. In concert, progress in medical treatment of these patients has rekindled the debate regarding the best management of carotid stenosis overall, both for symptomatic and asymptomatic disease. For symptomatic carotid stenosis, the major decision required is choosing the type of intervention best suited for individual patients — carotid endarterectomy (CEA) versus carotid artery stenting (CAS). For patients with asymptomatic carotid stenosis, intensive medical management has evolved significantly over the past decade to decrease the risk of ischemic stroke to match surgical intervention under most circumstances. This review will examine the supporting evidence for each intervention, and discuss the recent advances in medical and endovascular therapy that provide the data for a new era in clinical decision making.

Keywords

treatment; endarterectomy; carotid stenosis; carotid artery stent; angioplasty

Introduction

Carotid artery stenosis is one of the most common causes of stroke and is responsible for the highest risk of recurrence in the first seven days. There is an odds ratio (OR) of 3.3 for those with symptomatic stenosis compared to other stroke etiologies, and up to 26% overall risk in the first two years after the initial event in medically treated patients[1]. The annual incidence of stroke in asymptomatic individuals with carotid artery stenosis greater than 60% treated medically has been reported as 2.5%.[2] Two mechanisms contribute to the high risk of stroke in carotid stenosis: hypoperfusion and artery-to-artery embolism.

The recent publication of the interim analysis of the International Carotid Stenting Study (ICSS) and the final result of Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) have sparked renewed interest in determining the best treatment option for carotid artery stenosis. This review will focus on the therapeutic modalities available for carotid artery stenosis, in particular the advantages and disadvantages of carotid endarterectomy (CEA) versus carotid artery stenting (CAS), and will also consider advances in medical therapy that have altered the landscape of interventional treatment. Management of complete carotid artery occlusion is the object of the Carotid Occlusion Surgery Study

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Conflict of Interest Disclosures: none relevant

(COSS)[3], and will not be addressed in this article as direct revascularization of the carotid artery is not a treatment option.

Background – Early Trials of CEA and CAS

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was the first major study of symptomatic carotid stenosis. It compared CEA with medical therapy in patients with a recent ischemic event and varying degrees of stenosis. For carotid stenosis of 70–99%, when comparing the medical to the surgical arm, the risk of ipsilateral stroke at two years was reduced by CEA from 26% to 9% ($p<0.001$)[4]. For stenosis of 50% to 69%, there was a modest reduction of stroke rate from 22.2% in the medical arm to 15.7% in the CEA arm ($p=0.045$); there was no benefit for stenosis $<50\%$ [5]. Of note, the medical therapy among all patients in this study was suboptimal by current standards; aspirin was used in 96 to 99%, antihypertensive therapy in 68% and, lipid lowering agents in only 40% of patients[1]. The findings of NASCET were followed by the European Carotid Surgery Trial (ECST) which had essentially the same management strategy, and produced nearly identical results[6].

The NASCET study excluded patients considered high surgical risk, which emphasized the need for an alternative treatment strategy. Angioplasty of the carotid artery was developed over the ensuing years, heralding a new era in carotid artery treatment. Its first major test was in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which showed no significant difference in the rates of disabling stroke or death at 30 days (6.4% vs. 5.9%) for angioplasty compared with CEA. The claim for safer treatment of carotid disease was supported by the significantly lower rates of cranial nerve palsy and hematoma requiring surgery or extending the hospital stay in the angioplasty arm compared to surgery (. 0% vs. 9% and 1% vs. 7% respectively)[7]. In the longer term, however, angioplasty was associated with higher rate of restenosis and recurrence of ischemic events, mostly transient ischemic attacks (TIAs), compared to CEA [8]. To address the durability of results and the angioplasty procedural risk, the use of carotid stents and embolism protection were subsequently promoted in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. In that trial, focusing on high surgical risk patients, CAS was found not to be inferior to CEA at 30 days and 3 years [9, 10]. However, the absence of a medical arm brought into question whether the stroke rates might actually have been lower with medical treatment alone than with either intervention in these patients. Enthusiasm for stent-angioplasty was dampened by the Stent Protected-Angioplasty versus Carotid Endarterectomy (SPACE) trial, completed in Europe more recently, which included standard risk patients. This trial failed to show non-inferiority of CAS compared to CEA at 30 days[11], although after 2 years the rate of stroke was similar in both treatment arms[12]. One criticism of this trial was that an embolism protection device that may have reduced the rate of stroke was used in only 26% of cases, sustaining the debate as to whether protection devices do in fact lower periprocedural stroke rate[13]. There is evidence from several studies that the number of DWI lesions on MRI is higher with CAS even in experienced hands [14, 15]. The effectiveness of these protective devices may depend on individual patient selection. Overall, their use has continued to date.

