Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Carotid Angioplasty and Stenting With and Without Cerebral Protection: Clinical Alert From the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) Trial

Stroke 2004;35;18-20; originally published online Dec 4, 2003;
DOI: 10.1161/01.STR.0000106913.33940.DD
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Carotid Angioplasty and Stenting With and Without Cerebral Protection

Clinical Alert From the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) Trial

EVA-3S Investigators

Background and Purpose—Whether cerebral protection during carotid angioplasty and stenting (CAS) is associated with a lower risk of periprocedural stroke or death remains to be established. We report on 80 patients randomized in the CAS arm of the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis trial comparing CAS (with or without cerebral protection) with carotid surgery in patients with recently symptomatic, severe carotid stenosis.

Summary of Report—The Safety Committee recommended stopping unprotected CAS, because the 30-day rate of stroke was 3.9 (0.9 to 16.7) times higher than that of CAS with cerebral protection (4/15 versus 5/58).

Conclusion—Although this result was not based on a randomized comparison of unprotected versus protected CAS, it suggests that the use of cerebral protection devices during CAS reduces periprocedural strokes. **(*Stroke*. 2004;35:e18-e21.)**

Key Words: angioplasty ■ carotid endarterectomy ■ carotid stenosis ■ cerebral ischemia, transient ■ stents ■ stroke

In the past few years, evidence has accumulated that carotid angioplasty and stenting (CAS) might become an alternative to carotid endarterectomy[1] for the treatment of patients with high-grade symptomatic carotid artery disease. Randomized clinical trials are in progress to compare these techniques. In order to reduce embolization of plaque fragments to the brain during CAS, cerebral protection devices have been developed, but it remains to be established whether these devices modify the risk of periprocedural complications.

Using data from the ongoing Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial, we report evidence that CAS with a cerebral protection device may be safer than CAS without cerebral protection.

Methods

EVA-3S is a multicenter, randomized, open, assessor-blind, non-inferiority study, with national research organization funding. The primary objective of this study is to evaluate whether CAS (with or without cerebral protection) is as safe and effective as carotid surgery as regards (1) the risk of stroke and death within 30 days of the procedure and (2) the long-term risk of ipsilateral carotid territory stroke, in patients with recently symptomatic, severe (≥70% NASCET) carotid stenosis. To join the study, each center must comprise a neurologist, an interventionalist, and a vascular surgeon. The interventionalist must document at least 12 cases of carotid angioplasty and stenting or at least 5 cases of carotid angioplasty and stenting and 30 cases of endovascular treatment of other supra-aortic trunks. In centers in which the local interventionalist does not meet full requirement, angioplasty is performed under the responsibility of a tutor from another center, until he/she becomes self-sufficient, according to predefined criteria. Carotid angioplasty consists of primary stenting with or without use of cerebral protection. Any device can be used in EVA-3S provided that (1) the device is approved by the technical committee of the study and (2) the interventionalist can document at least 2 cases of patients treated with this device outside the trial. Patients must receive aspirin (100 to 300 mg daily) and either ticlopidine (250 mg twice daily) or clopidogrel (75 mg daily) for 3 days before and for 1 month after the procedure. Heparin is given during the procedure.

See Editorial Comment, page e20

Patients are followed-up by the study neurologist at 1 month, 6 months, and every 6 months thereafter for 2 to 4 years. All outcome events are reviewed blindly by a Clinical Event Adjudication Committee. A major stroke is defined as a stroke that increases the modified Rankin Scale to 3 or more, 1 month after the event.

Results

On January 30, 2003, the safety committee of EVA-3S recommended to stop unprotected CAS. At that time, 80 patients had been randomized in the CAS arm of the trial. The procedure could not be performed in 6 (7.5%) patients because of catheterization difficulties (CAS failure); these

Received July 21, 2003; final revision received September 18, 2003; accepted September 23, 2003.

A list of contributors from the EVA-3S Investigators appears in the Appendix.

