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Treatment of Symptomatic Carotid Stenosis: Carotid Stent Placement Versus Endarterectomy

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Abstract The mainstay of treatment options for symptomatic carotid stenosis is focused around medical management, carotid endarterectomy, and carotid angioplasty and stent placement. The International Carotid Stenting Study (ICSS), also called Carotid and Vertebral Artery Transluminal Angioplasty Study 2 (CAVATAS 2), the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial, the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, and the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) were five major trials which compared carotid endarterectomy and carotid angioplasty and stent placement. We review the results of the trials and incorporation of the results into clinical decision making.

Keywords Carotid endarterectomy · Carotid artery stenosis · Carotid angioplasty · Carotid stent placement · Ischemic stroke · Atherosclerosis

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Introduction

Symptomatic carotid stenosis is described as the occurrence of the sudden onset of focal neurologic deficits which correlate with the corresponding carotid artery distribution (e.g., the symptoms being ipsilateral to the affected atherosclerotic carotid vessel) within the previous 6 months [1, 2]. Symptoms may include one or more transient ischemic attacks (TIAs), transient monocular blindness, or one or more nondisabling ischemic strokes. The mainstay of treatment options for symptomatic atherosclerosis is focused around medical management, carotid endarterectomy (CEA), and carotid angioplasty and stent placement (CAS) [1]. Among these, CEA has demonstrated greater safety and efficacy than best medical treatment in randomized controlled clinical trials in the reduction of risk in ischemic stroke in both symptomatic and asymptomatic patients with carotid artery atherosclerosis, under certain settings [1, 3]. On the basis of the results of these studies, CEA in conjunction with low-dose aspirin (81–325 mg/day) administered perioperatively and for at least 3 months after the procedure is the recommended treatment in a patient population that has recently developed symptomatic carotid stenosis of 70–99 % usually within the past 6 months (class 1—level of evidence B). Aspirin therapy can then be continued on the basis of the patient's overall condition [4, 5]. Other requirements which describe an optimal candidate for CEA include a patient population that has a life expectancy of at least 5 years, a carotid lesion that is surgically accessible, the absence of other risk factors such as significant cardiac, pulmonary, or other comorbidities that may make the patient a poor surgical candidate, and no previous history of ipsilateral CEA [1, 3].

Clinical Trials Evaluating CEA Versus Best Medical Treatment

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) [6, 7] and the European Carotid Surgery

Trial (ECST) [2] were two major trials that focused on the role of CEA in the setting of symptomatic carotid disease.

North American Symptomatic Carotid Endarterectomy Trial

NASCET [6, 7] was a randomized, prospective, multicenter trial of 659 patients that assessed the efficacy of CEA treatment compared with medical treatment in patients with symptomatic carotid atherosclerotic disease. The subject group in the trial was composed of patients with hemispheric or retinal TIA or a nondisabling stroke within the 120 days before entry and who had stenosis of 70–99 % in the symptomatic ipsilateral carotid artery. The study was terminated prematurely after 18 months because the data demonstrated that CEA was beneficial in this selected group of patients, with a number needed to treat (NNT) of 6 at 5 years in patients who were enrolled before the study was terminated and who continued to be followed. The study showed that in a 2-year follow-up, CEA had a lower risk of any stroke or death (15.8 % versus 32.3 %), a lower risk of any ipsilateral stroke (9 % versus 26 %), a lower risk of major or fatal ipsilateral stroke (2.5 % versus 13.1 %), and a lower risk of any major stroke or death (8.0 % versus 19.1 %), all of which were statistically significant. When stratified by severity, symptomatic patients with carotid stenosis of 50–69 % had a smaller benefit from CEA, with an NNT of 22 at 5 years. In addition, the presence of comorbidities adversely affected the outcome. Patients with multiple comorbidities had a higher postoperative mortality rate. For optimal benefit, the patients had to undergo the procedure soon after their TIA or stroke, preferably within the first 2 weeks. Patients with stenosis of less than 50 % did not benefit from surgery [8].

