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Review Article

Carotid artery stenting vs. carotid endarterectomy in the management of carotid artery stenosis: Lessons learned from randomized controlled trials

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Abstract

Background: Carotid artery stenosis, both symptomatic and asymptomatic, has been well studied with several multicenter randomized trials. The superiority of carotid endarterectomy (CEA) to medical therapy alone in both symptomatic and asymptomatic carotid artery stenosis has been well established in previous trials in the 1990s. The consequent era of endovascular carotid artery stenting (CAS) has offered another option for treating carotid artery stenosis. A series of randomized trials have now been conducted to compare CEA and CAS in the treatment of carotid artery disease. The large number of similar trials has created some confusion due to inconsistent results. Here, the authors review the trials that compare CEA and CAS in the management of carotid artery stenosis.

Methods: The PubMed database was searched systematically for randomized controlled trials published in English that compared CEA and CAS. Only human studies on adult patients were assessed. The references of identified articles were reviewed for additional manuscripts to be included if inclusion criteria were met. The following terms were used during search: carotid stenosis, endarterectomy, stenting. Retrospective or single-center studies were excluded from the review.

Results: Thirteen reports of seven large-scale prospective multicenter studies, comparing both interventions for symptomatic or asymptomatic extracranial carotid artery stenosis, were identified.

Conclusions: While the superiority of intervention to medical management for symptomatic patients has been well established in the literatures, careful

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selection of asymptomatic patients for intervention should be undertaken and only be pursued after institution of appropriate medical therapy until further reports on trials comparing medical therapy to intervention in this patient group are available.

Key Words: Asymptomatic, stroke, symptomatic, transient ischemic attack

INTRODUCTION AND BACKGROUND

Carotid artery stenosis, both symptomatic and asymptomatic, occupies a unique place among surgically treatable diseases. While the medical literature demonstrates many examples of large prospective multicenter randomized trials comparing various treatment regimens, the surgical literature has lagged somewhat behind in this regard. The reasons for this are many, and beyond the scope of this article. However, carotid artery stenosis is one surgically treatable disease that has been meticulously studied with robust prospective multicenter randomized trials. Trials such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[7] European Carotid Surgery Trial (ECST),[4] and the Asymptomatic Carotid Artery Stenosis Trial (ACAS)[2] established in the 1990s showed the superiority of carotid endarterectomy (CEA) to medical therapy alone, both in symptomatic and asymptomatic carotid artery stenosis. The subsequent development of endovascular carotid artery stenting (CAS) has given physicians another option for treating carotid artery stenosis. A series of randomized trials have been conducted to compare CEA and CAS in the treatment of carotid artery disease and to determine which subgroups may benefit from one therapy over the other.[1,3,8,11-13,18,21,25,29,31,37,39] Due to the large number of similar trials, much confusion has been created by these studies. Here, the authors review the best quality data from randomized, prospective, controlled trials comparing CEA and CAS in the treatment of symptomatic and asymptomatic carotid artery stenosis.

MATERIALS AND METHODS

Our research question was defined using the patient, interventions, comparisons, and outcomes strategy. The aim of this review is to identify the current literature body of class I evidence, directly comparing CEA to CAS in patients with extracranial carotid stenosis in regards to peri-procedural complications and long-term outcomes. The PubMed database was searched for English articles through August 2017, using the following terms: "carotid stenosis," "endarterectomy," "stenting." Only studies published after 1991 were considered, in order to cover the magnetic resonance imaging era. The references of retrieved articles were also reviewed to identify possible additional publications if inclusion criteria were met. The initial search yielded 275 articles of which 241 (87.6%) were excluded by abstract screening [Figure 1]. All the abstracts were independently assessed by three reviewers (M.S., A.A., and M.F.). The following inclusion criteria were applied: prospective randomized controlled trials (RCTs), multicenter studies, direct comparison of endarterectomy to stenting in adult patients with symptomatic or asymptomatic carotid artery stenosis, 100 or more patients in each treatment arm, reporting of periprocedural complications in both groups, and available long-term follow-up of at least 1 year. Single-center randomized trials or retrospective studies were excluded. Seven large-scale prospective multicenter studies comparing both interventions were included [Table 1]. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e., PRISMA).[26] Additional quality assessment of the included studies was performed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [Table 2].[22]

