

Carotid artery stenting versus surgery: adequate comparisons?

A moratorium on carotid artery stenting (CAS) has been recently proposed.¹ Current randomised evidence supports the notion that carotid endarterectomy (CEA) is better than CAS. A meta-analysis of the randomised trials compared the two strategies² and included data from the recent International Carotid Stenting Study (ICSS).³ This meta-analysis indicated that patients who received CAS had a significant increased risk of 30-day death or stroke compared with patients who received CEA (odds ratio 1.60; 95% CI 1.26–2.02).² As randomised clinical trials are the gold standard of clinical investigation, it seems unwise to challenge them. However, for the comparison of CAS versus CEA, most of the randomised trials should be considered not only scientifically but also ethically questionable because the endovascular experience required for interventionalists to be eligible for the studies was minimal (table). As a consequence, patients allocated to CAS might have been exposed to unnecessary risk and the assessment of safety and efficacy of the endovascular approach confounded.

In the French Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study,⁸ a lifetime experience of at least 12 CAS interventions was required. Alternatively, a minimum of five CAS procedures was deemed to be sufficient if the interventionalist had a lifetime experience of at least 30 stenting procedures in supra-aortic vessels. The rationale for this adjustment is difficult to understand given that subclavian and carotid interventions differ substantially. For investigators who did not comply with these minimum requirements, the EVA-3S protocol allowed the procedure “under the supervision of

an experienced tutor”, defined in the protocol as “a clinician who qualified to perform stenting in this study”.⁸ In later correspondence,¹⁰ the investigators acknowledged that only 16% of the 265 patients treated with stenting were managed by operators who had done more than 50 CAS procedures in their lifetime and that 39% of patients were treated by physicians in training. Although such a track record can hardly be defined as good clinical practice or trial conduct, the information was not thought to be sufficiently relevant to be reported in any of the EVA-3S publications.

Concerns about CAS safety in the EVA-3S trial were raised after the enrolment of 80 patients in the endovascular arm. The safety committee recommended stopping the performance of CAS without the use of embolic protection devices, because the 30-day rate of stroke among patients undergoing unprotected CAS was 26.7%, which was 3.9 times higher than that of patients treated with embolic protection (8.6%).¹¹ However, in the clinical alert published by the EVA-3S investigators,¹¹ the experience of the interventionalists was not questioned because “a learning effect is also unlikely to explain the different complications rates, since protected CAS is a more complex technique than unprotected CAS”. This quote reveals a fundamental gap in understanding of the CAS procedure. In real-life practice, the use of embolic protection devices is widely embraced by experienced CAS interventionalists, whereas those with less expertise might be reluctant to use these devices. Additional evidence of the little endovascular experience among the investigators of EVA-3S is derived from the high rate of emergent conversion from CAS to CEA (5%). The fact that CAS was never reimbursed in France did not help the investigators to gain exposure to the procedure.

According to the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study,⁶ a minimum

of 25 successful consecutive CAS procedures was needed to participate as an investigator. However, a subsequent report⁷ revealed that, during the course of the trial, the protocol was amended to allow for tutoring of physicians who had only undertaken ten CAS procedures. Finally, in ICSS,⁹ a minimum of 50 total stenting procedures was required as long as at least ten of these involved the carotid artery. Tutor-assisted procedures were allowed for investigators with insufficient experience, again raising the concern of adequacy of training.

The inexperience of the EVA-3S, SPACE, and ICSS investigators might have exposed the endovascular patients to an increased risk, not only because of insufficient operator skills, but also (and equally important) owing to inappropriate selection of patients. Interventions in patients with complex anatomy at the level of the aortic arch and supra-aortic vessels require more catheter manipulation than in patients with less tortuous or diseased vessels and place patients at increased risk of periprocedural stroke.



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	Year	n*	Lifetime endovascular requirements
CAVATAS ⁴	2001	504	Training in neuroradiology and angioplasty (but not necessarily in the carotid artery); tutor-assisted procedures allowed
SAPPHIRE ⁵	2004	334	Procedures submitted to an executive review committee; CAS periprocedural death or stroke rate had to be <6%; no tutor-assisted procedures allowed
SPACE ^{6,7}	2006	1200	At least 25 successful CAS or assistance of a tutor for interventionalists who have done at least 10 CAS
EVA-3S ⁸	2006	527	≥12 CAS cases or ≥5 CAS and ≥30 cases of endovascular treatment of supra-aortic trunks; tutor-assisted CAS allowed for centres not fulfilling minimum requirements
ICSS ⁹	2010	1710	A minimum of 50 total stenting procedures, of which at least ten should be in the carotid artery; tutor-assisted procedures allowed for interventionalists with insufficient experience

CAS=carotid artery stenting. CAVATAS=Carotid and Vertebral Artery Transluminal Angioplasty Study. EVA-3S=Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial. ICSS=International Carotid Stenting Study. SAPPHIRE=Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy. SPACE=Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study. *Total number of patients in the trials (allocated to either CAS or endarterectomy). Modified from Roffi and colleagues.²

Table: Requirement of endovascular expertise in randomised trials of carotid endarterectomy versus stenting that enrolled more than 300 patients

The trials clearly missed the main goal of randomised testing of any new procedure—namely to assess whether it is at least as efficacious as the gold standard in the hands of skilled operators for selected (favourable) patients.

