What is the Role of Carotid Stenting in Patients with Carotid Artery Disease?

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Abstract

• Objective: To discuss treatment with carotid stenting in patients with carotid artery disease.
• Methods: Historical overview and evidence review.
• Results: Carotid stenosis is responsible for approximately 1 in 5 strokes. To decrease the risk of stroke and stroke-related death in patients with carotid stenosis, the main treatment modality has been carotid endarterectomy (CEA). Several randomized trials have established the benefit of CEA over medical management in symptomatic and asymptomatic patients in the prevention of stroke and death. Over the past years, carotid artery stenting (CAS) has emerged as a less invasive alternative, with a number of studies indicating that CAS is feasible, safe, and effective. However, results from various randomized controlled trials comparing CAS to CEA have been ambiguous, mainly due to the heterogeneous nature of these trials. The periprocedural risk for CAS is somewhat higher, while over the longer term, both treatments show rather equivalent results.
• Conclusion: The steady improvement of CAS techniques will likely further improve outcomes of CAS, and the procedure is likely to emerge as a viable revascularization strategy in all patients with carotid disease.

Cerebrovascular stroke is a major health problem associated with a high morbidity and mortality and prohibitively high societal and health care costs [1]. About 780,000 people suffer a stroke every year, of which approximately 140,000 are fatal strokes. Stroke is the third leading cause of death in the United States. Carotid stenosis accounts for around 20% of strokes, and this proportion is even higher in elderly patients [2]. Carotid revascularization is the only proven method of stroke prevention for patients with carotid stenosis [3]. Since the 1950s, carotid endarterectomy (CEA) has been performed in patients with symptomatic carotid artery stenosis, although definitive data supporting CEA over medical therapy did not emerge until much later. The European Carotid Surgery Trial (ECST) [4] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [5] evaluated the safety and efficacy of CEA in symptomatic patients (after a first cerebrovascular event) and demonstrated dramatic reduction in future stroke risk with CEA. The baseline risk of stroke in asymptomatic patients with carotid artery stenosis is much lower, and the absolute benefit of CEA in this population is considerably smaller. The Asymptomatic Carotid Atherosclerosis Study (ACAS) [6] and the Asymptomatic Carotid Surgery Trial (ACST) [7] demonstrated convincingly that CEA was associated with a reduction in long-term risk of stroke in asymptomatic patients if the procedure could be performed with a low perioperative risk. Based on these studies, CEA has become the gold standard therapy for carotid artery stenosis. Current guidelines support the use of CEA if the periprocedural stroke risk is 6% or less for symptomatic patient and 3% or less for an asymptomatic patient [8].

Following the widespread use of coronary percutaneous angioplasty, it was natural that endovascular therapy would be explored in patients with carotid artery disease. The first report on a percutaneous intervention to a carotid stenosis was published in 1980 followed by small case series from select institutions [9]. The potential for procedural embolization and a high risk for stroke became evident early, and widespread application of the technique had to await development of emboli protection devices and dedicated stents [10–12]. During the last decade, there have been multiple systematic evaluations of the procedure, and various randomized trials have compared the efficacy of carotid artery stenting (CAS) with the more established CEA. CAS is now being offered to select patients (Figure 1).

Evidence on Carotid Artery Stenting

The major trials that have compared CEA with CAS are listed in Table 1. The 3 important initial multicenter trials were
CAROTID ARTERY STENTING

