

Carotid Artery Stenting Versus Carotid Endarterectomy

An appraisal of prospective randomized clinical trials.

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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 interventionists. Many perceived advantages of percutaneous interventions compared to open surgical reconstruction hold true in carotid artery stenting (CAS) when compared to carotid endarterectomy (CEA), including avoidance of surgical incision, decreased procedural discomfort, decreased patient anxiety, and avoidance of general anesthesia.

Since CAS was approved in 2004 by the FDA for clinical application, this percutaneous procedure has become a treatment alternative in patients who are deemed high risk for CEA. In contrast to many endovascular peripheral arterial interventions, percutaneous carotid stenting represents a much more challenging procedure because it requires complex catheter-based skills to use the .014-inch guidewire system and distal protection device. Moreover, current carotid stent devices predominantly utilize the monorail guidewire system that 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 stroke,

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which can occur due in part to plaque embolization during the balloon angioplasty and stenting of the carotid artery. Because these various procedural components require high technical proficiency, many early clinical investigations of CAS, which included physicians with little or no CAS 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 procedure-related complications between the two treatment modalities. A recent Cochrane review noted that before 2006, a total of 1,269 patients had been studied in five randomized controlled trials comparing percutaneous carotid intervention and surgical carotid reconstruction.⁴ These trials revealed that CAS had a greater procedural risk of stroke and death when compared to CEA (odds ratio, 1.33; 95% confidence interval [CI]; .86 to 2.04). Additionally, a greater incidence of carotid restenosis was noted in the CAS group than in the CEA cohorts.⁴

TABLE 1. COMORBID FACTORS ASSOCIATED WITH HIGH OPERATIVE RISK FOR CEA**Anatomical Factors**

- High lesion (above C2 vertebral body)
- Low lesion (below clavicle)
- Previous neck irradiation
- Previous radical neck dissection
- Contralateral carotid occlusion
- Previous ipsilateral CEA

Physiological Factors

- Age ≥ 80 y
- Need for coronary artery bypass grafting
- Left ventricular ejection fraction $\leq 30\%$
- Class III/IV congestive heart failure
- Class III/IV angina pectoris
- Recent myocardial infarction (MI)
- Severe chronic obstructive pulmonary disease
- Renal failure
- Severe coronary artery disease

However, the constant improvement of endovascular devices, procedural techniques, and adjunctive pharmacological therapy will likely improve the treatment success 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 results of several prospective randomized trials comparing percutaneous carotid intervention and CEA. Although excellent clinical results of CAS have been demonstrated in various industry-sponsored investigational device exemption trials, including ARCHER (sponsored by Guidant Inc., now Abbott Vascular, Abbott Park, IL), BEACH (sponsored by Boston Scientific Corporation, Natick, MA), and SeCURITY (sponsored by Abbott), 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 four randomized prospective clinical trials will be individually presented followed by a close appraisal of their clinical outcomes. Specifically, these prospective randomized trials include the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial, and the Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs Endarterectomy (SPACE) trial.

CAVATAS

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). Two hundred and thirteen patients in the endovascular groups underwent successful treatment. Among them, 55 patients (26%) received carotid stents, while 158 (74%) were treated with balloon angioplasty alone. The study showed no differences in 30-day major outcome between the two groups. Significantly lower complications in cranial neuropathy were noted in the endovas-

cular group when compared to the surgical group (0% vs 8.7%; $P<.0001$). Decreased groin or neck hematoma was also noted in the endovascular group when compared to the surgical group (1.2% vs 6.7%; $P<.0015$). At 1-year follow-up, severe (70% to 99%) ipsilateral carotid stenosis occurred more frequently in the endovascular treatment arm (14% vs 4%; $P<.001$). At 3 years after the study randomization, however, no difference in the rate of ipsilateral stroke was noted between the two groups.

