Clinical Controversies

Prospective Randomized Trials of Carotid Artery Stenting Versus Carotid Endarterectomy: An Appraisal of the Current Literature

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Carotid artery stenting has emerged as a treatment alternative in patients at high risk for carotid endarterectomy. Recent technological advances in catheter-based intervention have both facilitated the procedure and possibly improved the clinical outcome of this percutaneous intervention. The reduction in device profile of introducer sheaths and stents, as well as the ubiquitous use of neuroprotection devices, has resulted in a greater application of this treatment modality in patients with carotid bifurcation disease. The efficacy of carotid artery stenting must be carefully evaluated against carotid endarterectomy in a prospective randomized manner, as the latter treatment has long been considered the standard treatment of carotid occlusive disease. Several recent clinical trials comparing carotid artery stenting versus carotid endarterectomy have yielded mixed results with regard to the efficacy of this percutaneous intervention. This article analyzed the results of these prospective randomized trials comparing carotid artery stenting and carotid endarterectomy. Critical appraisal of these trials, as well as relevant methodological issues of these investigations, is discussed in this article.

Keywords: carotid artery stenting; carotid endarterectomy; clinical trials

Endovascular treatments using percutaneous transluminal angioplasty or stenting have become an established therapeutic modality for peripheral and coronary arterial disease. The application of endoluminal therapy in carotid artery occlusive disease represents a seemingly natural progression for endovascular interventionalists. Many perceived advantages of percutaneous interventions compared with open surgical reconstruction hold true in carotid artery stenting (CAS) when compared with carotid endarterectomy (CEA), including avoidance of surgical incision, decreased procedural discomfort, decreased patient anxiety, and avoidance of general anesthesia.

Since CAS was approved by the Food and Drug Administration (FDA) for clinical application in 2004, this percutaneous procedure has become a treatment alternative in patients who are deemed high risk for endarterectomy. In contrast to many endovascular peripheral arterial interventions, percutaneous carotid stenting represents a much greater challenging procedure because it requires complex catheter-based skills using the 0.014" guidewire system and distal protection device. Moreover, current carotid stent devices predominantly use the monorail guidewire system, which requires more technical agility, in contrast to the over-the-wire catheter system that is routinely used in peripheral interventions. This percutaneous intervention often requires balloon angioplasty and stent placement through a long carotid guiding sheath via a groin approach. Poor technical skills can result in devastating treatment complications, such as

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stroke, which can occur due in part to plaque embolization during the balloon angioplasty and stenting of the carotid artery. Because of these various procedural components that require high technical proficiency, many early clinical investigations of CAS, which included physicians with little or no carotid stenting experience, have resulted in alarmingly poor clinical outcomes.1-3

The efficacy of a new treatment strategy must be assessed based on a randomized comparison against a conventional or established treatment modality. In the case of carotid occlusive disease, randomized comparisons between CAS and CEA are needed to determine the clinical efficacy as well as procedural-related complications between the 2 treatment modalities. A recent Cochrane review noted that, before 2006, a total of 1269 patients had been studied in 5 randomized controlled trials comparing percutaneous carotid intervention and surgical carotid reconstruction.4 Taken together, these trials showed that CAS had a greater procedural risk of stroke and death when compared with CEA (odds ratio 1.33; 95% CI, 0.86-2.04). Additionally, greater incidence of carotid restenosis was noted in the stenting group than in the CEA cohorts.4 However, the constant improvement of endovascular devices, procedural techniques, and adjunctive pharmacological therapy will likely improve the treatment of percutaneous carotid intervention. Several ongoing clinical trials will undoubtedly provide more insights on the efficacy of CAS in the near future.