Correspondence to Prof Jean-Louis Mas, Dept of Neurology, Hôpital Sainte-Anne, 1 rue Cabanis, 75674 Paris Cedex 14, France. E-mail mas@chsa.broca.inserm.fr

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000106913.33940.DD**

TABLE 1. Baseline Characteristics of Patients Treated With and Without Cerebral Protection and of Those With CAS Failure

	CAS With Cerebral Protection*	CAS Without Cerebral Protection†	*P*	Failure of CAS
n	58	15		6
Age, y	66.0 (42.1–82.0)	72.7 (51.8–83.6)	0.013	79.3 (60.3–82.1)
Male sex	42 (72.4%)	13 (86.7%)	0.330	4 (66.6%)
Qualifying event			0.770	
Stroke	35 (60.3%)	11 (66.7%)		1 (16.7%)
TIA	23 (39.7%)	5 (33.3%)		5 (83.3%)
% stenosis	85.0 (70.0–99.0)	80.0 (70.0–90.0)	0.136	92.5 (80.0–99.0)
Delay from randomization to treatment, d	7.5 (0.0–76.0)	6.0 (3.0–20.0)	0.962	...
Local anesthesia‡	55 (94.8%)	14 (93.3%)	1.00	
Predilatation	11 (19.3%)	1 (6.7%)	0.438	...
Procedure duration, min	75.0 (20.0–150.0)	60.0 (22.0–150.0)	0.113	...

CAS indicates carotid artery stenting.

Data are numbers (percentages) or median (extremes). Categorical variables were compared with Fisher's exact test. Continuous variables were compared with the Mann-Whitney test.

*The stents used were Carotid Wallstent monorail, Boston Scientific (n=40); Acculink 0.014, Guidant (n=11); Carotid Wallstent OTW, Boston Scientific (n=5); Precise 0.018, Cordis (n=2). Cerebral protection devices included Guardwire PercuSurge, Medtronic (n=40); EmboShield, Perclose-Abbott, (n=11); Filter Wire EX, Boston Scientific (n=4); Angioguard XP, Cordis (n=3).

†The stents used were Carotid Wallstent monorail, Boston Scientific (n=13); Acculink 0.014, Guidant (n=1); Precise 0.018, Cordis (n=1).

‡Versus general anesthesia.

patients were subsequently treated by surgery. One patient had a stroke before planned angioplasty. CAS was performed in 73 patients, using a femoral (n=71), radial (n=1), or carotid (n=1) route. Cerebral protection devices were used in 58 (79.5%) patients. Except for a younger age of patients treated with cerebral protection, no significant difference was found between patients with or without cerebral protection (Table 1).

Twelve events were reported: 1 minor stroke after randomization but before procedure, 1 minor stroke during a failed procedure, and 9 strokes (3 major strokes) and 1 sudden death within 30 days of the 73 completed procedures. The overall combined stroke and death rate was 15.0% (95% CI, 8.0% to 24.7%) and that of major stroke and death was 5.0% (95% CI, 1.4% to 12.3%).

Table 2 shows the numbers of strokes and deaths within 30 days of the 73 completed procedures with and without cerebral protection. The 4 events in patients without cerebral protection occurred in 3 different centers, and the 6 events in patients with cerebral protection occurred in 5 different centers. Crude and age-adjusted odds ratios were all >2.5, although the lower limits of the confidence intervals were compatible with an absence of difference. As regards stroke, unprotected CAS was associated with a number needed to harm of 6.