European Carotid Surgery Trial

ECST [2] was a randomized, multicenter, prospective trial with 2,518 patients with nondisabling ischemic stroke, TIA, or retinal infarct due to a stenotic lesion in the ipsilateral carotid artery who were randomized to receive either medical management with aspirin or surgery. At 3 years, in patients treated with CEA there were significant reductions in the incidence of ipsilateral ischemic stroke (2.8 % versus 16.8 % with aspirin alone) and in the total risk of perioperative mortality, perioperative stroke, ipsilateral ischemic stroke, or any type of stroke (12.3 % versus 21.9 %). The risk varied with age and sex, with less benefit in women and over a narrower range of carotid stenosis in younger patients. The reduction in the risk of having a recurrent stroke after CEA was present up to the 10-year follow-up. CEA was also beneficial for patients with 50–69 % symptomatic stenosis. The NNT to prevent one stroke over 5 years in this group was 22, with an attributable relative rate of 4.6 % [8]. CEA was not beneficial in patients with symptomatic carotid stenosis of 30–49 %. CEA was harmful for symptomatic patients with less than 30 % stenosis [2].

Carotid Artery Stent Placement

With the advances in interventional procedures, CAS has become an alternative option for treatment of carotid artery stenosis [9]. In comparison with primary carotid angioplasty, CAS reduces the rates of long-term complications such as the risk of embolization, thrombosis of the involved vessel, carotid artery recoil, and restenosis. Multiple studies have suggested that CAS and CEA have similar long-term outcomes for symptomatic patients with carotid artery stenosis. However, the 30-day periprocedural stroke rate is greater in patients who underwent CAS compared with CEA. In contrast, the 30-day periprocedural myocardial infarction (MI) rate is greater in patients who underwent CEA compared with CAS [10].

As per current guidelines, CEA is the preferred treatment for most patients with symptomatic carotid atherosclerosis. However, the appeal of CAS due to its less invasive nature may offer more optimal outcomes with continued technical advances, especially in the subgroup of patients who may be at greater risk of poor outcomes from CEA. Under certain conditions, CAS may be a better treatment choice than CEA. This subgroup includes patients with ipsilateral symptomatic carotid stenosis of 70–99 % where the lesion is in a location not easily accessible to surgery (e.g., with high cervical carotid bifurcations). It may also be a more optimal choice in scenarios including carotid stenosis induced by radiation, or if the patient has had an endarterectomy and undergoes restenosis. In addition, stent placement may be preferred in a patient population consisting of poor surgical candidates such as those with cardiac or pulmonary disease. This recommendation applies when the periprocedural risk of stroke and death with CAS for the operator or center is less than 6 % [9].

Major Randomized Trials Comparing CEA Versus CAS

The International Carotid Stenting Study (ICSS), also called Carotid and Vertebral Artery Transluminal Angioplasty Study 2 (CAVATAS 2) [7], the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial [11], the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial [12], the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial [13], and most importantly the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) [14] were five major trials which compared CEA and CAS (Table 1).

SPACE Trial

The SPACE trial [11] was a randomized, multicenter, European, noninferiority trial that compared CAS with CEA for

Table 1 Overview of major trials comparing carotid endarterectomy (*CEA*) and carotid angioplasty and stent placement (*CAS*)

Study	Year	Design	Symptomatic vs asymptomatic	Results
SAPPHIRE	2004	Randomized, prospective, multicenter	96/238	CAS not inferior to CEA in symptomatic or nonsymptomatic patients in the high surgical risk group
SPACE	2006	Randomized, prospective, multicenter, European noninferiority trial	1,196/0	Ended after the second interim analysis owing to lack of recruitment
EVA-3S	2006	Randomized, prospective, multicenter	527/0	CEA had better end point outcomes vs CAS for symptomatic stroke
ICSS	2010	Randomized, prospective, multicenter	1,710/0	CAS had a higher rate of stroke, death, and MI versus CEA for symptomatic stroke
CREST	2010	Randomized, prospective, multicenter, parallel, open label	1,326/1,176	CEA and CAS have similar safety and efficacy profiles