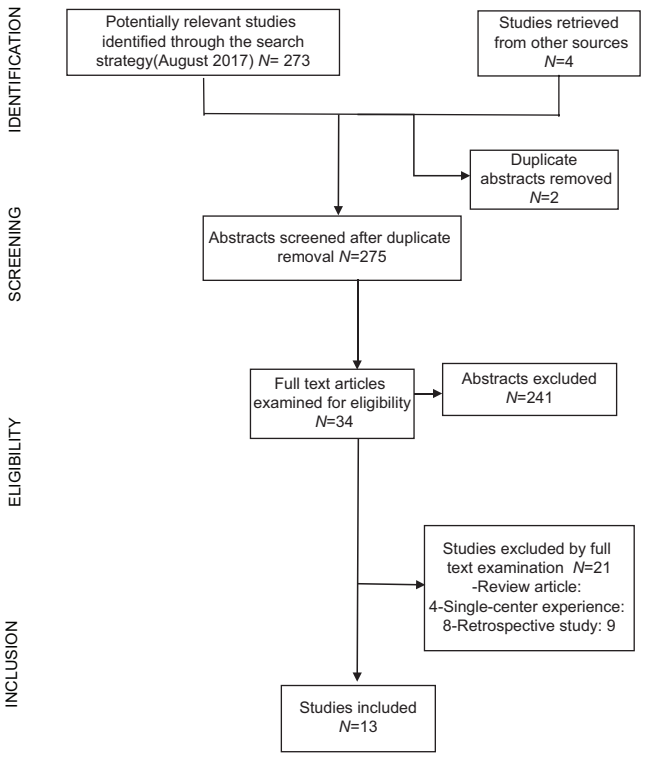

Figure 1: PRISMA flow diagram that details the results of the search and selection of studies

Table 1: Summary of randomized clinical trials

Trial	Evidence level (USPSTF)	Date of publication	Number of centers	Number of patients	Study population	Primary endpoint	CAS (%)	CEA (%)	*P*	Comments
CAVATAS	I	2001	22	504	Symptomatic and asymptomatic patients >50% stenosis	30-day death or stroke	10	9.9	NS	
						3 year death or stroke	14.3	14.2	0.9	
SAPPHIRE	I	2004	29	334	Symptomatic >50% stenosis Asymptomatic >80% stenosis	30-day stroke, MI, death 1-year ipsilateral stroke, death	12.2	20.1	0.004	
EVA-3S	I	2006	30	527	Symptomatic >60% stenosis	30-day stroke or death	9.6	3.9	0.01	
						4-year: 30-day stroke, death and ipsilateral stroke	11.1	6.2	0.03	
SPACE	I	2006	35	1196	Symptomatic >70% stenosis	30-day stroke or death	6.84	6.34	0.06	
						2 year: 30-day stoke, death or ipsilateral stroke	9.5	8.8	0.06	
CREST	I	2010	117	2502	Symptomatic Asymptomatic >50% stenosis	30-day stroke, MI, death	5.2	4.5	0.38	
						4-year ipsilateral stroke	7.2	6.8	0.51	
						10-year ipsilateral stroke	6.9	5.6		HR 0.99; 95% CI, 0.64 to 1.52
ICSS	I	2010	50	1713	Symptomatic >50% stenosis	120-day stroke, MI, death	8.5	5.2	0.006	
ACT-1	I	2016	62	1453	Asymptomatic >70% stenosis	30-day stroke, MI or death	2.9	1.7	0.33	
						1 year ipsilateral stroke				Freedom from stroke 97.8% CAS vs. 97.3% CEA

Table 2: Risks of bias of randomized controlled trials

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Blinding of participants and personnel (performance bias)	Blinding of outcomes assessment (detection bias)	Incomplete outcome data (attrition bias)	Other bias
CAVATAS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SAPPHIRE	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
EVA-3S	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
SPACE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CREST	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ICSS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ACT-1	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk

SUMMARY OF RANDOMIZED CLINICAL TRIALS

Endovascular vs. surgical treatment in patients with carotid stenosis in the carotid and vertebral artery transluminal angioplasty study (CAVATAS)

This was the first of these trials to report its results in 2001, randomly assigning 504 patients who were equally eligible for both surgery (n = 253) and stenting (n = 251). In the successfully treated endovascular arm, stent was used in 26% of cases, while balloon angioplasty alone was used in 74% of patients. The 30-day rate of stroke or death did not differ between the surgery and the stenting group (9.9% vs. 10%). The 1-year follow-up showed a higher ipsilateral restenosis rate in the endovascular arm ($P < 0.0001$). However, no differences in the ipsilateral stroke rate between the two groups were noted at the 3-year follow-up appointment [adjusted heart rate (HR) =1.04, 95% confidence interval (CI) 0.63–1.70, $P = 0.9$].[3] Long-term follow-up results were published in 2009, investigating the incidence of restenosis between the two groups, with a median follow-up of 5 years. Severe restenosis (≥70%) was three times more likely to occur in the endovascular

arm than the endarterectomy group (adjusted HR 3.17, 95% CI 1.89–5.32; $P < 0.0001$). The 5-year restenosis incidence was 30.7% in the endovascular group vs. 10.5% in the endarterectomy arm.[9]