In this article, we examined the result of several prospective randomized trials comparing percutaneous carotid intervention and CEA. Although excellent clinical results of CAS have been shown in various industry-sponsored investigational device exemption trials, including the ARCHer (sponsored by Guidant Inc), BEACH (sponsored by Boston Scientific), SECurity (Sponsored by Abbott Lab), these studies all shared a common drawback of commercial sponsorship as well as potential patient selection bias due in part to their nonrandomized study design, which largely included low-surgical risk patients. In our analysis, clinical outcome of 4 randomized prospective clinical trials will be individually presented followed by a close appraisal of their clinical outcome. Specifically, these prospective randomized trials include (a) Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS trial), (b) Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE trial), (c) Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S trial), and (d) Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE trial).

**CAVATAS Trial**

The aim of the CAVATAS study was to compare endovascular therapy, including balloon angioplasty and/or stenting, with CEA.5 A total of 504 patients were randomized to either endovascular treatment (n = 251) or CEA (n = 253). In all, 213 patients in the endovascular groups underwent successful treatment. Among them, 55 patients (26%) received carotid stents, whereas 158 (74%) were treated with balloon angioplasty alone. The study showed no differences in 30-day major outcome between the 2 groups. Significantly lower complications in cranial neuropathy were noted in the endovascular group when compared with the surgical group (0% vs 8.7%; P < .0001). Decreased groin or neck hematoma was also noted in the endovascular group when compared with the surgical group (1.2% vs 6.7%; P < .0015). At 1-year follow-up, severe (70%-99%) ipsilateral carotid stenosis occurred more frequently in the endovascular treatment (14% vs 4%, P < .001). At 3 years following the study randomization, however, no difference in the rate of ipsilateral stroke was noted between the 2 groups.

**SAPPHIRE Trial**

The aim of the SAPPHIRE trial was to test the hypothesis that CAS with neuroprotection was not inferior to CEA in high-risk surgical patients.6 Inclusion criteria include patients with either a symptomatic carotid artery stenosis of at least 50% of the luminal diameter or an asymptomatic stenosis of at least 80%, and patients were randomized to these treatment groups. At the end of enrollment in June 2002, 406 patients had been included in the stenting registry considered by the surgeons as too high risk and a total of 334 patients were equally randomized to carotid stenting (n = 167) and CEA (n = 167). The primary end point of the study was the cumulative incidence of a major cardiovascular event at 1 year; a composite of death, stroke, or myocardial infarction (MI) within 30 days after the intervention; or death or ipsilateral stroke between 31 days and 1 year. At 1 year, the cumulative major adverse event was lower in
the stenting group than in the CEA group (12.2% vs 20.1%, \( P = .05 \)). The difference in these adverse events was largely due to the lower incidence of MI in the CAS group than in the CEA group (2.5% vs 8.1%, \( P = .03 \)). On the basis of these findings, the authors concluded that CAS with neuroprotection was not inferior to CEA in high-risk patients.

**EVA-3S Trial**

The objective of the EVA-3S study was to assess whether CAS was noninferior to CEA for stroke prevention in patients with high-grade symptomatic carotid stenosis.\(^7\) With 30 different French institutions participating in patient enrollment, 259 patients underwent CEA, whereas 261 patients were treated with CAS within 2 weeks following study randomization. Cerebral protection devices were not routinely used in all CAS patients. Dual antiplatelet therapy was recommended but not uniformly administered in CAS patients. The study showed that CAS patients were 2.5 times more likely to have a stroke or die within 1 month of the intervention than were CEA cohorts (95% CI, 1.2-5.1). The 30-day incidence of stroke or death was 9.6% (95% CI, 6.4-14.0) in the CAS group and 3.9% (95% CI, 2.0-7.2) in the CEA group. The CAS also increased the 30-day risk of a disabling stroke or death and resulted in a higher incidence of any stroke or death within 6 months (11.7% vs 6.1%; \( P = .02 \)) compared with CEA. The CAS was associated with more-frequent cranial-nerve injury (7.7% vs 1.1%; \( P < .001 \)) and a longer duration of hospital stay (median duration 4 days vs 3 days; \( P = .01 \)) than CAS. The study was stopped prematurely because of significantly higher stroke and death rates in the CAS group than the CEA group.

