

Comparative Review of the Treatment Methodologies of Carotid Stenosis

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Abstract

The treatment of carotid stenosis entails three methodologies, namely, medical management, carotid angioplasty and stenting (CAS), as well as carotid endarterectomy (CEA). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) have shown that symptomatic carotid stenosis greater than 70% is best treated with CEA. In asymptomatic patients with carotid stenosis greater than 60%, CEA was more beneficial than treatment with aspirin alone according to the Asymptomatic Carotid Atherosclerosis (ACAS) and Asymptomatic Carotid Stenosis Trial (ACST) trials. When CAS is compared with CEA, the CREST resulted in similar rates of ipsilateral stroke and death rates regardless of symptoms. However, CAS not only increased adverse effects in women, it also amplified stroke rates and death in elderly patients compared with CEA. CAS can maximize its utility in treating focal restenosis after CEA and patients with overwhelming cardiac risk or prior neck irradiation. When performing CEA, using a patch was equated to a more durable result than primary closure, whereas eversion technique is a new methodology deserving a spotlight. Comparing the three major treatment strategies of carotid stenosis has intrinsic drawbacks, as most trials are outdated and they vary in their premises, definitions, and study designs. With the newly codified best medical management including antiplatelet therapies with aspirin and clopidogrel, statin, antihypertensive agents, strict diabetes control, smoking cessation, and life style change, the current trials may demonstrate that asymptomatic carotid stenosis is best treated with best medical therapy. The ongoing trials will illuminate and reshape the treatment paradigm for symptomatic and asymptomatic carotid stenosis.

Keywords

- carotid artery stenosis
- carotid endarterectomy
- carotid angioplasty and stenting

Stroke has repercussions that extend beyond the suffering of the patients and their families. It is the fourth leading cause of death in the United States,¹ imposing a formidable 74 billion dollar financial burden on the society in 2010.² It is often treatable especially when suspected early, and creative methods of facilitating the diagnosis of stroke have shown effectiveness. One such strategy is educating children about the cardinal signs of stroke using hip hop, so that they can recognize a stroke and initiate early medical evaluation

process.³ Although the incidence of stroke has followed a downward trajectory in recent years in both Whites and African Americans,⁴ approximately 795,000 stroke still occurs each year. Of this, approximately 20 to 30% comprises of carotid stenosis in its etiology,^{5,6} emphasizing the importance of effective treatment of carotid stenosis and the secondary prevention of its recurrence.

The treatment of carotid stenosis centers on the following three major modalities: medical management, carotid artery

angioplasty and stenting (CAS), and carotid endarterectomy (CEA). The best medical management (BMM) of stroke entails a combination antiplatelet therapy with aspirin and clopidogrel, statin, antihypertensive agents, smoking cessation, and possibly strict diabetic control and lifestyle changes. The benefits and progression of BMM have been extensively reviewed elsewhere.⁷ This article is a perusal of the most prominent randomized clinical trials (RCTs) examining different treatment modalities of carotid stenosis. It is also a review of the latest literature published in the past 10 years regarding the evolving techniques of CEA.

Symptomatic Carotid Stenosis

Two landmark studies have codified the management paradigm of patients with symptomatic carotid stenosis. These RCT enrolled patients with a recent stroke, reversible ischemic neurologic deficit, transient ischemic attack (TIA), retinal infarct or amaurosis fugax, and an ipsilateral carotid stenosis. A considerable amount of time has elapsed since these trials, and the control of these trials was treatment with aspirin, which was considered the BMM at that time. Near occlusion of internal carotid artery (ICA) defined as 95% or greater in North American Symptomatic Carotid Endarterectomy Trial (NASCET) was excluded from this analysis of the NASCET and European Carotid Surgery Trial (ECST) for the purpose of a more equitable comparison⁸ (→Table 1).

It is important to be cognizant of the crucial differences between NASCET and ECST, most notable of which is the methodology of calculating the degree of stenosis. Both trials used the residual luminal diameter of the narrowest part of the ICA as the numerator, but the NASCET utilized the diameter of the undiseased internal carotid as the denominator. ECST on the contrary used the predicted outer diameter of the ICA in the same diseased portion involving atherosclerosis and stenosis. Additional studies demonstrated a linear correlation between NASCET and ECST methods—50% steno-

sis in NASCET correlates with 65% stenosis in ECST; 70% in NASCET corresponds to 82% in the ECST method.^{9,10} Another salient point is, at the time of these trials, aspirin alone was considered the best medical treatment, which, in the current era, encompasses statin, aspirin, clopidogrel, and antihypertensives, as mentioned previously. These discrepancies mandate further investigation.