Embolism protection was used in most patients enrolled in another European trial, the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial. This study reported results favoring CEA due to higher rates of any stroke or death in the CAS arm at 30 days (9.6% after stenting vs. 3.9% after endarterectomy, $p=0.01$), leading to the trial's premature discontinuation [16]. At 4 years, the higher rate of stroke or death in the CAS arm persisted (11.15 vs. 6.2%, $P=0.03$).[17] The nonprocedural stroke or death rates, however, were low, and similar between treatment arms (4.49% after

CAS vs. 4.94% after CEA, hazard ratio HR=1.02). The excess number of strokes was therefore explained by the higher periprocedural risk of stenting. In a meta-analysis from 6 CEA vs. CAS trials, including CAVATAS and SAPHIRE the 30-day stroke and death rates associated with CAS and CEA were not significantly different[18].

The impact of CAS and CEA on the surrogate markers for brain injury has also been studied. Neuron-specific enolase (NSE) and S100 β appear to be higher in patients who undergo CAS compared to CEA[19]. Regarding imaging evidence for brain injury, several studies have demonstrated positive MRI findings after both CEA and CAS [19, 20]. CEA appears to cause fewer lesions, although they tend to be larger. Only a minority of lesions are still visible on follow-up MRI, notably those larger than 60 mm[21]. The presence of MRI lesions, even if not associated with frank stroke symptoms, may produce a decline in mental status[19], although these effects may be transient[22].

ICSS and CREST Trials

In the past year, 2 large international trials have recently further fuelled the debate regarding the efficacy of CEA vs CAS. First was the International Carotid Stenting Study (ICSS), a multicenter international randomized trial with blinded adjudication of outcomes that enrolled 1713 patients[23]. Short term results only have been published to date, using an outcome of stroke, death, or procedural myocardial infarction within 120 days of randomization. This combined endpoint occurred more often in the stenting group compared to the endarterectomy group (8.5% vs. 5.2% $p=0.006$). The difference was driven by nondisabling stroke. There was no difference in disabling stroke and death between the two groups in this time period. The number of myocardial infarcts was higher in the endarterectomy group overall, although overall the numbers were small (4 non-fatal following CEA vs. 3 fatal following stenting). Also, as expected, incidence of cranial nerve palsies and neck hematomas was higher in patients undergoing endarterectomy, including hematomas requiring transfusion or extending hospitalization. The presence of DWI-positive lesions was 3 times higher after CAS than after CEA, and this was not mediated by embolism protection devices[20]. A moratorium on CAS has been proposed until the final results of ICSS become available[24].

