Chapter 27
In Patients with Symptomatic Carotid Artery Stenosis Is Endarterectomy Safer Than Carotid Stenting?

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Abstract Stroke is a leading cause of morbidity, mortality, and health care expenditure in the United States. Carotid disease accounts for a significant number of ischemic strokes and debate continues as to the most appropriate management for symptomatic carotid stenosis. The importance of surgical intervention, i.e. carotid endarterectomy (CEA), for symptomatic carotid stenosis has been widely accepted based on multiple well-constructed trials published in the early 1990s. Carotid artery stenting (CAS) was initially approved by the FDA in 2004, and has gained momentum as an alternative to CEA. A number of multicenter trials have demonstrated the safety of CAS in both asymptomatic and symptomatic patients; however questions remain as to the long-term durability, as well as the proper patient selection for CAS. In this chapter, we review the current methods of treatment of symptomatic carotid stenosis, and discuss factors that influence the decision to perform CEA or CAS. In general, if the surgeons risk of stroke is acceptably low, CEA should be performed for patients with a >50 % symptomatic carotid stenosis. CAS should only be considered as an alternative for those with prohibitive medical comorbidities, and those with hostile anatomy.

Keywords Carotid endarterectomy • Carotid stenting • Carotid stenosis • Stroke care • Safety

Introduction

Stroke is the fourth leading cause of death in the United States, and is a leading cause of disability and healthcare expenditure. In fact, almost 800,000 Americans experience a new or recurrent stroke each year, which resulted in direct and indirect

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costs of $36.5 billion in 2010. It is estimated that 87 % of strokes are ischemic, with an estimated 20–30 % thought to be the result of atherosclerotic carotid artery disease [1, 2]. Given these data, the prevention of stroke and TIA due to extra-cranial carotid occlusive disease is an important health care goal, which has been the topic of large amounts of research, and controversy remains regarding the optimal management of this disease.

Multiple clinical trials have demonstrated the superiority of CEA over medical management in patients with symptomatic carotid disease [3–5]. Over the past two decades however, the management of symptomatic carotid disease has evolved with the increased use of carotid artery stenting and improved medical therapy. While CEA remains the most frequently performed operation for stroke prevention, the rate of CAS has increased dramatically. Dumont and colleagues queried the Nationwide Inpatient Sample (NIS) between 1998 and 2008 and found that the number of CEAs performed remained fairly stable, at about 21,000 per year. As the NIS database represents roughly one fifth of patients treated in the US, the number of CEAs performed per year is estimated at 105,000. During this same period, the rate of CAS increased from 2.8 to 12.6 % of all carotid revascularization procedures. The total number of CAS performed in the US was estimated at 3235 in 1998, and 15,655 in 2008 [6]. For symptomatic carotid disease, the current Society for Vascular Surgery (SVS) guidelines recommend CEA as the first-line therapy for patients with a greater than 50 % stenosis, with CAS being reserved for those with unfavorable anatomy (prior surgery, radiation, high lesions), or prohibitive medical comorbidities (severe CAD, COPD, or CHF) [7]. In addition, a multi-specialty consensus statement broadly recommends CAS as an alternative to CEA in symptomatic patients with greater than 50 % ICA stenosis if the expected periprocedural stroke or mortality rate is less than 6 % [8]. This chapter addresses reported safety of CAS versus CEA for symptomatic carotid stenosis.

Search Strategy

A computer-assisted literature search of English language publications from 1991 to 2014 was used to identity published data on the safety of CAS and CEA in symptomatic carotid stenosis, using the PICO outline (Table 27.1). Databases searched were Medline, and Cochrane Evidence Based Medicine. Terms used in the search were “symptomatic carotid stenosis, AND endarterectomy, AND stent”, “carotid endarterectomy AND carotid stenting AND outcomes”, “carotid endarterectomy versus carotid stenting”, and “CEA versus CAS”. Electronic links to related articles and reference lists of selected articles were hand-searched to retrieve more studies. Articles were excluded if they specifically addressed asymptomatic carotid stenosis. The data was classified using the GRADE system.