Table 1. Characteristics of the Major Trials Comparing Carotid Endarterectomy (CEA) to Carotid Stenting (CAS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Intervention</th>
<th># of Patients</th>
<th>Periprocedural Death or Stroke</th>
<th>Follow-up, mo</th>
<th>Distal protection, %</th>
<th>Stent, %</th>
<th>Asymptomatic Patients, %</th>
<th>Mean Age, yr</th>
<th>Stopped Early?</th>
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<tbody>
<tr>
<td>Leicester</td>
<td>1998</td>
<td>CEA</td>
<td>12</td>
<td>0</td>
<td>30 days</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>66.7</td>
<td>Yes (high stroke rate with stenting)</td>
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<tr>
<td></td>
<td></td>
<td>CAS</td>
<td>11</td>
<td>5</td>
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<td>100</td>
<td>na</td>
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<tr>
<td>WALLSTENT</td>
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<td>CEA</td>
<td>112</td>
<td>5</td>
<td>12</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>70</td>
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<td></td>
<td></td>
<td>CAS</td>
<td>107</td>
<td>13</td>
<td>0</td>
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<td>66.5</td>
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<td></td>
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<td>CAVATAS</td>
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<td>CEA</td>
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<td>25</td>
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<td>66.6</td>
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<tr>
<td>KENTUCKY B</td>
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<td>CEA</td>
<td>42</td>
<td>0</td>
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<td></td>
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<td>66.6</td>
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<td>SAPPHIRE</td>
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<td>CEA</td>
<td>167</td>
<td>8</td>
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<td>71.2</td>
<td>72.6</td>
<td>72.5</td>
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<tr>
<td></td>
<td>2008</td>
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<td></td>
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<td>EVA-3S</td>
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<td>42.5</td>
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<td></td>
<td></td>
<td>CAS</td>
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<td>92</td>
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<td>SPACE</td>
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<td>CEA</td>
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<td>38</td>
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<td>0</td>
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<td>67.6</td>
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<td>Steinbauer et al</td>
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<td>68.4</td>
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<tr>
<td></td>
<td></td>
<td>CAS</td>
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<td>1</td>
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<td>100</td>
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<tr>
<td>ICSS</td>
<td>2009</td>
<td>CEA</td>
<td>857</td>
<td>28*</td>
<td>30 days</td>
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<td>70</td>
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<td></td>
<td></td>
<td>CAS</td>
<td>853</td>
<td>61*</td>
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<td>68.9</td>
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*Per-protocol data.

SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) [13], SPACE (Stent protected Percutaneous Angioplasty of the Carotid artery vs. Endarterectomy) [14] and EVA-3S (Endarterectomy vs. Angioplasty in patients with Symptomatic Severe carotid Stenosis) [15]. These studies showed a trend toward lower risk of periprocedural stroke with CEA, but the endpoint of death and disabling stroke combined did not differ between strategies. In addition, the results of these trials were limited by the varying techniques and varying operator experience associated with CAS strategy [16].

In 2010, two additional large trials were completed: The European ICSS (International Carotid Stenting Study) [17] and the North American CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) [18]. With the results of these trials, the question of comparative efficacy is still not settled. The authors of ICSS, which enrolled symptomatic patients, found the periprocedural risks of stenting to be significantly higher than those of CEA and concluded that CEA is superior to CAS.

The CREST trial was a well-designed trial that compared contemporary CAS with CEA in patients with carotid stenosis. CREST had an elegant design and applied a multispeciality collaborative approach to the care of carotid disease. All patients were evaluated by neurologists who were blinded to the treatment choice, and all the operators were highly experienced. A total of 2502 patients with carotid stenosis, about half symptomatic and half asymptomatic, were enrolled in the study. The primary endpoint was a composite of stroke, myocardial infarction (MI), or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. The study found no significant
difference with regard to the primary endpoint between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11 [95% confidence interval, 0.81–1.51]; \( P = 0.51 \)). The CREST investigators concluded that both approaches are equivalent. An interesting interaction with age was observed, with patients under 70 years having better results with stenting and older patients having better results with surgery.

While the CREST trial is considered by many to reflect the current state of the art of carotid revascularization in the United States, it is important to evaluate the results in the context of the totality of the evidence. Previous studies have shown or suggested inferiority of CAS vs. CEA for the treatment of carotid stenosis. What may account for these disparate results?