**SPACE Trial**

The SPACE trial was designed to show noninferiority of CAS as compared with CEA in patients with high-grade symptomatic carotid lesion.\(^8\) This study encompassed 35 hospitals from 3 countries (Germany, Austria, and Switzerland), which randomized 1200 patients to either CAS (\( n = 605 \)) or CEA (\( n = 595 \)). All patients underwent carotid intervention within 30 days following treatment randomization. The study showed the rate of death or ipsilateral ischemic stroke was 6.84% in the CAS group and 6.34% with the CEA group (absolute difference 0.51%, 90% CI, 1.89% to 2.91%). The study did not prove noninferiority of CEA compared with CAS for the periprocedural complication rate. The authors concluded that CAS does not justify the widespread use in the short-term of carotid artery stenting for treatment of carotid artery stenoses.

**Discussion**

Before the balloon angioplasty or stenting became a commonly performed endovascular procedure, CEA has long been considered as the standard treatment of choice in patients with high-grade carotid occlusive disease. The advent of endovascular techniques has made carotid stenting an attractive treatment alternative in patients with carotid occlusive disease, due in part to its percutaneous treatment modality as well as reduced procedural discomfort. The clinical adaptation of this catheter-based treatment modality must be evaluated in a prospective randomized fashion with CEA in which the percutaneous intervention is compared with the conventional standard of care.

The CAVATAS trial was the first randomized investigation, which compared endovascular carotid interventions with CEA patient with carotid or vertebral stenosis, which found equivalency between the 2 treatment modalities with regard to neurologic complications and freedom from stroke at 3 years.\(^5\) In this study, a total of 504 patients were randomized to either CEA (\( n = 253 \)) or percutaneous carotid interventions (\( n = 251 \)). The great majority of the patients was symptomatic (96.5%) and had severe stenosis (mean 86.5% by the common carotid method). It is noteworthy that carotid stenting was only used in 26% of patients randomized to carotid angioplasty treatment. Because this trial was conducted before the advent of the neuroprotection device, all carotid stenting procedures were performed without distal cerebral protection. One remarkable finding from this study was the comparable treatment outcome between the surgical and the endovascular group. In fact, there was no significant difference in the occurrence of periprocedural stroke or death between the carotid angioplasty and the CEA groups (9.9% vs 9.9%). With regard to major stroke and death rate, no difference was found between the carotid angioplasty and the CEA groups (6.4% vs 5.9%). It is surprising that the complication rates reached a sufficiently high level between the CEA and the carotid angioplasty groups (10% vs 9.9%).\(^5\)
Proponents of endovascular intervention pointed out that CAVATAS was the first randomized study, which proved many of the intuitive benefits of percutaneous treatment, particularly when analyzing its minor procedural complications. Because no incision is needed in the carotid angioplasty patient group, the incidences of wound hematoma were significantly lower than the CEA group (1.2% vs 6.7%). Conversely, the incidence of cranial nerve palsies in the carotid angioplasty group was significantly lower than the CEA cohorts (0% vs 8.7%). However, many physicians have criticized the findings of CAVATAS trial as irrelevant to their current clinical practice. Because no carotid neuroprotection device was used and only 1 quarter of patients received carotid stenting in the angioplasty group, this does not reflect the current treatment modality of endovascular carotid intervention. In fact, the rate of stroke within 30 days following carotid angioplasty or stenting was 10%, a high complication rate which might have been reduced with the use of a distal protection device. Additionally, many physicians also expressed concern regarding the high incidence of restenosis (>70%) in patients treated with balloon angioplasty, which was 14% in the angioplasty group compared with 4% in the surgical group. Other critiques of this study pointed out the high risk of stroke and/or death rate in the CEA group which was 9.9%, even though the majority of patients enrolled in this trial had symptomatic carotid lesions. One possible explanation may be related to a less strict screening of patient enrollment, as well as less stringent credentialing criteria of operating surgeons and interventionalists in the CAVATAS trial, which may in part result in the higher procedural complication rates seen in this study.