Table 27.1 PICO table for safety of CEA over CAS for symptomatic carotid artery stenosis

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with symptomatic carotid stenosis	CEA or CAS	Best medical management, CAS, or CEA	Myocardial infarction, stroke, death

Results

Major Trials

The current SVS guidelines for treatment of symptomatic carotid disease recommend surgical intervention for patients with symptomatic carotid stenosis of 50 % or greater [7]. The benefit of carotid endarterectomy for symptomatic carotid stenosis is widely accepted. Multiple randomized, multicenter trials have demonstrated this benefit [3–5]. The NASCET trial was one of the first such studies, and included over 600 symptomatic patients across 50 centers in the US and Canada. In this study, symptomatic patients with ≥70 % stenosis of the internal carotid artery (ICA) based on carotid duplex criteria, were randomized to either medical management alone (antiplatelet agent, antihypertensive agents, antilipid therapy, and antidiabetic therapy), or medical management in addition to CEA. Randomization was terminated early in February of 1991 due to strong evidence of benefit for CEA over medical management alone in patients with high-grade stenosis. They demonstrated an absolute risk reduction (ARR) of 17 % for ipsilateral stroke at 2 years. This was in the context of perioperative risk of stroke or death of 2.1 %. Months after this paper was published, the smaller, VA cooperative study was released and further illustrated the benefit of CEA in symptomatic male patients. This trial randomized 193 men with symptomatic carotid stenosis of ≥50 % to either CEA with medical management, or medical management alone. They demonstrated an ARR of 11.7 % for CEA vs. medical management. In patients with >70 % stenosis, this benefit was even more profound with an ARR of 17.7 %. The risk of stroke in patients undergoing CEA was 7.7 % over 11.9 months, compared with 19.4 % in nonsurgical patients. The perioperative stroke or death rate was 5.5 % in this study (2.2 % stroke, 3.3 % mortality) (VA coop study). The European Carotid Surgery Trial (ECST) was published 7 years later, and showed benefit of CEA in symptomatic patients with greater than 80 % stenosis. They randomized 3024 symptomatic patients across 97 centers in Europe and Australia. The risk of major stroke or death in the perioperative period was 7 %. They were only able to show benefit for CEA in patients with 80 % stenosis, and this benefit was gained at 3 years from surgery, with an ARR of 11.6 %. Their analysis also demonstrated higher perioperative risk in women, leading to their recommendation to operate on symptomatic carotid stenosis of 90 % or greater in women. However, the criteria on degree of stenosis were significantly different between NASCET and ECST. For example, 80 % stenosis based on ECST criteria is

equivalent to roughly 70 % stenosis by NASCET criteria. In 2002, the ECST group published long-term data that demonstrated a 4.5 % risk of ipsilateral stroke at 10 years, suggesting that CEA is a durable treatment for symptomatic carotid stenosis [9]. Finally, in 2011, Rerkasem and Rothwell published a review comparing the results of the NASCET, VACSP, and ECST trials. They highlighted the fact that one of the major differences in the trials was in the measurement of carotid stenosis on angiograms, resulting in higher levels of stenosis in the ECST trial compared to both NASCET and VASCP. The authors obtained the patient data from all three trials and merged them into a single composite database. The ECST angiograms were reviewed and stenosis recalculated based on the methods used in NASCET and VASCP to achieve uniformity between the three studies. They found no significant difference in operative stroke or death rate, which was 7 %, and higher in women. Their analysis showed that the benefit of CEA increases with increasing degree of stenosis. The number needed to treat to prevent one event at 5 years was six for ipsilateral stroke and operative stroke or death. In a comparison between ECST and NASCET, the NNT (number needed to treat to prevent one event) at 5 years for patients with 50–99 % stenosis was nine for men, and 36 for women. Age also had an effect, with a NNT of five for age ≥75, and 18 for age <65. Thus, they showed a benefit for CEA in women with ≥70 % stenosis, and men with stenosis ≥50 % [10].

