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Carotid angioplasty and stenting : caveat emptor !

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Abstract

Carotid endarterectomy effectively reduces stroke in patients with TIA or minor stroke and a high-grade carotid stenosis. Carotid endarterectomy is also beneficial in male asymptomatic patients younger than 75 years with high-grade stenosis. Carotid stenting has not been as thoroughly evaluated as carotid endarterectomy in randomized trials. The few trials that have been performed up to now show either inferior results or suggest equivalence. Before accepting carotid stenting as a mainstream treatment for carotid stenosis, this therapy should be as critically evaluated as carotid endarterectomy was in the 1980s and 1990s.

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Carotid surgery : established treatment of carotid stenosis

Carotid endarterectomy is one of the very few surgical procedures that have been thoroughly evaluated in randomized clinical trials. The evidence favoring carotid endarterectomy (CEA) in the treatment of symptomatic carotid stenosis is overwhelming. Two major randomized trials that included 6092 patients with 35000 years of follow-up showed that surgery increased the 5-year risk of ipsilateral ischaemic stroke in patients with less than 30% stenosis measured using NASCET criteria, had no effect in patients with 30-49% stenosis, was of marginal benefit in those with 50-69% stenosis, and was highly beneficial in those with 70% stenosis or greater without near-occlusion (1). The benefit is largest in patients treated within the first two weeks after symptom onset, after that the benefit is reduced to 50% in the 3 to 4 week period and declines even further after this period (2). This is mainly due to the extremely high short-term risk of stroke in these patients (3). Patients with amaurosis fugax as the presenting symptom of carotid stenosis seem to have a lower risk of stroke as previously taught in textbooks.

Two trials that included 4782 patients with 15000 years of follow-up favor CEA in patients with asymptomatic carotid stenosis although the effect of treatment is more modest and requires exposing many patients to surgery with benefit for few patients (4, 5). In patients with asymptomatic carotid stenosis there is no benefit beyond age 75 and probably only a modest benefit if at all exists in women (6). The operation is beneficial in patients with contralateral carotid occlusion, contrary to the common skepticism that the operation is not beneficial because of very high surgical risk in these patients (4). It is unclear if benefit extends to all patients with carotid stenosis as patients enrolled in trials were highly selected or the stenosis was found in patients who had previous contralateral surgery. Systematic screening for carotid stenosis still seems unwarranted, however opinions differ widely on this subject. Screening in patients with established peripheral disease might be warranted.

Is carotid stenting an established method of treatment for carotid stenosis ?

Although CAS has been adopted by many centers as an established alternative to CEA the evidence supporting CAS is surprisingly weak when compared to the robust data obtained with carotid surgery. In order to become the preferred treatment modality of carotid stenosis more high quality data on several issues should be obtained. Additional data should address technical and safety questions, but also demonstrate that CAS is at least as effective in reducing ipsilateral stroke and is as durable as CEA. Finally, CAS has to be reasonably cost-effective.

Safety issues in carotid angioplasty and stenting

With regard to *safety*, data from the global carotid artery stent registry indicate that experienced centers can perform CAS without excess adverse events, however reporting in this registry is voluntarily and the data are unmonitored (7). Monitored studies frequently combine the risks in asymptomatic and symptomatic patients making comparisons with RCT of CEA hazardous. These procedures are typically performed in centers experienced in CAS. The degree of selection bias in

these studies is also not known. A small trial, the so called Leicester trial, was stopped due to excessive risk in the stenting group (8). Two early randomized trials (CAVATAS and WALLSTENT) showed an unacceptable safety profile (9, 10). The WALLSTENT trial was a randomized trial of 219 patients with symptomatic carotid stenosis. In the carotid stenting group there were 5 study related deaths (4.6%) and 7 strokes (6.5%) compared to 2 deaths in the carotid surgery arm (1.8%) and no strokes. CAVATAS was an exploratory randomized trial of 504 symptomatic and asymptomatic carotid stenosis patients. In both study arms there was a 10% risk of stroke and death. Restenosis (70-99% stenosis) or occlusion occurred in 14% of patients, irrespective of whether a stent had been placed or not. Although the significance of this finding is unknown it casts doubts about the long-term durability of the procedure (11). Especially in-stent restenosis is a feared complication for which the optimal management is still undefined. The role of drug-eluting stents in carotid disease has not been extensively tested.