The first prospective randomized trial comparing CAS with neuroprotection and CEA was the SAPPHIRE trial. In contrast to the CAVATAS study, all patients randomized to percutaneous carotid intervention were treated with the Smart stent (Johnson & Johnson, Warren, New Jersey) and with the AngioGuard neuroprotection (Johnson & Johnson). Published in the New England Journal of Medicine in 2004, the study showed that carotid stenting was not inferior to CEA in patients with either anatomical or medical risk factors for increased operative complications (Table 1). The results of this study brought both vindication for CAS enthusiasts as well as controversy for CEA proponents.

Although authors of this study only included patients who were deemed to have high risk based on associated conditions (Table 1), it is noteworthy that most of the patients in this study (224 of the 324 randomized patients) had asymptomatic carotid lesions. The study showed a perioperative risk for death and stroke, 6.7% in patients treated with carotid stenting. Considering that the majority of these patients were asymptomatic, this astoundingly high perioperative complication rate in the CAS group clearly outweighs any benefit of stroke reduction in asymptomatic patients. This issue could have been addressed if the SAPPHIRE study included a control group, which received a medical regimen only.

The cumulative major adverse event including stroke, death, or myocardial infarction, was lower in the stenting group than in the CEA group at 1 year (12.2% vs 20.1%, \( P = .05 \)). The major factor that attributed to the difference in the treatment groups in the composite endpoint is related to the higher incidence of MI in the surgical group than in the CAS cohorts. When excluding MI as an end point, there was no difference in the rates of stroke or death between carotid stenting and endarterectomy at either 30 days (3.6% vs 3.1%) or at 1 year. For
many surgeons, the inclusion of MI as an end point in a study comparing percutaneous carotid intervention versus surgical carotid reconstruction remains controversial because MI was not included as a composite end point in previously published large CEA trials. Because general anesthesia was used in the CEA group while local anesthesia was used for the stenting procedure, the increased incidence of MI may be partially attributed to the anesthetic factor rather than the difference in carotid intervention. Additionally, all patients treated with carotid stenting received clopidogrel, whereas patients who underwent CEA did not receive clopidogrel. The beneficial effect of clopidogrel in antiplatelet therapy may have played a role in the reduced incidence of MI in the stenting group as there is convincing evidence supporting clopidogrel and aspirin in lowering the risk of heart attack.

It is noteworthy that more than 20% of patients in either CEA or CAS groups had recurrent carotid artery stenosis, a finding which may result in outcome bias favoring CAS. This is because repeat CEA in patients with recurrent carotid stenosis is typically associated with higher rates of cranial nerve complications than primary CEA operation. Additionally, CAS for recurrent carotid stenosis, which is predominately caused by intimal hyperplasia, is associated with less cerebral embolization risk than CAS in complex ulcerating carotid plaques. Critiques of the SAPPHIRE trial further point out that in this trial all endovascular devices including the carotid stent and the neuroprotection device were made by a single manufacturer. The lack of other comparative stent or neuroprotection devices in this trial limits a broad interpretation of the study finding on other carotid stenting devices in the treatment of carotid occlusive disease. Furthermore, the inventor of the Angioguard neuroprotection device served as the principal investigator of this trial in which the findings were in part submitted to the FDA for device approval, and some critiques have raised a concern of a potential conflict of interest. Nonetheless, both the Smart stent and the Angioguard neuroprotection device have received FDA approval for carotid stenting in symptomatic patients at high surgical risk.