Endarterectomy vs. angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S)

This trial compared CAS and CEA in symptomatic patients with 60% stenosis or higher. The study was designed as a noninferiority study with a goal patient accrual of 872 patients. The primary endpoint was stroke or death within 30 days of treatment. The trial was stopped early after 527 patients were enrolled due to safety concerns as patients in the CAS group were demonstrated to suffer from higher rates of both stroke and death. The 30-day relative rate of stroke or death was 2.5 when CAS was compared to CEA (95% CI 1.2–5.1).[28] The rates of stroke and death remained elevated after CAS compared to CEA at 1 year (11.7% vs. 6.1%, $P = 0.02$) and 4 years (11.1 and 6.2%, $P = 0.03$), respectively. While the majority of patients (91.9%) were treated with a distal embolic protection device (EPD), the stroke rate was markedly increased in those patients not treated with an EPD (18/227 [7.9%] with EPD vs. 5/20 [25%] without EPD, $P = 0.03$), thus firmly entrenching the importance of these devices.[29]

Stenting and angioplasty with protection in patients at high risk for endarterectomy (SAPPHIRE)

The study evaluated the risk of peri-procedural events in high-risk CAS and CEA patients. Again, this trial was designed as a noninferiority study in both symptomatic patients with 50% or higher stenosis as well as asymptomatic patients with 80% or higher narrowing. The primary composite endpoints were defined as the rate of death, stroke, or myocardial infarction (MI) at 30 days as well as the 1-year rate of death or ipsilateral stroke. The absolute difference in primary endpoints was 7.9% lower with CAS (20 patients) compared to CEA (32 patients) ($P = 0.004$ for noninferiority). However, the results proved significant only in the asymptomatic group, while the results proved equivalent in symptomatic patients.[39]

Stent-supported percutaneous angioplasty of the carotid artery vs. endarterectomy (SPACE)

Also designed as a noninferiority trial, this study enrolled symptomatic patients with stenosis of 70% or higher within 180 days of either transient ischemic attack (TIA) or stroke. The primary endpoint of 30-day ipsilateral stroke or death was reached in 6.84% CAS patients and 6.34% CEA patients ($P = 0.09$), thus failing to result in significant evidence to demonstrate noninferiority of CAS to CEA.[34] The 2-year follow-up results, however, showed no difference in recurrent stroke or death rates between stenting and endarterectomy groups (9.5% vs. 8.8%, $P = 0.62$).[18]

Carotid revascularization endarterectomy vs. stenting trial (CREST)

This remains the largest multicenter randomized trial directly comparing CAS and CEA to-date. Sponsored by the National Institute of Health (NIH), the trial enrolled 2502 patients at 108 centers in the United States and Canada. The most notable difference in the design of this trail was that any proceduralist participating in trial centers (whether surgeon or interventionalist), had to meet a rigorous set of standards to be allowed to participate in the trial. Both symptomatic and asymptomatic patients were enrolled. Here, symptomatic patients had to demonstrate a 50% or higher carotid stenosis on angiography or >70% stenosis on ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA), while asymptomatic patients had to demonstrate a 60% or higher stenosis on angiography, 70% or higher on ultrasound, and 80% or higher on CTA or MRA. The primary composite endpoint was defined as the rate of stroke, MI, or death at 30 days or ipsilateral stroke within 4 years. There was no statistically significant difference demonstrated in the rate of primary endpoints between CAS (7.2%) and CEA (6.8%) ($P = 0.51$), neither in the symptomatic nor in the asymptomatic group. However, significant subgroup differences were seen in the rate of MI between CAS and CEA (1.1 and 2.3%, $P = 0.03$) and peri-procedural stroke (4.1 and 2.3%, $P = 0.01$). The increased rate of stroke was attributed to increased risk of events in elderly patients with CAS due to significant vessel tortuosity.[13]

Recently, the 10-year follow-up results of CREST were published.[14] Among the 2502 patients enrolled, no significant difference was found in the primary endpoint of stroke, MI, or death between the stenting group (11.8%) and the CEA group (9.9%). The 10-year follow up postprocedural stroke rates were not significantly different between the two groups (HR 0.99; 95% CI 0.64–1.52). Additionally, stratification by symptomatic status did not yield any difference between the two groups.