CREST Carotid Revascularization Endarterectomy Versus Stenting Trial, *EVA-3S* Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis, *ICSS* International Carotid Stenting Study, *MI* myocardial infarction, *SAPPHIRE* Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy, *SPACE* Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy

the treatment of severe symptomatic carotid stenosis. The trial included 1,183 patients randomized to either the CAS or the CEA treatment group. High-risk patients with uncontrolled hypertension, severe concomitant disease, and a poor prognosis were excluded. Patients with recurrent carotid stenosis after surgery or stent placement were also excluded. The trial was stopped after the second interim analysis because it was underpowered to demonstrate statistical significance from lack of adequate recruitment and funding problems.

The 30-day postprocedure results demonstrated no statistically significant difference between CAS and CEA in regard to the risk of death or ipsilateral ischemic stroke (6.8 % versus 6.3 %, respectively, absolute difference 0.51 %, 90 % confidence interval −1.89 to 2.91 %) [15]. There was no statistically significant difference between CAS and CEA for the risk of periprocedural stroke or death and ipsilateral ischemic stroke up to 2 years after the procedure in both intention-to-treat analysis (9.5 % versus 8.8 %) and per protocol analysis (9.4 % versus 7.8 %). However, there was a greater probability of recurrent carotid stenosis of more than 70 % in the CAS group in both analyses. In the SPACE trial, the use of embolic protection devices with stenting was optional. Only 27 % of patients treated with CAS used embolic protection devices, which may have skewed the outcome. However, there was no statistically significant difference in the 30-day outcome of death or ipsilateral ischemic stroke in patients who were provided with embolic protection versus those who were not (7.3 % and 6.7 %, respectively, odds ratio 1.1, 90 % confidence interval 0.53–2.25) [11].

SAPPHIRE Trial

The SAPPHIRE trial [13, 16], conducted from 2000 to 2005, was a randomized, parallel study which compared CAS with CEA in the treatment of carotid artery disease in patients at increased risk of CEA. The study results demonstrated that CAS was not inferior to CEA in patients with symptomatic or asymptomatic carotid stenosis in this high surgical risk group. For example, in patients with symptomatic carotid artery stenosis, the percentage of patients reaching the primary end point of composite death, stroke, or MI at 1 year was similar to that for asymptomatic patients (16.8 % versus 16.5 %, respectively). In the post procedural period, a lower proportion of symptomatic patients reached the primary end point, as compared to asymptomatic patients (2.1 % versus 9.3 %, respectively) reached the primary end point. One of the limitations of the study was that more than 70 % of the patients in the trial had asymptomatic carotid disease. Therefore, the results were not applicable to those with symptomatic carotid stenosis [13].

EVA-3S Trial

The EVA-3S trial [12] was a randomized, multicenter trial, similar to the SPACE trial, which was based on the hypothesis that CAS is not inferior to CEA for the treatment of severe symptomatic carotid stenosis. The patients were randomly assigned to either the CAS group or the CEA group. High-risk patients were excluded, including those with unstable angina, uncontrolled diabetes, or uncontrolled hypertension, as were patients with a previous history of carotid revascularization. The results showed the incidence of stroke or death at 30 days was significantly higher with CAS than with CEA (9.6 % versus 3.9 %) [12] (Table 2). The risk of periprocedural stroke or death, and nonperiprocedural ipsilateral stroke occurring within 4 years of follow-up was also significantly higher with CAS than with CEA (11.1 % versus 6.2 %) [17]. The risk of ipsilateral stroke after the periprocedural period was low, and was similar in both treatment groups. The periprocedural risk of cranial nerve injury