CREST was a randomized controlled trial with blinded end-point adjudication. Enrolling 2505 patients, the trial compared stenting with endarterectomy in asymptomatic and symptomatic carotid stenosis patients followed for 4 years[25]. Primary end points were a composite of stroke, myocardial infarction and death during the periprocedural period (first 30 days), or ipsilateral stroke over 4 years. Overall results were that with a mean follow up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; $P=0.51$). Asymptomatic as well as the symptomatic patients had similar outcome from both procedures ($p=0.84$) and there was no differential benefit by gender ($p=0.34$). The 4 year rate of stroke or death (excluding periprocedural MI) was higher in the stented arm (6.4% vs. 4.7%, HR 1.5; $p=0.03$), whether symptomatic (8% vs. 6.4%, HR 1.37; $p=0.14$) or asymptomatic (4.5% vs. 2.7%, HR 1.86, $p=0.07$), supporting earlier observations that the higher risk of overall stroke with stenting is related to the periprocedural period. There was no significant difference in the number of major strokes between the two procedures. Cranial-nerve palsy were again as expected more frequent after CEA than CAS (4.7% vs. 0.3%, $p<0.01$). Individual components of the end points differed in incidence between the stenting and endarterectomy groups: stroke was more frequent with stenting (4.1% vs. 2.3%, $p=0.01$), but myocardial infarction was less frequent (1.1% vs. 2.3%, $p=0.03$). The rate of death was higher in the stented arm but did not reach significance (0.7% vs. 0.3%, 0.18).

After the periprocedural period, the incidences of ipsilateral stroke with stenting and with endarterectomy were low and not significantly different (2.0% and 2.4%).

Interestingly, beyond the primary endpoints there was an interaction between age and treatment group ($p=0.02$), suggesting that patients younger than 70 years may benefit more from stenting and the older ones from endarterectomy (Fig. 1). The finding may in part be attributable to increased vascular tortuosity or increased calcification in the elderly patients[26], making CAS more risky. Also, although CEA was associated with an increased number of myocardial infarctions compared to CAS, strokes, which occurred more in the CAS group, had a significant impact on quality of life according to the SF-36 physical and mental components, whereas the impact of myocardial infarction was less clear.

Overall, patients in both groups did well in this trial. Among symptomatic patients, stenting resulted in 6.0% strokes or death, fewer compared to prior trials (6.8% in SPACE after exclusion of contralateral stroke, 9.6% in EVA-3S or 7.4% in ICSS). For the same patients, endarterectomy performed in CREST was also associated with lower rate of stroke and death, 3.2% vs. 6.3% in SPACE and was similarly safe to EVA-3S (3.9%) and ICSS (3.4%). Among asymptomatic patients, the rate of stroke or death decreased both in the CAS and in CEA arms, 2.5% and 1.4% respectively, and was similar or lower than that in the ACAS and ACST trials. The overall improvement in outcome of both CAS and CEA and the similar primary outcome in both the periprocedural period as well as at the end of the study may reflect a positive evolution in the training and credentialing process of the physicians performing both types of procedures as well as the technological advances in the design of stent and embolism protection devices. Even more could have been done, however, with medical management. At 48 months, one third of patients had uncontrolled systolic blood pressure in and the mean LDL was 89 in both treatment arms; current AHA guidelines recommend controlling LDL to <70 in patients at high risk. Also, the number of smokers after intervention was significantly higher in the CAS arm (21.8 vs. 13.8, $p<0.05$). Better control of all these risk factors could theoretically have resulted in even lower stroke rates among all study participants.

Asymptomatic Carotid Stenosis -the question of medical management

Special consideration is warranted for patients with asymptomatic carotid stenosis since their natural history risk is lower and therefore tolerance of the procedural risk must also be lower to be able to show any benefit of intervention. The Asymptomatic Carotid Atherosclerosis Study (ACAS) showed a reduction of stroke and death by 53%, but the absolute risk reduction was from 2% to 1% per year, with a perioperative hazard of 3%. [2] The Asymptomatic Carotid Surgery Trial (ACST) demonstrated similar outcomes in stroke risk[27]. Since the time of these first trials in 1995, with the introduction of more comprehensive medical management of cerebrovascular risk factors and decreased threshold for their management, a gradual reduction of the annual stroke risk by 1.5% to 3.2% has been reported in patients with asymptomatic carotid stenosis, leading to a theoretical loss of statistically significant advantage of CEA in the prevention of stroke among asymptomatic patients [28, 29]. Although CREST showed that the patients with carotid stenosis benefit regardless of symptomatic status, there was no non-interventional arm to determine if the benefit would have been lower compared to optimal medical therapy.