International carotid stenting study (ICSS)

This study evaluated the long-term efficacy of CAS vs. CEA in 1713 patients at 50 centers worldwide. Enrolled patients had to be symptomatic and demonstrate a 50% or greater stenosis and deemed well suited for either treatment. Again, endpoints of death or disabling strokes did not differ between the groups (HR 1.06, 95% CI 0.72–1.57, $P = 0.77$). However, the rates for any stroke (whether disabling or nondisabling) were more frequent with CAS when compared to CEA (HR 1.71, 95% CI 1.28–2.30, $P < 0.001$). Functional outcomes (as measured by Modified Rankin Score) at 1 year, 5 years, or final follow-up did not differ between the groups, indicating the increased stroke rate in CAS did not result in significantly disabling strokes.[8]

Asymptomatic carotid trial-1 (ACT-1)

Being the most recent of the retrieved studies, ACT-1 was originally designed to complement the CREST trial by comparing CEA to CAS in asymptomatic patients with carotid stenosis. The study was initially designed to enroll 1658 patients, but was stopped early after accrual of 1453 patients (87%) due to slow enrollment.[35] All patients were ≤79 years old and within standard risk for surgical complications, with asymptomatic status being defined as freedom from stroke, TIA, or amaurosis fugax 6 months prior to enrollment. The 5-year follow-up results were reported with a primary composite endpoint of death, stroke, MI within 30 days postprocedure or ipsilateral stroke within a year. Stenting was noninferior to endarterectomy in regards to the primary endpoint; the rate of stroke or death within 30 days was 2.9% in the stenting cohort vs. 1.7% in the endarterectomy group. From 30 days to 5 years postprocedure; the rate of freedom from ipsilateral stroke was 97.8% in the stenting group vs. 97.3% in the endarterectomy group, with overall survival rates of 87.1 and 89.4%, respectively. Finally, the cumulative 5-year rate of stroke-free survival was 93.1% in CAS group vs. 97.4% in the CEA group.[35]

EXPERT OPINION

"The bigger question is not whether to use CEA or CAS for symptomatic disease but rather whether any procedural therapy should be offered for the less severely stenotic subgroups (in the 60–80% range) of asymptomatic patients"—Bob S. Carter, MD, PhD, Harvard University and MGH, Boston MA.

In CEA and CAS, we have two efficacious tools for dealing with symptomatic carotid stenosis based on a multiplicity of trials demonstrating noninferiority between the two therapies. Because the cervical carotid artery is readily accessible, and the associated morbidity of CEA is typically low, open techniques have not experienced the same degree of erosion in procedural volume by endovascular techniques as has been seen in other neurovascular or systemic vascular diseases. Frankly, the bigger question is not whether to use CEA or CAS for symptomatic disease but rather whether any procedural therapy should be offered for the less severely stenotic subgroups (in the 60–80% range) of asymptomatic patients. Future studies will help us further refine our understanding of what degree of stenosis can still justify a procedural intervention for an asymptomatic patient, who may equally benefit from modern medical management.

"CEA vs CAS: Where do we go from here?" This is a title intro for the expert opinion segment, highlighting the expected future directions around this debate, or in other words how should we move forward in regards to the ongoing debate about CEA and CAS.

Several studies have been published to compare both treatments, including 13 RCTs.[8,11-13,18,19,21,28,29,34,36,37,39] Nevertheless, there were disparities among the results. In a meta-analysis that included these trials in addition to 3 prospective controlled studies and 20 retrospective comparative studies, CAS had higher risk of stroke and mortality within 30 days of treatment compared to CEA (4.7% vs. 3.5%).[41] Similar results were reported in other large studies.[30,36,38] The risk is even higher in patients older than 70 years of age.[10] However, with follow-up period more than 2 years, the risk of stroke and mortality following CAS decreases to approach that following CEA.[41] The use of EPD was shown to effectively reduce the stroke rate after CAS, and has been recommended in all cases.[23,40] CAS also has a higher restenosis rate compared to CEA at 1-year (7.4% vs. 3.6%) and 2-year follow-up (6.6% vs. 5.0%).[41] However, long-term follow-up data from the CREST trial at 10 years showed no difference in the risk of ipsilateral stroke in both CEA and CAS arms. As medical management improves, the risk of stroke in asymptomatic carotid stenosis approaches that of treated patients with symptomatic carotid stenosis. Should treatment even be offered to asymptomatic carotid stenosis? CREST 2 which will commence shortly has been structured to answer this question and will be the first trial to compare medical management to CAS.