**Heterogeneity Among Trials**

Of the 6 major studies, only 3 (SAPPHIRE, CREST and Brooks et al [19]) enrolled asymptomatic patients. The SAPPHIRE trial included patients who were deemed at high risk for endarterectomy. The study population included about 70% asymptomatic and 30% symptomatic patients. The primary endpoint (cumulative incidence of death, stroke, or MI within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year) did not differ significantly between the 2 groups but tended to be lower for the CAS group (12.2% vs. 20.1%; \( P = 0.004 \) for noninferiority and \( P = 0.053 \) for superiority). Long-term data at 3 years reflected similar results; there was no significant difference between the endpoint of death/stroke/MI between the 2 groups (26.2% vs. 30.3% for CEA, \( P = 0.71 \)) [20]. In the CREST trial, about half the patients were asymptomatic. At the end of 4 years, there was no significant difference in the primary endpoints (stroke, MI, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization). In contrast with these results, many trials that included symptomatic patients showed more favorable outcomes for CEA. Evidence from studies of asymptomatic patients is still scarce and more data are needed.

Further, surgical risk may play a major role in determining the choice of revascularization strategy. In the SAPPHIRE trial, which focused on high-risk patients, the outcomes for CAS were superior.

**Confounding Bias**

A major confounder is the temporal trend in outcomes.
Carotid artery stenting (CAS) is associated with CEA. Over the years, there was an improvement of technique and equipment and an optimization of patient selection, improved training of operators, and improvement in adjunct pharmacotherapy. Earlier trials are difficult to compare with newer trials, and even within a trial such advances over time may influence outcomes. This time trend is even more problematic in the context of a generally slow recruitment rate in most of these trials. By the end of the study, slow rates of recruitment meant that procedural technology was often already outdated because of newer devices and newer co-treatments.

A further confounding factor that may explain some across-trial differences is the “operator learning curve.” In most trials, operators performing CAS were rather inexperienced, while those performing CEA had better experience. In this regard, the CREST trial differed, as it had a “lead-in” phase to assure sufficient experience and quality of the operators. Surgeons performing CAS had to do at least 12 procedures per annum, with rates of complication and death less than 3% among asymptomatic patients and less than 5% among symptomatic patients [17]. On the other hand, in EVA-3S, operators were required to have performed 12 CAS procedures or 5 CAS procedures and 30 endovascular procedures in the supra-aortic trunk over their lifetime. In ICSS, 50 total stenting procedures were required, of which only 10 had to be carotid procedures (while surgeons were required to have done at least 10 CEA per year); but even interventionalists with less experience were accepted in ICSS. Those not fulfilling these criteria were supervised by an outside proctor. This also resulted in a high rate of abortion of CAS procedures. In 126 patients (15%) allocated to CAS, the procedure could not be completed and the patients either underwent CEA or received medical therapy alone. In contrast, in the CREST trial, only 3% of the planned CAS procedures had to be aborted, suggesting the influence of operator experience and better patient selection.

Early stoppage of many of the trials may have introduced even more confounding to current evidence. Almost half of the trials had to be stopped prematurely, before the prespecified sample size was reached. Early stopping can lead to overestimation of treatment effects, as shown in multiple previous analyses [21,22]. However, for many of the stopped trials the decision was not based on differential outcomes but on funding [14] or recruitment issues [20]. In 3 trials, the premature termination was based on large differences between outcomes for CEA versus CAS [23–25]. These 3 trials may have led to some overestimation of the superiority of CEA.

Endpoints
The majority of studies used the composite endpoint of stroke and death, which has been used traditionally for most trials in the field of CEA. This composite endpoint appears meaningful as an efficacy endpoint but neglects surgical complications such as cranial neuropathy. Some studies

Figure 2. Flow chart with a clinical decision tree for patients with carotid artery stenosis. CAS = carotid artery stenting; CEA = carotid endarterectomy.
included MI in the composite endpoint (ICSS, SAPPHIRE, and CREST) [17,18,20]. Depending on severity, cranial nerve injuries and MIs can have a comparable impact on a patient’s quality of life as a stroke. Including MI in the primary composite endpoint, however, is a subject of debate. In CREST, for example, although there was no difference in the composite primary outcome, there was an increased risk of stroke with CAS. The increased risk of stroke was not offset by the reduction in MI, since stroke had a much greater impact on quality of life [3]. In addition, studies used sensitive methods such as cardiac markers to detect MIs, while diagnosis of stroke was based on a clinical assessment, not on imaging.