Asymptomatic Carotid Stenosis

About 3.5 to 5% of asymptomatic patients with stenosis greater than 80% have a stroke each year.¹¹ Although experts agree that this is not a negligible rate, they disagree on the optimal treatment method for asymptomatic patients. The Asymptomatic Carotid Atherosclerosis (ACAS) and Asymptomatic Carotid Stenosis Trial (ACST) comparing BMM and CEA in asymptomatic patients suggested that an aggressive intervention with CEA produces more advantageous outcomes than BMM alone (→Table 2). The limitations of the ACAS trial are using only aspirin as BMM and its subgroup analysis that failed to demonstrate the benefits of CEA in women although this study was not powered to show gender difference. The ACST utilized aspirin and antihypertensives without statin, which also does not meet the current standard of care for medical treatment of carotid stenosis.

Carotid Angioplasty and Stenting versus Carotid Endarterectomy

A prior study called the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) compared endovascular treatment with CEA but used only balloon angioplasty without stenting, which showed more frequent restenosis with percutaneous intervention and demanded further investigations involving stenting.¹² Two major RCTs shed light on the comparative efficacy of CEA versus CAS (→Table 3). The SAPHIRE trial was a small noninferiority trial that

Table 1 Major RCT's comparing CEA versus BMM in symptomatic carotid stenosis^{8,56-60}

	Year, location	Patients, n	Inclusion criteria	Absolute risk reduction of ipsilateral stroke	Number needed to treat	Critiques
NASCET	1998, Mostly United States and Canada	659 severe stenosis ^a 858 moderate stenosis ^a	Stenosis ≥ 30%	Sever stenosis: 15% at 2 y ^b Moderate stenosis: 6.5% at 5 y	6.7 for severe 15.4 for moderate	Post-stenotic ICA used in stenosis degree calculation alters its value
ECST	1998 14 European countries	429 severe stenosis ^a 646 moderate stenosis ^a	Any degree of stenosis	Severe stenosis ^c : 21.1% at 5 y ^b Moderate stenosis ^c : 5.7% at 5 y	4.7 for severe 17.5 for moderate	"Uncertainty principle" leading to nebulous inclusion and exclusion criteria

Abbreviations: BMM, best medical management; CEA, carotid endarterectomy; ECST, The European Carotid Surgery Trial; ICA, internal carotid artery; NASCET, The North American Symptomatic Carotid Endarterectomy Trial; RCT, randomized clinical trials.

^aSevere stenosis > 70%, moderate stenosis between 50 and 69%.

^bp < 0.05.

^cDegree of stenosis was recalculated using the NASCET method.

Table 2 Major RCT's comparing CEA versus BMM in asymptomatic carotid stenosis^{14,61,62}

	Year, location	Patients, <i>n</i>	Inclusion criteria	Absolute risk reduction of stroke	Number needed to treat	Critiques
ACAS ⁶¹	1995, United States, Canada	1,659	Stenosis \geq 60%	5.9% ^a at 5 y	16.9	BMM included only aspirin No significant benefit of CEA in women
ACST ⁶²	2004, 30 European countries	3,120	Stenosis \geq 60%	5.4% ^a at 5 y for < 75 y old	18.5	"Uncertainty principle" leading to nebulous inclusion and exclusion criteria BMM included only aspirin and antihypertensives Statins were added later during the trial

Abbreviations: ACAS, Asymptomatic Carotid Atherosclerosis; ACST, Asymptomatic Carotid Stenosis Trial; BMM, best medical management; CEA, carotid endarterectomy; RCT, randomized clinical trials.