These landmark studies were instrumental in designating CEA as the gold standard in the treatment of symptomatic carotid stenosis. CAS was first performed in 1994, and was approved by the FDA in 2004. The safety of CAS has been evaluated in multiple studies (Table 27.2). The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was one of the first studies to investigate endovascular treatment as a therapy for carotid occlusive disease [11]. This study enrolled both symptomatic and asymptomatic patients, and randomized them to either CEA or endovascular treatment (angioplasty and/or stent). Of a total of 504 randomized patients, they had a 10 % stroke or death rate in the endovascular arm, and a 9.9 % rate in the CEA arm. The rate of cranial nerve injury was 8.7 % in the surgery arm, and none were reported in the endovascular arm. This study was the first to suggest that CAS was at least as safe as CEA in treating carotid stenosis. However the study is criticized for having an unacceptably high stroke or death rate for CEA. The durability of CAS was also called in to question based on their finding of significantly increased rate of ipsilateral high-grade stenosis in the CAS group at 1 year. Nonetheless, technical advances in CAS have resulted in the more widespread use of embolic protection devices, as well as stenting, rather than angioplasty alone.

The first major trial to evaluate CAS was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. This trial enrolled symptomatic and asymptomatic patients who had at least one high-risk criterion. 334 patients were randomized to CEA or CAS with embolic protection. Cranial nerve palsy was observed in 4.9 % of CEA patients, and again, none for CAS patients. The 30-day stroke, MI, or death rate was 4.4 % in the CAS arm, and 9.9 % in the CEA arm (P = 0.06). This outcome was similar in the subgroup analysis for symptomatic patients. They concluded that CAS was not inferior to CEA in high risk patients with symptomatic and asymptomatic carotid stenosis. In fact, the

Table 27.2 Major trials comparing CAS and CEA in symptomatic patients with carotid stenosis

Trial	Symptomatic patients/total patients	30-day outcome (%) (CAS/CEA)	≥1 year outcome (%) (CAS/CEA)	Cranial nerve injury (%) (CAS/CEA)
CAVATAS	488/504	Stroke or death 10/10 (Includes 16 asymptomatic patients)	Disabling stroke, death 14.3/14.2 (3 years)	0/8.7
SAPPHIRE	96/334	Stroke, death, or MI 2.1/9.3 (p=0.18)	Stroke, death, or MI 16.8/16.5 (p=0.95) (1 year)	0/4.9
CREST	1321/2502	Stroke, death, or MI 6.7/5.4 (HR 1.26)	No symptomatic subgroup analysis	0.3/4.7
SPACE	1214/1240	Ipsilateral stroke or death 6.8/5.5 (RR 1.24) (excluding major protocol violations)	Ipsilateral ischemic stroke or vascular death 10.3/9.4 (HR 1.18) (2 years)	Not given
EVA-3S	527/527	Stroke or death 9.6/3.9 (RR 2.5)	Non-procedural ipsilateral stroke 1.5/1.5 (4 years)	Not given
ICSS	1710/1710	Stroke, death, or MI 7.4/4 (p=0.003)	Fatal or disabling stroke 3.4/4.3 (p=0.03)	0.1/5.4

CAS carotid artery stent, *CEA* carotid endarterectomy, *MI* myocardial infarction, *HR*: hazard ratio, *RR* relative risk, *CAVATAS* the carotid and vertebral artery transluminal angioplasty study, *SAPPHIRE* stenting and angioplasty with protection in patients at high risk for endarterectomy, *CREST* carotid revascularization endarterectomy versus stenting trial, *SPACE* stent-protected angioplasty versus carotid endarterectomy, *EVA-3S* endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis, *ICSS* international carotid stenting study

primary endpoint incidence (30-day death, stroke, or MI, plus 1-year ipsilateral stroke or death from neurologic causes) was significantly lower in the CAS arm. This study would eventually lead to the approval of CAS for symptomatic, high-risk patients. Furthermore, 3-year outcomes of the SAPPHIRE study participants continued to show non-inferiority of CAS, with no significant difference in risk of target vessel revascularization, stroke, or other major adverse event at 3 years [12]. Critics of the SAPPHIRE trial cite potential bias based on commercial funding, and the participation of the inventor of the protection device as an investigator [13]. In addition, the high rate of stroke in the CEA arm is thought to be unacceptably high and non-applicable to most centers of excellence.