SAPPHIRE

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 included patients with either a symptomatic carotid artery stenosis of at least 50% of the luminal diameter or an asymptomatic stenosis of at least 80% 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 CAS (n=167) and CEA (n=167). The primary endpoint of the study was the cumulative incidence of a major cardiovascular event at 1 year; a composite of death, stroke, or 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 rate was lower in the stenting group than 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%; $P=.03$). Based on these findings, the investigators concluded that CAS with neuroprotection was not inferior to CEA in high-risk patients.

EVA-3S

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 French institutions participating in patient enrollment, 259 patients underwent CEA, while 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 to 5.1). The 30-day incidence of stroke or death was 9.6% (95% CI; 6.4 to 14) in the CAS group and 3.9% (95% CI; 2 to 7.2) in the CEA group. 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. CEA 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 due to significantly higher stroke and death rates in the CAS group than the CEA group.

SPACE

The SPACE trial was designed to show noninferiority of CAS as compared to CEA in patients with high-grade symptomatic carotid lesions.⁸ This study encompassed 35 hospitals from three countries (Germany, Austria,

and Switzerland), which randomized 1,200 patients to either CAS ($n=605$) or CEA ($n=595$). All patients underwent carotid intervention within 30 days of treatment randomization. The study showed a rate of death or ipsilateral ischemic stroke of 6.84% in the CAS group and 6.34% with the CEA group (absolute difference, .51%; 90% CI; 1.89 to 2.91). The study did not prove noninferiority of CAS compared with CEA for the periprocedural complication rate. The investigators concluded that CAS does not justify the widespread use in the short-term of CAS for the treatment of carotid artery stenoses.

DISCUSSION

Before balloon angioplasty or stenting became a commonly performed endovascular procedure, CEA had long been considered as the standard treatment for patients with high-grade carotid occlusive disease. The advent of endovascular techniques has made CAS 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 that compared CEA and balloon angioplasty/stenting in patients with carotid or vertebral

TABLE 2. ONGOING PROSPECTIVE RANDOMIZED TRIALS COMPARING CAS AND CEA

Trial Name	Anticipated Patient Enrollment	Inclusion Criteria of Carotid Stenosis	CAS:CEA Randomization Ratio	Primary Study Endpoints
Carotid Revascularization: Endarterectomy Versus Stent Trial (CREST)	2,500	$\geq 60\%$ luminal stenosis	1:1	30-d stroke/death/MI; 4-y ipsilateral stroke
Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects with Significant Extracranial Carotid Occlusive Disease Trial (ACT I)	1,658	$\geq 80\%$ luminal stenosis	3:1	30-d stroke/death/MI; 1-y ipsilateral stroke
Transatlantic Asymptomatic Carotid Intervention Trial (TACIT)	3,700	$\geq 60\%$ luminal stenosis	1:1:1 (CAS:CEA: Medical)	Stroke/death/MI; 3-y ipsilateral stroke

stenoses. The study found equivalency between the two treatment modalities regarding neurological 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 majority of the patients were symptomatic (96.5%) and had severe stenosis (mean, 86.5% by the common carotid method). It is noteworthy that CAS 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 CAS procedures were performed without distal cerebral protection. One remarkable finding from this study was the comparable treatment outcome between the surgical and endovascular group. In fact, there was no significant difference in the occurrence of periprocedural stroke or death between the carotid angioplasty and CEA groups (9.9% vs 9.9%). With regard to major stroke and death rate, no difference was found between the carotid angioplasty and CEA group (6.4% vs 5.9%). It is surprising that the complication rates reached a sufficiently high level between the CEA and angioplasty groups (10% vs 9.9%).⁵