^a*p* < 0.05.

randomized patients with high surgical risks: severe cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, restenosis after prior CEA, previous radical neck surgery or radiation therapy to the neck, and an age older than 80 years. Some notable criticisms of the SAPHIRE study are the sponsorship of the trial and the involvement in the study design by the stent company, Cordis, which inherently induces biases. The authors of the SAPHIRE trial also acknowledge that the trial was not powered enough to render a definitive conclusion on the benefit of CAS or CEA in asymptomatic patients.¹³ Others have noted flaws in randomization because of the surgeons' exclusion of high-risk patients at their discretion and their relative inexperience in CEA.¹⁴

The CREST is a large RCT that generated many pivotal questions. It was conducted by interventionalists and surgeons chosen after a more robust credentialing process. It found CAS equally effective as CEA in preventing ipsilateral stroke. The initial conclusion was that both symptomatic and asymptomatic patients had no significant discrepancy in stroke and death rate after 4 years. The conclusions of the CREST have been challenged after subgroup analyses. It has been criticized for giving antiplatelets more aggressively with CAS.¹⁴ In symptomatic patients, CAS had significantly more stroke and death as opposed to CEA (overall hazard ratio 1.9, perioperative hazard ratio 1.89).¹⁵ Women¹⁶ also had significantly more stroke and death with CAS than with CEA (hazard ratio 1.35). Furthermore, the efficacy of CAS showed a negative correlation with increasing age. CAS increased the stroke rate 1.77 times for each 10-year interval in age.¹⁷ For ipsilateral stroke, CAS patients older than 75 years have a hazard ratio of 2.17 periprocedurally and 2.15 at 4 years after the procedure. Interestingly enough, this notion was not observed with CEA.

The SPACE trial is a noninferiority trial that enrolled only the symptomatic patients with greater than 70% stenosis. After 2 years of follow-up, the noninferiority was not proven. The limitations of the SPACE trial are that CAS was performed by interventionalists with as few as 10 prior procedures under the guidance of a tutor and that the antiembolic device was used in only 27% of CAS, making a fair comparison difficult.¹⁴ The trial was prematurely terminated because of the funding issues and low conditional power.¹⁸

The EVA-3S is a French study that resulted in significantly higher incidents of ipsilateral stroke and death with CAS after 4 years is mostly accounted for by the 30-day perioperative events and the risks equalize thereafter.¹⁹ This trial was also prematurely terminated for safety and futility. Its authors ascribed the risks with CAS to anatomical difficulties and the interventionalists' varying experience.²⁰ A composite analysis of three trials, EVA-3S, SPACE, and International Carotid Stenting Study (ICSS) recommends CAS be performed by only those who do more than six procedures per year.²¹

The ICSS is an RCT exploring similar questions. It needs a long-term analysis but the 120-day analysis had more favorable results for CEA. As opposed to the other CAS trials, the ICSS was associated with higher myocardial infarction (MI) in CAS instead of CEA. Another discrepancy in ICSS is prevent cerebral ischemia in this study.²²

Patch Carotid Endarterectomy versus Primary Closure Carotid Endarterectomy

Recent literature has probed the different techniques of CEA. The following three major techniques prevail in CEA: primary closure of endarterectomy, patch closure (pCEA), and eversion carotid endarterectomy (eCEA). A recent abstract published in *Stroke*

Table 3 Major RCT's comparing CAS and CEA^{13,18,19,63–67}

	Year, location	Patients, <i>n</i>	Inclusion criteria	Results	Comments, critiques
Symptomatic and asymptomatic patients					
SAPPHIRE	2008, United States, Canada	237	Symptomatic: stenosis ^a ≥ 50% Asymptomatic: Stenosis ^a ≥ 80% High surgical risk	No significant difference in ipsilateral stroke at 1 and 3 y	Embolism protective device in CAS Noninferiority trial No BMM control group Low conditional power
CREST	2010, United States	2,502	Symptomatic: stenosis ^a ≥ 50% on angio, ≥ 70% on U/S, CTA, and MRA Asymptomatic: Stenosis ^a ≥ 60% on Angio, ≥ 70% on U/S, ≥ 80% on CTA and MRA	No significant difference in ipsilateral stroke at 2.5 y and estimated 4 y (HR, 1.1 with CAS) Stroke risk 1.77 times ^a higher with CAS per 10 y after 75 No difference regarding symptomatic status in ipsilateral stroke or death in 4 y	Sporadic use of embolism protective device in CAS CAS received more strict antiplatelet control
Symptomatic patients only					
SPACE	2006, 3 European countries	1,183	Stenosis ^b ≥ 70%	Noninferiority could not be validated Restenosis ≥ 70% greater in CAS ^c at 2 y	Early termination: low conditional power, funding issue Embolism-protective device used in only 27% Surgeons/interventionalists had as few as 10 procedures Noninferiority study
EVA-3S	2006 France	527	Stenosis ^a ≥ 60% (initially 70% but expanded to include 60%)	Any stroke or death higher with CAS ^c at 30 d (RR, 2.5) Ipsilateral stroke or death higher with CAS ^c at 4 y (HR, 1.97)	Early termination
ICSS	2010 Europe	1,710	Stenosis ^a ≥ 50%	Stroke, death, and MI higher with CAS ^c at 120 d (HR, 1.69) Any stroke, all-cause death higher with CAS ^c at 120 d	Needs a long-term analysis