Efficacy of carotid stenting

The efficacy of CAS has been tested in 6 randomized trials. The Leicester, Wallstent and CAVATAS studies have already been discussed above. The two small, "Kentucky" trials were underpowered to claim superiority or efficacy (12, 13). The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy *(*SAPPHIRE) trial is widely publicized as the first positive randomized trial of CAS versus CEA (14). The goal of this trial was to determine whether CAS with an embolic protection device was as good as CEA in a highly selected group of patients with severe asymptomatic and symptomatic carotid stenosis. The patients were referred by their practicing physicians who already had decided that intervention was required on these patients. A panel consisting of a neurologist, an interventionalist and a vascular surgeon evaluated the patient and decided together that both procedures could be performed. All patients were at high surgical risk because of relative (e.g. carotid restenosis after previous CEA), perceived contraindications (contralateral carotid occlusion) or severe concomitant cardiac or pulmonary disease. The trial used a sequential design. This allowed the trial to be stopped at interim analysis if the prespecified hypothesis of equivalence was met. The primary end point of the trial was a combination of the incidence of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. The threshold for equivalence was met after 334 patients were enrolled in the study. The primary end point occurred in 12.2% of patients assigned to stenting and in 20.1% of patients assigned to surgery for an absolute difference of –7.9 percentage points (95 percent confidence interval, –16.4 to 0.7 percentage points ; p = 0.004 for non-inferiority). Several criticisms can be voiced with regard to SAPPHIRE. First, the trial did not include a control group of patient who did not undergo any procedure, in order to know if these patients required any revascularization at all : the inclusion of a large number of older patients and women indicates that this is probably the case. Whether the results of SAPPHIRE can be extrapolated to more common situations remains doubtful. Secondly, the inclusion of cardiac events as an endpoint is inherently biased against surgical procedures. Moreover, more patients assigned to CAS had undergone coronary revascularization procedures possibly creating another bias against CEA. People have also been concerned by counting very mild postoperative CK-MB increases as MIs. Finally, people have criticized the presence of conflicts of interests as the lead investigator was the inventor of the embolic protection device used in the trial. Long term (> 2 years) results from SAPPHIRE are also lacking.

Two additional trials have been presented at international conferences and were recently published (15, 16). The Stent-Protected Percutaneous Angioplasty of the Carotid vs Endarterectomy (SPACE) study was a German trial, whose primary goal was to demonstrate equivalence of CAS with CEA (17). One thousand one hundred eighty three patients with symptomatic internal carotid artery stenosis of > 70% on duplex ultrasound were enrolled. Symptoms had been present in the past 6 months. The primary hypothesis was to show that the rate of ipsilateral stroke or death at 30 days of CAS was within 0.5% of the risk associated with CEA. One hundred seventy two patients (28.7%) in the CAS arm received a protection device. The risk of ipsilateral stroke and death was 6.84% in CAS versus 6.34% with CEA and equivalence could not be proven (p = 0.09).

EVA 3S was a French study of CAS versus CEA in patients with symptomatic carotid high grade stenosis of more than 60% in the past 4 months. Five hundred twenty seven patients were enrolled. Because of a high rate of complications, unprotected stenting was abandoned early in the trial (18). The primary endpoint of 30-day risk of stroke or death was significantly increased in the stenting group compared with endarterectomy (9.6% vs 3.9%, respectively ; unadjusted relative risk [RR], 2.5 ; 95% confidence interval [CI], 1.2-5.1 ; P = .01). A significant benefit was seen for stenting with cerebral protection for 30-day stroke or death (n = 227 ; 7.9%) over stenting without cerebral protection (n = 20 ; 25% ; P = .03). The different centres and experience of the interventionists had no significant effects on the relative risks of stroke or death.

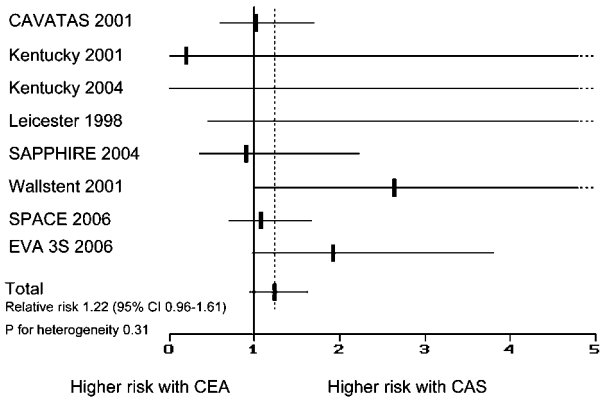

FIG. 1. — Meta-analysis from randomized trials of carotid artery stenosis comparing carotid endarterectomy (CEA) with carotid angioplasty and stenting (CAS). The effect of endovascular treatment versus endarterectomy for patients with carotid artery stenosis on the combined outcome "death or any stroke within 30 days of procedure" is shown. Results are expressed as relative risks with a fixed effects model. RR < 1 suggests endovascular treatment to be superior to endarterectomy.

We updated a previous Cochrane metaanalysis to include these two trial results (Fig. 1) (19). The meta-analysis shows that there is a non-significant trend towards a benefit with CEA compared to CAS, with a higher relative risk with CAS of 1.21 (95% CI 0.96-1.61, p = 0.13) for stroke or death. The quite wide confidence intervals suggest that equivalence with this new procedure is not yet proven.

Is CAS more cost-effective than CEA ?

Initially hailed as a more *cost-effective* treatment than CEA, the introduction of embolic protection devices with CAS has challenged this notion. Generally, the duration of hospitalization is shorter as general anesthesia is not required. However, embolic protection devices are expensive. It is unclear at this moment if these devices are required in every procedure or if high-risk patients can be identified. Some of the ongoing trials do not require the use of these protection devices, while others consider them the standard of treatment. If higher rates of restenosis are confirmed with CAS, the cost of additional procedures should also be added to the cost of this intervention.

Finally, several *technical and medical issues* are open. Given the profusion of different devices it is unclear at this moment which is the optimal device type. Also, the degree of dilatation that is required for optimal stent results is debated. Which antithrombotic regimen to use in the first months after the procedure is also a topic of discussion.

Conclusion

CAS is a promising potential alternative to CEA. Several issues remain open before widespread application can be recommended. More importantly, high grade evidence from large, randomized controlled trials favoring this procedure is currently lacking.

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