From a mechanistic standpoint the result of medical therapy may be in stabilization of carotid plaques. Asymptomatic embolization detected by transcranial Doppler (TCD) is frequently seen in carotid stenosis[30], and has been demonstrated as a risk factor for stroke [31]. Microemboli correlate with other known markers of increased risk, including recent symptoms, ulcerated plaque, and stenosis[32]. In one study of patients with asymptomatic

carotid stenosis, microemboli were present in 10% and predicted a risk of stroke of 15.6% in the first year compared to 1% in those without microemboli [33]. In addition, while not all microembolic signals result in a clinical stroke, accumulation of small asymptomatic subcortical infarcts have been associated with cognitive impairment.[34] Even transient ischemia caused by microemboli may be less than benign. Whereas by definition, neurological recovery is complete following a TIA, the focal symptoms have been shown to re-emerge days to weeks after the event in response to a short-acting GABA agonist[35], suggesting that the brain tissue is affected for a longer period of time after TIA has resolved. Asymptomatic stenosis patients with microemboli may thus represent a target group for more intensive medical intervention.

Other evidence that asymptomatic patients may be helped by medical therapy includes longitudinal studies. Spence et al. recently showed that among asymptomatic patients with ICA stenosis >60% a lower event rate of stroke, death, myocardial infarction and carotid endarterectomy (pursued when the patient became symptomatic) coincided with changing practices in medical therapy over time [36]. Compared with patients enrolled between 2000 and 2003 who had an event rate of 17.6%, those enrolled between 2003 and 2007 had an event rate of 5.6%. Higher use of statins, antihypertensives, and antiplatelet agents, as well as lower serum lipids were all noted in the later group. In other medical intervention studies, pravastatin decreased wall shear stress and blood velocity in the internal carotid artery [37], suggesting a medical impact on the underlying pathophysiology, and statin-treated patients with familial hypercholesterolemia, coronary heart disease and pronounced atherosclerosis were shown to have an equivalent number of brain lesions as healthy controls in later middle age, again suggesting a statin-protective effect [38]. The recognition that intensive medical management may affect the pathophysiology of atherosclerosis regardless of its effect on degree of stenosis has led to the concept of treatment of the arteries rather than broadly treating conventional risk factors. In a recent observational study, after the introduction of a more intensive program that consisted of optimal control of hypertension, hyperlipidemia, hyperglycemia, smoking cessation, and antiplatelet medication, the proportion of patients whose total plaque area measured by ultrasound decreased rose from 19.6% to 50.1%[39].

Conclusion

There is still much unknown about why patients with similar degrees of carotid stenosis have dramatically different risk for stroke. In addition to plaque ulceration and microembolism, tandem distal stenosis[40], incomplete circle of Willis[41] and impaired cerebrovascular reactivity[42] have all been postulated to play a role. With progress in medical management, a direct comparison of medical therapy with stenting and endarterectomy is imperative. The SPACE-2 trial is designed to address the question of intervention vs. maximal medical therapy in asymptomatic patients[43], and ACST-2 will evaluate CAS vs. CEA in asymptomatic patients in whom intervention is thought to be needed but unclear which procedure is best[44]. Finally, innovation in device manufacturing may improve on results from prior studies; for example, a flow reversal device introduced recently aspirates the particulate matter resulting from stenting and was shown to be equally effective at decreasing the number of DWI lesions noted on MRI as the distal protection devices[45]. Thus in order for the management of patients with carotid stenosis to continue to evolve, a continual reassessment of the best medical management strategies and of new interventional techniques needs to be undertaken with appropriately designed clinical trials and scientifically sound physiological studies.

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Fig. 1. The interaction between age and type of intervention. This diagram illustrates the finding from the CREST trial suggesting a differential benefit of carotid endarterectomy for older patients and of carotid artery stenting for younger patients. (courtesy of NEJM, 2010).