Discussion

In the first 80 patients randomized to the CAS arm of the EVA-3S trial, the overall stroke and death rate within 30 days

TABLE 2. Risk of Stroke or Death Within 30 Days of CAS With or Without Cerebral Protection

	CAS With Cerebral Protection* (n=58)	CAS Without Cerebral Protection† (n=15)	Unadjusted Odds Ratios (95% CI)	Age-Adjusted‡ Odds Ratios (95% CI)
Any stroke	5 (8.6%)	4 (26.7%)	3.9 (0.9–16.7)	2.8 (0.6–12.8)
Major stroke	1 (1.7%)	2 (13.3%)	8.8 (0.7–100.0)	5.8 (0.5–71.0)
Any stroke or death	6 (10.3%)	4 (26.7%)	3.2 (0.8–13.0)	2.5 (0.6–10.8)
Any major stroke or death	2 (3.4%)	2 (13.3%)	4.3 (0.6–33.3)	3.8 (0.5–31.6)
Any procedural stroke§	3 (5.2%)	2 (13.3%)	2.8 (0.4–18.7)	2.3 (0.3–15.7)

CAS indicates carotid artery stenting.

* Three strokes occurred on the day of the procedure and 2 in the second week following the procedure. One sudden death occurred 30 days after the procedure. The modified Rankin scores at 1 month were 0, 0, 1, 2, 3.

†Two strokes had an onset on the day of the procedure and 2 during the second week. The modified Rankin scores at 1 month were 0, 2, 3, 4.

Stroke was caused by cerebral infarction in 7 patients and by intracerebral hemorrhages in 2. The 2 hemorrhagic strokes occurred 7 and 10 days after CAS with cerebral protection.

‡Odds ratios were calculated using a logistic regression model.

§Strokes occurring within 24 hours of the procedure.

was 15.0% (95% CI, 8.0% to 24.7%). Most of these strokes were nondisabling strokes, giving a combined major stroke and death rate of 5% (95% CI, 1.4% to 12.3%). While several single-center studies on CAS have been published,[2,3] there is only a single completed prospective multicenter trial (Carotid and Vertebral Artery Transluminal Angioplasty Study [CAVATAS])[4] to which we can compare our results. The rates of death or any stroke (minor strokes lasting <7 days were excluded) or death within 30 days was 10% in 251 patients randomly assigned to endovascular treatment, whereas the rate of disabling stroke (equivalent of modified Rankin grade ≥3) or death was 6%. Most patients (77%) underwent carotid angioplasty without stenting, and no procedure was performed with cerebral protection devices. The rate of technical success was 89%, similar to that found in our study (92.5%).

In our study, the risk of any stroke within 30 days of unprotected CAS was about 3 times that of patients treated with cerebral protection. Based on these data, the Safety Committee recommended stopping unprotected CAS, although the lower limits of the confidence intervals were compatible with an absence of difference. It should be stressed that our study was not designed to randomly compare CAS with and without cerebral protection and that the number of events is small. A center effect is unlikely to explain these results, since the 10 events occurred in 8 different centers. A learning effect is also unlikely to explain the different complications rates, since protected CAS is a more complex technique than unprotected CAS. Our findings are consistent with a systematic review of observational studies, in which the 30-day stroke and death rate in both symptomatic and asymptomatic patients was 1.8% in 896 patients treated with protection devices compared with 5.5% in 2537 patients treated without protection devices.[5]

Our results, in keeping with uncontrolled studies, suggest that CAS with cerebral protection may be safer than unprotected CAS. Further data from ongoing randomized clinical trials are awaited to confirm this finding.

Appendix

Contributors

Writing Committee: J.L. Mas, G. Chatellier, B. Beyssen. Scientific Committee: J.L. Mas, G. Chatellier, A. Branchereau, J.P. Becquemin, J.F. Bonneville, D. Crochet, J.C. Gaux, V. Larrue, D. Leys, J. Watelet. Clinical Event Validation Committee: T. Moulin, S. Bracard, M. Hommel, J.L. Magne, F. Mounier-Vehier. Interventional Techniques and Surgery Committee: B. Beyssen, J.F. Bonneville, L. Boyer, J.P. Favre, M. Giroud, K. Hassen-Kodja, J.B. Ricco. Imaging Committee: J.P. Pruvo, J.F. Meder, C. Arquizan, F. Becker, F. Cattin, J.M. Debray, J.M. Jausseran, A. Long, P.J. Touboul. Safety Committee: M. Lièvre, J.P. Beregi, J. Bogousslavsky, M. Testart.