Table 2 Primary end points in major trials for CEA versus CAS

Trial	Number of patients	30-day risk of stroke, death, or MI (%)		2–4 year ipsilateral stroke or death (%)	
		CEA	CAS	CEA	CAS
SAPPHIRE	334	10	5	30	27
EVA-3S	527	5	10	6	11
SPACE	1,183	6	8	9	10
CREST	2,500	5	5	7 %	7

was significantly higher after CEA than after CAS, especially systemic complications, mainly pulmonary. However, these differences were not statistically significant. The trial was stopped prematurely owing to an excess number of deaths in the CAS group [12]. The EVA-3S trial had design limitations. The level of operator experience was limited because it only required interventional physicians to perform a minimum of two procedures with any new device to qualify. Secondly, five different stents and seven different cerebral protection devices were used in the trial. Another limitation was embolic protection for a patient assigned to the CAS group was optional early in the trial. This was important because the 30-day outcome of any stroke or death was significantly lower in patients treated with embolic protection (7.9 % and 25 %, respectively) [18, 19].

International Carotid Stenting Study

The ICSS [7] was a randomized, prospective, multicenter trial in 2010, composed of 1,713 subjects, aged 40 years and older, with recently symptomatic carotid artery stenosis. These patients were randomized to either the CEA treatment group or the CAS treatment group. Patients with a history of major stroke without useful recovery of function, those with a history of a previous CEA or CAS procedure performed in the stenotic artery, or those requiring major surgery such as coronary artery bypass graft surgery were excluded from the treatment groups. Inclusion criteria consisted of all patients who had more than 50 % carotid stenosis on noninvasive imaging such as duplex ultrasonography, as defined by NASCET criteria on noninvasive imaging such as duplex ultrasonography. The complete trial results are not yet accessible, but the 120-day intention-to-treat analysis demonstrated that the CAS group had a significantly higher rate of any type of stroke (7.7 % versus 4.1 %), death (2.3 % versus 0.8 %), or MI than the CEA group as an end point (8.5 % versus 5.2 %). In addition, a subgroup analysis of 231 patients in the trial who underwent brain magnetic resonance imaging (MRI) found that a greater number of patients in the CAS group compared with the CEA group had new ischemic brain lesions on diffusion-weighted MRI at a median of 1 day after treatment (50 % versus 17 %) [7].

Carotid Revascularization Endarterectomy Versus Stenting Trial

CREST was a randomized, prospective, multicenter trial which started in 2000. The trial compared the efficacy and safety of CAS and CEA in 2,502 patients with carotid atherosclerotic disease [14]. However, unlike previous trials, it included patients with both asymptomatic (47 %) and symptomatic (53 %) carotid disease. CREST demonstrated that both CAS and CEA had similar safety and efficacy profiles. The benefits were similar for men and women, and in asymptomatic versus symptomatic patients. The primary end point for the trial was any stroke, MI, or death within 30 days after the procedure plus any ipsilateral stroke during long-term follow-up (median 2.5 years). The primary end points for both CEA and CAS were similar (7.2 % versus 6.8 %), as was the rate of ipsilateral stroke occurring from 30 days after the procedure to 4 years of follow-up (2.0 and 2.4 %, respectively) [20].

Differences in the results of CEA and CAS were more evident when age, rate of periprocedural stroke, and risk of MI were compared. Patients aged 70 years and older had better outcomes with CEA for the primary end point and adverse events. Younger patients had greater benefit from CAS than older patients. The CAS group had a greater percentage of patients with stroke within the 30-day postprocedure group (4.1 % versus 2.3 %). However, the CAS group had a lower rate of MI events within 30 days of the procedure (1.1 % versus 2.3 %). The quality of life after 1 year of follow-up was significantly lower for patients who had developed stroke after the procedure than for those who had an MI [21]. Substudies based on CREST demonstrated that patients who underwent CAS for treatment of symptomatic carotid disease had a higher periprocedural rate of stroke and death than patients who underwent CEA (6.0 % versus 3.2 %). Another substudy that analyzed the primary end point and quality of life showed that stroke had a greater and statistically significant detriment on the quality of life 1 year post-procedure versus MI and cranial nerve palsy. However, even though the subgroup analysis showed a higher rate of stroke with CAS, the quality of life after 1 year between the CAS and CEA groups was not significantly different [22].