Why did the leadership of EVA-3S, SPACE, and ICSS propose such limited requirements for endovascular experience and how were such protocols accepted by ethics committees? The reasons might have been the absence of procedural insight or concerns about funding or slow enrolment. Regardless, no surgeon would have ever allowed a peer with total lifetime experience of just ten CEA procedures to participate in a randomised trial. Importantly, the endovascular requirements in the mentioned trials do not comply with current minimum recommendations.^{12,13} Finally, the terms “tutors” and “randomised trials” should be thought of as mutually exclusive.

In conclusion, as angiologists, cardiologists, neurologists, radiologists, and vascular surgeons involved in the endovascular treatment of carotid disease, we believe that the EVA-3S, SPACE, and ICSS trials provide an inadequate comparison between CAS and CEA. Their findings run counter to our experience and the outcomes of thousands of patients observed in independently monitored and adjudicated CAS registries closely overseen by the US Food and Drug Administration.² Therefore, although we agree on a moratorium of randomised clinical testing as has been done so far, we encourage clinical investigation to be pursued in both surgical and endovascular high-volume centres.

In the meantime, we ask the leaders of the EVA-3S, SPACE, and ICSS studies to provide the scientific community with currently missing information such as training, total experience (surgical and endovascular), and outcomes of investigators before

study initiation; total volumes (surgical and endovascular) of centres and of individual investigators during the trials; number of patients included per centre per year; quality control implemented and sanctions in case of overt incompetence; and outcome variations between centres and between operators. These data will help to put the results of the trials in perspective, but will not obviate the need for further well designed investigations.

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Triallists' reply

Roffi and colleagues criticise the ethics of the recent randomised trials of carotid stenting versus carotid endarterectomy in patients with symptomatic carotid stenosis. This is a bold step, considering that the trials received research ethics approval in about 20 countries. Moreover, the three most recent trials, the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial,¹ the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial in symptomatic patients,² and the International Carotid Stenting Study (ICSS)³ included more than 100 academic vascular centres where surgeons, interventionalists, and neurologists all considered the designs of the individual trials appropriate

and ethical. Nevertheless, Roffi and colleagues' arguments that the trial design, and thus the results, are flawed need refuting.

The Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS)⁴ was the first trial designed to test endovascular treatment against endarterectomy for carotid stenosis. This trial was started in 1992, before the development of stenting, but by the time ICSS was started in 2001, carotid stenting was well established in many centres. By 2002, the Global Carotid Artery Stent Registry had recorded a total of more than 12 000 carotid stent procedures worldwide since 1997.⁵ Moreover, carotid stenting was being adopted without good evidence that it was as safe and effective as carotid endarterectomy. It was therefore right and timely to test carotid stenting in randomised clinical trials, rather than allow its unregulated expansion. It is a curious anomaly of regulatory agencies that surgical and endovascular devices can be introduced into clinical practice with very limited evidence of safety and no evidence of efficacy. Many investigators in the carotid stenting trials thought that it was far more ethical to treat patients with a new interventional treatment in the context of a randomised trial than to treat them outside trials, and it was the interventionalists who were treating patients outside the trial who were risking unethical practice.

One reason it is more ethical to include patients in a randomised trial than it is to treat them outside a trial is that patients who participate in a trial are protected by the requirements of the trial's protocol and by the additional attention to risk factor control during follow-up, and audit of the results is assured.

In Roffi and colleagues' opinion, the endovascular experience required for the operators to be eligible for the randomised trials was minimal. The experience of carotid stenting in the trials was indeed limited at some centres, but for all the large trials inter-

ventionalists had to have extensive experience in the techniques of cerebral angiography and stenting in other vascular trees. Thus, the inexperience of the operators only related to the deployment of a stent in the carotid artery, rather than another artery.

One might expect inexperienced interventionalists to obtain worse results than more experienced interventionalists. By contrast with this expectation, analysis within the trials did not support the contention that the results that favoured carotid endarterectomy were attributable to inexperienced interventionalists. In both EVA-3S and ICSS, the patients treated by inexperienced investigators had lower stroke and death rates after stenting than did those treated by more experienced investigators. Roffi and colleagues criticise the fact that only 16% of the patients in EVA-3S were treated by interventionalists who had done more than 50 carotid stent procedures, but did not point out that the 30-day risk of stroke or death in patients treated by these experienced interventionalists was 12.2%, compared with 11.0% in patients treated by those who had done 50 procedures or fewer and 7.1% in patients treated by interventionalists who were being proctored.⁶ Similarly, in ICSS, the rate of stroke or death within 30 days of stenting in the supervised centres was 6.9%, compared with 8.7% in the more experienced centres.³

Roffi and colleagues are also critical of the fact that, during a later stage of SPACE, tutored treatment was allowed for interventionalists who had previous experience of ten stent procedures. However, of 56 interventionalists, only six were tutored during 51 procedures. Only six primary outcome events in the per-protocol analysis were attributed to those tutored interventionalists. It is unlikely that these interventionalists made a difference to the overall results of SPACE. Hence, the suggestion that the terms "tutors" and "randomised trials" should be mutually exclusive is not supported by the evidence.



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