There are three more contemporary trials (SPACE, EVA-3S, and ICSS) comparing CEA and CAS for symptomatic patients. The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial was published in 2008, and randomized 1214 symptomatic patients to either CAS or CEA. [14] 60 patients were excluded for major protocol violations, resulting in a per protocol cumulative incidence of stroke or death within 30 days of 6.81 % for CAS, and 5.51 % for CEA. The rate of ipsilateral stroke between 30 days and 2 years was 2.2 % for CAS, and 1.9 % for

CEA. Again, recurrent stenosis was significantly more common in the CAS group than the CEA group (11.1 % vs. 4.6 %, P = 0.0009). This study also demonstrated an age-related benefit. Patients <68 years old had significantly less periprocedural risk with CAS than CEA, while CEA was significantly less risky in those over 68 years of age. The authors concluded that CEA had better outcomes in the periprocedural time in symptomatic patients compared to CAS, however at 2 years there was no difference in the prevention of recurrent neurologic events. This study was limited by lack of power to detect differences in CAS and CEA beyond the periprocedural time frame, as well as a significant dropout rate which may have skewed their results.

In 2008, 4 year results of the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial were published [15]. This study randomized 527 symptomatic patients with >60 % stenosis to either CEA or CAS (with embolic protection). They found that 6.2 % of CEA patients suffered either ipsilateral stroke or death within 30 days of their procedure, compared to 11.1 % of CAS patients (a hazard ratio of 1.97). In addition, they again showed increased risk of CAS in patients over 70 years of age. They found that the 4 year cumulative risk of stroke or death was higher for CAS, and that this risk was primarily during the periprocedural period. They concluded that CAS is effective at preventing medium term ipsilateral stroke, but that the procedure should be improved in order to be accepted as an alternative to CEA in symptomatic patients.

Short-term results of the International Carotid Stenting Study (ICSS) were published in 2010. This was an international, multicenter, randomized, controlled trial comparing CEA to CAS in patients with recently symptomatic carotid stenosis. It is the largest trial to date comparing stenting to endarterectomy in symptomatic patients. They randomized a total of 1713 patients to either CEA or CAS, and had 821 patients in the per protocol CEA arm, and 828 in the per protocol CAS arm. Embolic protection was used in 72 % of CAS cases. They demonstrated a 30-day procedural risk of stroke, death, or MI that was higher in the CAS arm (7.4 % vs. 4 %). The rate of cranial nerve injury for CEA was 5.4 % (with only 1 event resulting in disability), and hematoma requiring intervention or extended hospital stay was 0.9 % in the CAS arm, and 3.4 % in the CEA arm ($p = 0.0007$). The authors concluded that CEA was safer than CAS for patients with symptomatic carotid stenosis, with CAS having an almost doubled risk of stroke, death, or MI. The trial is criticized for lack of consistent usage of embolic protection device and heterogeneous experience of stent operators. In 2014, long-term results of the study were published. The 5-year cumulative risk of fatal or disabling stroke was not significantly different between the two groups (6.4 % for CAS, 6.5 % for CEA). CEA had a lower risk of procedural stroke or death, and ipsilateral stroke during follow up, than CAS (7.2 % vs. 11.8 % cumulative 5-year risk). This difference was mainly due to more non-disabling strokes in the CAS group. The authors therefore concluded that stenting was as effective as endarterectomy in preventing fatal or disabling stroke up to 10 years after treatment [16, 17].