DISCUSSION

CEA has been well established as an effective modality for treatment of carotid stenosis. Two main techniques are currently used for this procedure: conventional and eversion endarterectomy. The former involves obtaining proximal control over the common carotid artery, then distal control around external carotid artery and internal carotid artery (ICA). Subsequent longitudinal arteriotomy of ICA is followed by either a patch angioplasty or primary vessel closure. The patch method is more commonly used and has been associated with better outcome in some studies.[27,33] The eversion technique involves oblique arteriotomy of the ICA at the carotid bifurcation, prior to plaque excision via eversion of the artery and reimplantation of the ICA at the carotid bulb. Both techniques have been found to be almost equally effective, as demonstrated by plentiful studies throughout the literature.[6,15,24,32]

Intraoperative monitoring of brain function to detect the potential ischemia resulting from ICA cross-clamping is an essential part of the procedure. Bypassing the surgical clamp via shunting (routine or selective) is used as a preventive measure by some surgeons. However, these shunts have been reported to have their own side effects such as distal embolization and carotid dissection.[20] Thus aiming to reduce shunt rates, various intraoperative

modalities have been proposed, with the optimal method remaining controversial. These modalities include electroencephalography, somatosensory-evoked potential, transcranial Doppler sonography, near-infrared spectroscopy, and carotid stump pressure. The technical surgical details such as the type of anesthesia, shunts, patches, intraoperative monitoring were widely variable between the trials, and mostly left to the surgeon's discretion.

On the contrary, the ongoing advancements in the endovascular field have bolstered CAS as a widely accepted alternative to open surgery,[13] especially for patients with suboptimal surgical risk profile (e.g., severe cardiac, renal disease, high carotid bifurcation, previous neck dissection/irradiation, etc.). The procedure is performed in the angiographic suite under mild sedation to monitor the patient's neurologic status. The stenosed area is crossed by a wire, upon from the distal filter is deployed into the ICA, followed by balloon angioplasty and placement of the stent across the stenotic lesion. Distal filters (EPD) utility were limited in the early trials. For instance, EPD was not used in the CAVATAS trial because they were not available at the time, and only 26% of patients in the endovascular arm were treated with stents, leading to a higher stroke and restenosis rates in the 8-year follow-up period.[9] On the contrary, the CREST protocol mandated the usage of one type of stent (RX Acculink stent), and the RX Acculink EPD whenever technically feasible in all endovascular procedures.[13]

The randomized prospective trials comparing CAS and CEA have in large part demonstrated fairly consistent data over the past decade. EVA-3S demonstrated significantly worse outcomes with CAS over CEA. However, as this was one of the earliest of these trials comparing the two modalities, less sophisticated materials were available for these patients. This is evident in the relatively low usage of EPDs, something that is now commonly utilized by most operators. Excluding the CAVATAS trial, which was underpowered to detect equality, the other five trials presented either demonstrated noninferiority between CAS and CEA (SAPPHIRE, CREST, ICSS, ACT-1) or came very close (SPACE). Thus, these randomized controlled multicenter trials have, by and large, demonstrated CAS as a comparably safe alternative to CEA in the treatment of carotid artery stenosis.

On further analysis of these trials, certain subgroups have been evaluated to help in patient selection. The CREST trial demonstrated equivalent results overall, but with increased rates of MI with CEA and stroke with CAS. The increased rate of MI in CEA has been attributed to the increased myocardial stress of the open operation as well as possibly the need for alterations in patients' antiplatelet medications at the time of the operation. The increased rate of peri-procedural stroke with CAS was related to the patient's age; surprisingly, the older patients (>70 years old) demonstrated increased stroke rates with the less-invasive CAS over CEA. This is believed to be related to the increased tortuosity of the access vasculature in older patients. Thus, while CAS and CEA demonstrate similar safety profiles overall, it is our opinion that CAS should be chosen in patients with significant cardiac risk factors at the time of procedure, while CEA should be chosen in patients over 70 years old.

While these previous trials have demonstrated similar safety profiles with CAS and CEA, the question of true efficacy remains elusive. Treatment in symptomatic disease with either CAS or CEA is indicated and has been demonstrated to be highly effective. However, current evaluations of the natural history of asymptomatic carotid stenosis continue to demonstrate lower risks of strokes or TIAs than previous reported. This is generally attributed to increased utilization and effectiveness of medical therapy, namely antiplatelet and lipid-lowering medications.[5,16,17] The planned CREST 2 trial will directly examine this question with a very similar trial as CREST but in asymptomatic patients only. Until the results of this trial are reported, very careful selection of asymptomatic patients only after institution of appropriate medical therapy should be undertaken.

DISCLOSURE

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conflicts of interest
There are no conflicts of interest.

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