Both EVA-3S and SPACE trials were the recent important randomized trials comparing CEA versus CAS from European colleagues. The EVA-3S clearly showed that CAS resulted in poor clinical outcomes compared with CEA, and the trial was stopped early after a higher 30-day procedural risk of stroke and death was noted in CAS patients at a planned interim analysis with 527 randomized patients (9.6% vs 3.9%; relative risk 2.5, 95% CI, 1.2-5.1, P = .01). Additionally, more local complications were found in the CAS patients than in the CEA group. The SPACE trial was a large trial in which the researchers aimed to recruit 1900 patients with symptomatic carotid lesions. However, the randomization was stopped at 1200 patients, partly due to a shortage of funding. The procedural 30-day risk of stroke and death showed a high trend in the CAS group than in the CEA cohorts (6.84% vs 6.34%, respectively), with a similar trend for disabling ipsilateral stroke in the CAS and the CEA groups (4.01% vs 2.91%, respectively). It is noteworthy that both of these prospective studies were powered to show noninferiority outcome of CAS and primarily randomized recently symptomatic patients with optional neuroprotection devices. Both studies showed that CAS did not provide similar clinical equivalency compared with CEA, whereas EVA-3S showed CEA to be significantly superior to CAS.

Both EVA-3S and SPACE trials were in sharp contrast to the SAPPHIRE study because the latter trial primarily randomized asymptomatic patients who were deemed high risk for CEA. In fact, 45% of patients in the EVA-3S study, which enrolled recently symptomatic patients, received either CEA or CAS less than a month following the onset of their symptoms. Interestingly, patients who underwent CAS under neuroprotection experienced a 7% death and stroke rate in both trials.

The disparity of these studies only highlights 2 important concepts. Carotid stenting has not been definitively proven to be superior or even equivalent to CEA. Additionally, CAS is a technically challenging procedure in which the outcome is related to the interventionalist’s experience, a finding proven in many previous reports. The issues of physicians’ experience in carotid stenting were underscored in both the EVA-3S and the SPACE trials. First, the most active sites in both studies only enrolled less than 10 patients per year during the trial period. Additionally, approximately 5% of patients undergoing CAS were deemed technically unsuccessful and were crossed over to the CEA treatment. The median procedural time of CAS was 70 minutes, which suggests that interventionalists were still in their learning phase, and this may have contributed to the suboptimal clinical outcome. Undoubtedly, the level of expertise of the interventionalist does play a major role in CAS. In the EVA-3S study,
Interventionalists used 5 different stents and 7 different cerebral protection devices, and they had to perform only 2 CAS procedures for any new device used. Similarly, the SPACE trial required a minimum of 25 CAS procedures which were monitored by a neurologist for complication. Moreover, neuroprotection device was not required in the SPACE trial, whereas 18% of CAS patients in the EVA-3S trial were treated without neuroprotection.

The importance of performing CAS under neuroprotection was underscored by the finding of EVA-3S in which the combined rate of stroke or death in patients treated without an embolic protection device was 25%. In our recent report, which examined the learning curve of consecutive 200 CAS procedures, we found that procedural time as well as stroke and death rates were significantly decreased after the first 50 cases of CAS.19 Undoubtedly, interventionalists who have not overcome the procedural learning curve of CAS may have been a contributing factor in the high stroke and death rates in these clinical trials.

All available randomized studies analyzing CAS and CEA have raised more questions than answers with regard to the superiority of treatment modality. In the end, these 2 treatment modalities will likely play a complementary role in patients with carotid occlusive disease. At the present time, it remains unclear which patient cohorts will definitively benefit from each intervention. The answer to the question of stroke prevention must be derived from randomized trials, which focus on symptomatic patients. Several ongoing clinical trials may provide insight with regard to the clinical efficacy of CAS and CEA in patients with high-grade carotid lesions (Table 2). Potential advantage for local anesthetic must be taken into account for comparison with CAS because nearly all randomized trials have compared CAS under local anesthesia versus CEA under general anesthesia. Last, the procedure must be durable and safe in which the outcome can be reproducible by all interventionalists regardless of their specialties.

### References

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