Most recently, the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) was published in 2010 and was a landmark multicenter prospective randomized study that enrolled both symptomatic and asymptomatic patients [18]. A

total of 2502 patients were randomized to either CEA, or CAS. There was no significant difference in the primary endpoint of periprocedural (within 30 days) stroke, MI, or death, between the two groups (7.2 % for CAS, 6.8 % for CEA). They did observe a significantly higher rate of periprocedural stroke in the CAS group (4.1 % vs. 2.3 %, P = 0.012), and a higher rate of MI in the CEA group (2.3 % vs. 1.1 %, P = 0.032). At 4 years, there was no significant difference in ipsilateral stroke. The risk of cranial nerve palsy for CEA was 4.7 %. They also showed that patients >70 years had better outcomes with CEA, while patients <70 were better served by CAS, which was also shown in the SPACE trial. Importantly, in symptomatic patients, CAS had a significantly higher stroke and death rate than CEA (6 % vs. 3.2 %). Critics of this study cite the inclusion of periprocedural MI as a primary end-point, especially given their inclusion criteria for MI which were quite mild and included minor myocardial infarctions that would be unlikely to cause significant effect on a patient's long-term health. CAS was again shown to have higher stroke and death rates in symptomatic patients, females, and older patients, which raised the question whether CAS and CEA are actually equivalent for symptomatic patients [19].

Local Complications

When considering the safety of CEA versus CAS, the risk of stroke and death are the major outcomes that are typically evaluated. Local complications should be considered as well given their potential to cause long-term morbidity, and secondary interventions. Cunningham et al. reviewed data from the ECST trial to estimate the risk of motor cranial nerve (CN) injury during CEA. 6.2 % of patients in the ECST trial suffered one or more cranial nerve palsies (including motor and sensory deficits). At four month follow up, 8 % of these injuries were persistent, and all of these persisted out to the 2 year follow up [20]. Schauber and colleagues prospectively reviewed 183 CEA procedures with thorough neurologic evaluations pre- and post-operatively. They reported an incidence of CN injury of 14.2 %, with 1.1 % being permanent [21]. CN injury is generally a minor, transient complication of CEA, however it can be permanent and given the essentially negligible risk associated with CAS, it should be considered when choosing one procedure over the other. This consideration is especially important in the re-operative patient or post-radiation patient, as well as those with a previous contralateral CN injury.

Personal View of the Data

Symptomatic carotid stenosis is frequently encountered in the clinical practice of vascular surgeons. The recommendation to intervene on symptomatic carotid stenosis is based on sound evidence (NASCET, ECST, and VASCP), however the choice of endarterectomy or stenting is less clear. It is reasonable to consider CEA in

symptomatic patients with ipsilateral carotid stenosis of ≥50 %, if the operative risk of stroke is <6 %. Patients should be expected to have reasonable functional status following the neurologic event that prompts surgical evaluation. In addition, data from CREST, and SPACE would suggest that in patients >70 years of age, CEA is safer than CAS. In patients with comorbidities prohibitive of general anesthesia, CAS is a reasonable alternative. Patients should be well informed of the risk of local complications, including cranial nerve injury, which is not negligible. Given the higher rate of cranial nerve injuries in certain groups of patients (prior ipsilateral operation, irradiation, stomas), CAS is also considered a reasonable alternative. Based on multiple large prospective randomized trials, CEA is a better option than CAS with lower periprocedural stroke and death rates. Long-term outcomes, excluding peri-operative events, appear to be similar between the two approaches. Information on how best medical therapy shapes the treatment decision and outcome is still lacking.

Recommendations

- In patients with symptomatic carotid stenosis intervention is recommended. (**Evidence quality is strong; recommendation is strong**).
- It is reasonable to consider CEA in symptomatic patients with ipsilateral carotid stenosis of ≥50 % (**Evidence quality is strong; recommendation is strong**),
- In patients with prohibitive comorbidities, CAS is a reasonable alternative (**Evidence quality is strong; recommendation is strong**).

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