Evidence Summary

In a meta-analysis, pooling all published data up to June 2009 and including 4796 patients (mostly symptomatic), CEA was associated with a lower risk for the primary endpoint of death or stroke in the short term, but the 2 treatments did not differ significantly for stroke or death (P = 0.314) in the intermediate term [26]. This analysis included preliminary data of the ICSS trial but did not include the CREST data. The results of the CREST trial mirror this analysis, and overall there appears to be no relevant difference between the 2 treatment options over the 4-year follow-up period.

The flow chart in Figure 2 proposes a decision tree based on the above mentioned data. Every patient with significant carotid stenosis should receive optimal medical therapy, regardless of further therapy. There is a large body of data supporting a reduction in stroke with contemporary primary preventive therapy, although it remains unclear if medical therapy suffices to bring the risk of stroke down to that seen after CEA [27]. All patients with carotid disease should be treated with a statin and aspirin and optimal control of hypertension. Smoking and use of tobacco in any form should be proscribed [28,29]. The decision to proceed with revascularization should take into account life expectancy, surgical risk, and the experience and expertise of the particular center in CEA or CAS.

In general, based on the totality of data, CEA is the preferred therapy unless surgical risk or patient choice favors CAS. However, it is important to recognize that in experienced hands and with careful attention to case selection, procedural technique, and periprocedural pharmacotherapy, CAS is being performed with excellent results.

High surgical risk is determined by anatomical factors or medical comorbidities (Table 2). Patients who are at high surgical risk and are symptomatic should be offered CEA provided the procedural risk is deemed to be less than 6%. In asymptomatic patients, those with anatomical factors should be offered CAS, while those at high medical risk need clear assessment of long-term prognosis. Patients with severe irreversible cardiac or pulmonary disease that prohibits CEA usually have a poor long-term prognosis and may not live long enough to derive any benefit from carotid revascularization. On the other hand, patients with severe valve disease or coronary artery disease and coexistent carotid disease may benefit immensely from cardiac percutaneous or surgical procedures, and a collaborative team approach with input from (at least) cardiologists, cardiac surgeon, and vascular surgeons is needed to define the best approach for these complex patients.

Conclusion

Despite the ongoing debate, CAS has an important role for patients with carotid stenosis. Based on current data, CAS appears most appropriate for patients at increased surgical risk. It is likely that ongoing technical improvements will translate into further improvement in CAS periprocedural outcomes. Better patient selection, rigorous operator training and credentialing, as well as meticulous attention to periprocedural therapy have resulted in excellent outcomes in recent series [30], and it is important to ensure that similar results can be obtained in routine clinical practice.

Table 2. Factors Determining High Surgical Risk for Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Medical high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe congestive heart failure (NYHA class III or IV)</td>
</tr>
<tr>
<td>Unstable angina or recent myocardial infarction (&lt; 4 weeks)</td>
</tr>
<tr>
<td>Severe nonrevascularized 3-vessel coronary artery disease or severe left main coronary artery disease</td>
</tr>
<tr>
<td>Severe aortic stenosis</td>
</tr>
<tr>
<td>Severe pulmonary hypertension</td>
</tr>
<tr>
<td>Severe pulmonary dysfunction (FEV-1 &lt; 30% predicted, home oxygen therapy)</td>
</tr>
<tr>
<td>Surgical or anatomical high risk</td>
</tr>
<tr>
<td>Contralateral internal carotid artery occlusion</td>
</tr>
<tr>
<td>Prior carotid endarterectomy</td>
</tr>
<tr>
<td>Prior ipsilateral radiation therapy to the neck</td>
</tr>
<tr>
<td>High cervical lesion or common carotid lesion below the clavicle</td>
</tr>
<tr>
<td>Contralateral laryngeal palsy</td>
</tr>
<tr>
<td>Tracheostomy stoma</td>
</tr>
<tr>
<td>Prior ipsilateral radical neck dissection</td>
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References


CORRECTION: In the article “Head CT findings compared with MRI done within 48 hours of emergency department presentation,” published in JCOM Vol. 17, No. 8, the research methodology was imprecisely described. The article should have explicitly stated that only negative CT scans were used for the analysis.