The complete list of investigators and centers can be found at http://eva3s.hegp.bhdc.jussieu.fr.

Acknowledgments

This work was funded by Programme Hospitalier de Recherche Clinique of the French Ministry of Health (AOM 97066), Assistance Publique des Hôpitaux de Paris.

References

1. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–116.
2. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, Lloyd AJ, London NJ, Bell PR. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg*. 1998;28:326–334.
3. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol*. 2001;38:1589–1595.
4. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357:1729–1737.
5. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke*. 2003;34:813–819.

Editorial Comment

With or Without Protection? The Second Important Question in Carotid Artery Stenting

This is already the second editorial comment within the last 6 months about protection devices in carotid artery stenting.[1] Obviously, this seems to be an important question. In the August issue of *Stroke*, Cremonesi and co-workers reported about their experience with these protection devices and suggested that the use is feasible and effective, but not without complications.[2]

And now, in this issue, the EVA-3S Trial committee reports the comparison of protected and unprotected stenting procedures.[3] Due to the better results when using protection devices, the safety committee recommended stopping unprotected stenting within the study.

From a scientific point of view, this recommendation was not absolutely necessary. A substantial number of patients treated without protection developed a stroke, not during the procedure but during the first 30 days. And this cannot be related to the nonuse of a protection device! However, this is a large randomized study and the reviewers and the editorial board of *Stroke* decided that the preliminary results have to be published! But, the publication of these results (or should I say, “of this opinion”?) should not be used to change all “stenting” procedures into “stenting with protection” procedures. They should be seen as part of a growing data pool, which it is hoped will allow us one day to make a definite decision based on real evidence. This report is clearly a piece of a puzzle and absolutely not the final proof for the protecting devices. The number of patients treated, the number of complications, and the type of complications

(delayed stroke) are not powerful enough to convince. But anyhow, this important decision of the safety committee cannot be ignored by the neurovascular community and should be discussed extensively.

I suggest that the steering committees of the Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy (SPACE) study (Germany) and Carotid and Vertebral Artery Transluminal Angioplasty Study 2 (CAVATAS 2; United Kingdom) should do an interim analysis with a focus on the difference between "protected" and "non-protected" patients as soon as the number of patients is powerful enough. We all know that protection devices are not free of complications and it is still questionable whether the latter is really outbalanced against the advantages.

Eckert and Zeumer[1] nicely pointed out that the current data indicate that protected carotid artery stenting has a combined stroke and death rate of 2.0%, whereas that of unprotected carotid artery stenting is 3.2%. However, if it turns out that this difference is true for larger study cohorts, we clearly have to use these devices. To analyze the complications, the learning curve, and at what point of the learning curve the protection devices game into game might be of major importance. If we—at our institution—would start with protection devices tomorrow, it might be that the protected results would be better than the unprotected stenting results from the past 2 years—but probably not really related to the protection, but mainly related to our improved skills and our increased experience with different anticoagulation regimens. To conclude, at our institution we will continue not to use the protection device. From a medicolegal point of view, scientific data still allow us to do the procedure both ways. But we have to be aware and we encourage all investigators to keep their eyes—at least one—on that problem. Coming back to the title: do not forget that we still do not have evidence that stenting is better than surgery. And this is clearly the most important question to answer.

Michael Forsting, MD, *Guest Editor*
Department of Neuroradiology
Institute of Diagnostic and Interventional Radiology
University of Essen
Essen, Germany

References

1. Eckert B, Zeumer H. Carotid artery stenting with or without protection devices? Strong opinions, poor evidence! *Stroke*. 2003;34:1941–1943.
2. Cremonesi A, Manetti R, Castriota F, Setacci F, Setacci C. Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. *Stroke*. 2003;34:1936–1943.
3. EVA-3S Investigators. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. *Stroke*. 2004;35:e18–e21.