Abbreviations: Angio, angiography; BMM, best medical management; CREST, The Carotid Revascularization Endarterectomy versus Stenting Trial; CAS, carotid angioplasty and stenting; CTA, CT angiogram; EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; HR, hazard ratio; ICSS, International Carotid Stenting Study; MI, myocardial infarct; MRA, magnetic resonance angiogram; RR, relative risk; SAPPHIRE, The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy; U/S, ultrasound.

^aDegree of stenosis was recalculated using the NASCET method.

^bDegree of stenosis was calculated using the ECST method.

^c*p* < 0.05.

featured a subanalysis of the CREST, which was notable for a significant decrease in restenosis rates and perioperative stroke rates with pCEA as opposed to primary closure.²³ Numerous

previous studies have also shown superior results with pCEA versus primary closure,^{24–28} but the optimal kind of the patch remains unclear. There are autografts using saphenous or jugular

vein, xenografts using bovine pericardium, as well as prosthetic grafts using polytetrafluoroethylene (PTFE), polyester, or Dacron, none of which has definitively proven superiority over the others. According to a systemic review of 13 RCTs, venous autograft, PTFE, and Dacron all had equivalent perioperative and long-term stroke, mortality, and restenosis rates.²⁹ The advantage of autogenous vein patches is that it is more consistent with intima thickness which potentially translates to less thrombosis.³⁰ Yet, it is associated with increased risks of pseudoaneurysm formation³¹ and restenosis.³² Synthetic grafts are more readily available, resistant to rupture, and foregoes the opportunity cost of the lack of a vein graft for future coronary bypass if need be.²⁹ However, Dacron was linked to higher infection rates and thrombogenicity,³³ whereas achieving hemostasis was more difficult when PTFE was used.²⁹ When pCEA using PTFE was compared with bovine pericardium pCEA, a prospective randomized study resulted in comparable neurological events and death in both the groups.³⁴

Eversion Carotid Endarterectomy versus Prosthetic pCEA and Primary Closure

In a prospective but nonrandomized single-center study, eCEA was associated with comparable rates of operative mortality and postoperative TIA, stroke, and death to primary closure and prosthetic pCEA using Dacron or PTFE.³⁵ The study suggested that eCEA may be associated with a lower restenosis rate presumably from postoperative hemodynamics that is closer to the normal one. Other studies have hinted at the potential of eCEA as an excellent alternative to pCEA.^{36,37}

Discussion

Direct comparisons of these various studies have intrinsic drawbacks. For example, primary end points were defined in slightly different ways among the different trials. These studies had variegated methods of calculating the degree of stenosis as noted earlier in comparing the NASCET and ECST. They also used different imaging modalities. The SAPHIRE trial used carotid duplex to measure the degree of stenosis, whereas the CREST used angiography, computed tomographic angiogram, magnetic resonance angiogram, as well as duplex, which may produce subtle yet important differences because of the varying sensitivities of these imaging modalities. Furthermore, there are different types and companies for stents which may or may not

have used an embolic-protection device. Despite these, we tried to analyze these studies using parallel and consistent parameters for comparison, by using the recalculated stenotic degree according to the NASCET method when possible and especially focusing on ipsilateral stroke and death rate as the primary end point.

Overwhelming evidence suggests CEA as the best treatment for symptomatic patients. Both the NASCET and ECST have set the treatment guidelines for symptomatic patients. A meta-analysis of the NASCET, ECST, as well as the Veterans Administration 309 Trial (VA309)³⁸ rendered consistent results among the three and superiority of CEA to BMM of that time which was aspirin alone.⁹

When CAS is juxtaposed to CEA, CAS has an inclination to more frequent ipsilateral stroke and death in symptomatic patients. CEA tended to have more MI, except in the ICSS trial. Current literature lacks in the evidence for CEA versus BMM comprised of the contemporary standard in both the symptomatic and asymptomatic patients. The conjecture is that CEA is better than even the most current standard of BMM as well as CAS especially in symptomatic patients, and the ongoing trials including ECST and CREST-2 will provide more robust evidence. From a technical perspective, pCEA appears as a sturdier repair than primary closure CEA, and eCEA is a promising new technique that needs further investigation.