Current Guidelines

The 2012 American Heart Association/American Stroke Association guidelines for the prevention of stroke in the setting of symptomatic carotid stenosis recommend that patients who have experienced a recent TIA or ischemic stroke within the past 6 months and have ipsilateral carotid artery stenosis of 70–90 % would be good candidates for CEA if the perioperative morbidity and mortality risk is less than 6 %. If patients have experienced a recent TIA or ischemic stroke and have 50–69 % stenosis, the decision to perform CEA will depend on factors such as age, comorbidities, and sex, with a perioperative risk of less than 6 %. In mild stenosis of less than 50 %, both CEA and CAS are not recommended. If a patient is a good candidate for CEA, surgery within 2 weeks is recommended if there are no contraindications [23].

CAS is recommended as an alternative to CEA in the setting of symptomatic internal carotid artery stenosis of more than 70 % as determined by noninvasive imaging or more than 50 % as determined by catheter angiography. CAS is also an alternative in severe symptomatic stenosis of more than 70 % in patients in whom surgical access to the internal carotids is difficult, in patients with radiation-induced stenosis, in patients with restenosis after CEA, and in those with high perioperative risk. Patients are also recommended to optimize medical therapy in the setting of symptomatic carotid artery stenosis with antiplatelet therapy, statin therapy, and risk factor modification [23].

Conclusions

Established clinical guidelines by the American Heart Association/American Stroke Association have focused treatment of symptomatic carotid stenosis around medical management and CEA. With advances in CAS, the field of treatment options has widened. CEA and CAS have been compared in several clinical trials to evaluate benefit as well as to define patient populations which would be suited for each of them. The ICSS (also called CAVATAS 2), the SPACE trial, the EVA-3S trial, the SAPPHIRE trial, and CREST were five major trials which compared CEA and CAS. Medical management and CEA remain the mainstay of therapy. However, CAS has been shown to be a viable option for a patient with high-grade carotid artery stenosis and who is a high surgical risk patient.

Conflict of Interest Syeda L. Alqadri declares no conflict of interest. Adnan I Qureshi declares no conflict of interest.

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References

1. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325(7):445–53.
2. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet. 1991;337(8752):1235–43.
3. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351(9113):1379–87.
4. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. Stroke. 1993;24(8):1125–8.
5. Chaturvedi S, Bruno A, Feasby T, et al. Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2005;65(6):794–801.
6. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke. 1991;22(6):711–20.
7. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet. 2010;375(9719):985–97.
8. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1998;339(20):1415–25.
9. Brott TG, Brown Jr RD, Meyer FB, Miller DA, Cloft HJ, Sullivan TM. Carotid revascularization for prevention of stroke: carotid endarterectomy and carotid artery stenting. Mayo Clin Proc. 2004;79(9):1197–208.
10. Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2012;9, CD000515.
11. Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet. 2006;368(9543):1239–47.
12. Cambria RP. Commentary on: Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med. 2006;355:1660–1671. Perspect Vasc Surg Endovasc Ther. 2007;19(2):201–3.
13. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351(15):1493–501.
14. Brott TG, Hobson 2nd RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11–23.
15. Stingele R, Berger J, Alfke K, et al. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. Lancet Neurol. 2008;7(3):216–22.
16. Yadav JS. Carotid stenting in high-risk patients: design and rationale of the SAPPHIRE trial. Cleve Clin J Med. 2004;71 Suppl 1:S45–6.
17. Mas JL, Trinquart L, Leys D, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. Lancet Neurol. 2008;7(10):885–92.
18. Furlan AJ. Carotid-artery stenting—case open or closed? N Engl J Med. 2006;355(16):1726–9.

19. Qureshi AI. Carotid angioplasty and stent placement after EVA-3S trial. Stroke. 2007;38(6):1993–6.
20. Silver FL, Mackey A, Clark WM, et al. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke. 2011;42(3):675680.
21. Voeks JH, Howard G, Roubin GS, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke. 2011;42(12):3484–90.
22. Cohen DJ, Stolker JM, Wang K, et al. Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). J Am Coll Cardiol. 2011;58(15):1557–65.
23. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(1):227–76.