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Proponents of endovascular intervention pointed out that CAVATAS was the first randomized study that proved many of the intuitive benefits of percutaneous treatment, particularly when analyzing its minor procedural complications. Because no incision is needed in the angioplasty group, the incidence of wound hematomas was significantly lower than in the CEA group (1.2% vs 6.7%). Conversely, the incidence of cranial nerve palsies in the angioplasty group was significantly lower than in the CEA cohorts (0% vs 8.7%). However, many physicians have criticized the findings of the CAVATAS trial as irrelevant to their current clinical practice. No carotid neuroprotection device was used, and only 25% of patients received CAS in the angioplasty group, which does not reflect the current treatment modality of endovascular carotid intervention. In fact, the rate of stroke within 30 days after carotid angioplasty or stenting was 10%, a high complication rate that 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 to 4% in the surgical group. Other critiques of this study noted the high rate of stroke/death 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 interventionists 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 SAPHIRE trial.⁶ In contrast to the CAVATAS study, all patients randomized to percutaneous carotid intervention were treated with the SMART stent (Cordis Corporation, a Johnson & Johnson Company, Warren, NJ) along with the AngioGuard neuroprotection device (Cordis). Published in the *New England Journal of Medicine* in 2004, the study showed that CAS was not inferior to CEA in patients with either anatomical or medical risk factors for increased operative complications (Table 1).⁶ The results of this study brought 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 6.7% perioperative risk for death and stroke in patients treated with CAS. 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 SAPHIRE study included a control group that received a medical regimen only.

The cumulative major adverse event rate, including stroke, death, or MI, was lower in the stenting group than in the CEA group at 1 year (12.2% vs 20.1%; $P=.05$).⁶ 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 endpoint, there was no difference in the rates of stroke or death between CAS and CEA at either 30 days (3.6% vs 3.1%) or 1 year. For many surgeons, the inclusion of MI as an endpoint in a study comparing percutaneous carotid intervention versus surgical carotid reconstruction remains controversial because

MI was not included as a composite endpoint in previously published large CEA trials.⁹⁻¹¹ Because general anesthesia was used in the CEA group while local anesthesia was used in the CAS procedure, the increased incidence of MI may be in part attributed to the anesthetic factor, rather than the difference in carotid intervention. Additionally, all CAS patients 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.¹²⁻¹⁴

It is noteworthy that >20% of patients in either the CEA or CAS groups had recurrent carotid artery stenosis, a finding that 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.¹⁵⁻¹⁷ 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 SAPHIRE trial further pointed out that, in this trial, all endovascular devices including the carotid stent and 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 AngioGuard neuroprotection device have received FDA approval for carotid stenting in symptomatic patients at high surgical risk.

Both the EVA-3S and SPACE trials were recent important randomized trials comparing CEA versus CAS with data from European colleagues. The EVA-3S clearly showed that CAS resulted in poor clinical outcomes compared to 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 to 5.1; $P=.01$). Additionally, more local complications were found in the CAS patients than in the CEA group.⁷

The SPACE trial was a large trial in which the researchers aimed to recruit 1,900 patients with symp-

tomatic carotid lesions. However, the randomization was stopped at 1,200 patients, partly due to a shortage of funding.⁸ The procedural 30-day risk of stroke and death showed a higher 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 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 demonstrated that CAS did not provide similar clinical equivalency compared to CEA, whereas EVA-3S showed CEA to be significantly superior to CAS.

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Both the EVA-3S and SPACE trials were in sharp contrast to the SAPHIRE 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 after 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 two important concepts. CAS 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 interventionist’s experience level, a finding proven in many reports.^{3,18,19} The issues of physician experience in CAS were underscored in both the EVA-3S and SPACE trials.²⁰ First, the most active sites in both studies only enrolled fewer 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, suggesting that interventionists were still in their learning phase and possibly contributing to the suboptimal clinical outcome. Undoubtedly, the interventionist’s experience level does play a major role in CAS.

In the EVA-3S study, interventionists used five different stents and seven different cerebral protection devices, and they were required to perform only two

CAS procedures for any new device used. Similarly, the SPACE trial required the interventionist to perform a minimum of 25 CAS procedures that were monitored by a neurologist for complications. Moreover, a 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 that examined the learning curve of 200 consecutive CAS procedures, we found that procedural time and the stroke and death rate were significantly decreased after the first 50 CAS cases.¹⁹ Interventionists 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.

CONCLUSION

All available randomized studies analyzing CAS and CEA have raised more questions than answers regarding the superiority of treatment modality. These two 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 that 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). The potential advantage of 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. Lastly, the procedure must be durable and safe, in which the outcome can be reproducible by all interventionists, regardless of their specialties. ■

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