In asymptomatic patients, the answer to the best treatment is more nebulous. Although the ACAS and ACST have demonstrated more advantageous outcomes with CEA versus BMM in stenosis greater than 60%, these trials were antiquated in their definition of BMM. The utility of CAS in asymptomatic patients is also questionable. CAS was associated with significantly higher periprocedural adverse events in many trials. The subgroup analyses of the CREST showed a higher stroke rate with CAS than with CEA in asymptomatic patients. The SAPHIRE trial was not powered enough, and their randomization was obscured by many factors. The noninferiority premise of many of these studies is not strongly substantiated, because many of these trials had design flaws. Moreover, the interventionalists' and surgeons' competency and familiarity with the procedure were often jeopardized by their relative lack of experience.

Of note, age had a negative effect on the outcome of CAS. The CREST demonstrated the inverse proportion between increasing age and the outcomes of CAS, which incrementally amplified the risks by 1.77 times for each 10 year increase in

Table 4 Currently ongoing trials

	BMM	CAS	CEA
Asymptomatic		ACST-2, ACT-1	
		SPACE-2 (3-armed)	
Symptomatic and asymptomatic		ECST-2, CREST-2 (2-armed)	

Abbreviations: ACT-1, Asymptomatic Carotid Trial-1; ACST-2, Asymptomatic Carotid Surgery Trial-2; CREST-2, Carotid Revascularization Endarterectomy versus Stenting Trial-2; ECST-2, European Carotid Surgery Trial-2; SPACE-2, Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy Trial-2.

age. A meta-analysis of EVA-3S, SPACE, and ICSS found CAS involving significantly higher risks for stroke and death in symptomatic patients older than 75 years.³⁹ Gender is another factor influencing the efficacy of CAS. The post hoc analysis of the CREST found female sex associated with significantly more frequent stroke, MI, and death when treated with CAS versus CEA (hazard ratio 1.84, $p = 0.047$).¹⁶ The authors of the trial noted that this notion was not observed in men and attributed this to women's increased embolic signals postoperatively,^{40,41} in addition to impaired cerebrovascular reactivity.^{42,43} This trial was not powered enough to delineate the interaction between symptomatic status and gender.

Another potential disadvantage of CAS versus CEA is the compromise of collateral blood supply. Although external carotid artery (ECA) normally supplies structures external to the brain, it can serve as a critical collateral supply to the brain when ICA flow is compromised.^{44,45} Several studies have demonstrated a significant increase in ECA occlusion⁴⁶ and stenosis^{47–49} after CAS as opposed to CEA. Furthermore, some studies have found more in-stent restenosis with ECA stenosis after CAS.^{50,51} CAS can maximize its efficacy in focal restenosis after CEA⁵² and certain populations, such as younger men or patients with overwhelming cardiac risk or previous neck irradiation.^{13,53}

In light of these observations, asymptomatic patients may be best treated with the most aggressive BMM rather than CAS or CEA. Evidence demonstrates that asymptomatic patients have an acceptable annual stroke rate of 1.13%^{14,54} when treated with BMM. It behooves us to remember that asymptomatic patients have a greater chance of cardiac ischemia than a cerebral vascular accident.⁵⁵ Current trials, called "Trials 2," will elucidate the best treatment paradigm for asymptomatic carotid stenosis as well as a systemic comparison of different treatment modalities (►Table 4). Experts agree that even those patients who undergo CEA should be maintained on the contemporary BMM regimen to deter disease progression and to prevent secondary events. Long-term follow-ups and continued evolution in risk stratification in different patient populations with respect to age, sex, and race will further enhance the outcomes of carotid stenosis treatment.

Conclusion

Despite the lack of direct comparison between the contemporary modality of BMM alone and CEA with BMM in symptomatic stenosis, there is a robust evidence for significant benefit of CEA in symptomatic carotid stenosis with severe stenosis and modest benefit for moderate stenosis. CAS faces questions about its efficacy regarding age- and sex-specific compromise. CAS can best serve focal restenosis after CEA, younger men, and patients with overwhelming cardiac risk or prior neck irradiation. Asymptomatic patients represent a treatment enigma at this point. While we await the results from the ongoing trials, they may be best treated BMM instead of more aggressive interventions.

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