The Stenting and Angioplasty with Protection in Patients at High Risk of Endarterectomy (SAPPHIRE) collaborators have attempted to perform a difficult trial. This is of special interest because the majority of their randomized patients were asymptomatic. Their article in the New England Journal of Medicine has already been much quoted and inevitably misquoted. The main result was that stenting with protection does not appear to be inferior to endarterectomy; particularly as far as peri-procedural risks are concerned. In asymptomatic carotid stenosis endarterectomy has been shown to halve stroke risk. So some are assuming that stenting with protection should now be recommended in patients with asymptomatic carotid stenosis. This is a worry and may not be in the best interests of patients.

A number of criticisms of the SAPPHIRE trial need to be considered. Firstly, the authors have misinterpreted the previous carotid surgery trials by saying that carotid endarterectomy is more effective than medical management in stroke prevention; however these trials actually compared best medical treatment with best medical treatment plus carotid endarterectomy. Best medical treatment has improved very considerably since the 2 major symptomatic and 2 asymptomatic trials were started, with better antiplatelet therapy, more efficient blood pressure control and the widespread use of statins. So the risks are now different, and historical controls may be misleading.

The patient characteristics in SAPPHIRE were not the same as in the carotid surgery trials. In particular there was a very high prevalence of significant coronary artery disease (approximately 85%), suggesting that their population had a cardiological bias. Fewer than 30% of patients with carotid stenosis were symptomatic and 70% were asymptomatic. Nearly 30% of patients had had previous carotid endarterectomy and a similar proportion had had previous angioplasty. Detecting restenosis during follow-up naturally produces a wish to attempt to correct it. However, the risks of cerebral emboli might be quite different from a smooth restenosis than from the initial, irregular and perhaps ulcerated, carotid plaque. Furthermore, the risks of repeat procedures are usually considered to be higher. There is no convincing evidence that treating recurrent stenosis is beneficial.

Only a minority of the patients in SAPPHIRE were actually randomized between stenting and carotid endarterectomy. 334 patients were randomized but 413 were not. Of this group, 406 had stenting with protection and only 7 had carotid endarterectomy. The reasons given for this huge discrepancy were that those entered on the stenting register were judged to be reasonable candidates by the interventionists but not by the vascular surgeons. Clearly the authors of the SAPPHIRE article are supporters of stenting. The lead author invented the protection device used. Two of the authors are employees of the stent and protection device manufacturer (Cordis) and 11 of the 15 authors acknowledge some financial support from the company.

At the end of 1 year, the cumulative incidence of primary end points in the symptomatic patients was 16.8% in the stenting group and 16.5% in the carotid endarterectomy group. These figures are high, but they were dealing with a higher risk group of patients. In the asymptomatic patients the risks appeared to be even higher, which goes against usual experience, with up to a 21.5% risk of a primary end point at 1 year and over the perioperative period, up to a 10% risk of death, myocardial infarction or stroke. These are complication rates that compare with those from the older CAVATAS study on symptomatic patients. These complication rates are not acceptable for treating asymptomatic patients where the chances of ipsilateral stroke are generally low and where there should be ≤3% peri-procedural risk.

Another problem with SAPPHIRE was that the trial had to be terminated early because of a dramatic fall in patient enrollment. Reliable subgroup analysis is therefore unavailable. We do not know the influence of age or sex. Enrollment fell because of the establishment of several nonrandomized stenting registries. This is a very worrisome trend. Entering patients into a registry has acquired a respectability that it does not deserve. Registries are fine for observational studies but they are not satisfactory for assessing new...
therapies. They are prone to significant bias.7 Often the registries will have no independent neurologist or stroke physician to assess end points so these will tend to be under-reported.

Carotid stenosis should not be viewed in isolation as a single arterial problem requiring simple correction but should be seen in context with the patient assessed as a whole. Patient selection is crucial. Asymptomatic1,5 and symptomatic3,4 carotid stenosis trials showed benefits from surgery, but there are important differences between asymptomatic patients and those recently symptomatic. In the latter, intervention should be considered urgently because of the 30% risk of stroke in the first few weeks8 after transient ischemic attack (TIA) onset. The number needed to treat (NNT) within the first two weeks is 5; after 12 weeks the NNT is 125.8 In asymptomatic patients, if an intervention is to be used at all, it should be regarded as a long term investment, not an acute necessity.2 The diagnosis of TIAs may not be as easy as some imagine. They may be misclassified as migraine, focal epilepsy, vertigo or even carpal tunnel syndrome. The basic differentiation between symptomatic and asymptomatic needs some expertise. They should not be lumped together.

The types of patient population are important. Those in the endarterectomy trials largely came from neurological or vascular surgical clinics, a different population from those derived from screening for example, in shopping malls, or from cardiological services where the risks and benefits may be different. The peri-procedural complication rates need to be low at 3% or less for asymptomatic patients. A slightly higher rate, say 5%, may be acceptable in the symptomatic where risks and benefits are higher. There are considerable differences in the NNT. Approximately 9 patients with more than 50% carotid stenosis who are symptomatic need to be treated to prevent one stroke.8 In asymptomatic patients, the NNT is 16 to prevent a stroke and 32 to prevent a disabling stroke.2 Gender is important—men are at higher risk (NNT for symptomatic men=9 and for women=36). The case for operating on asymptomatic women6 is significantly weaker than in men. There did appear to be a statistical benefit in the Asymptomatic Carotid Surgery Trial (ACST)2 but not in the Asymptomatic Carotid Atherosclerosis Study5 and when the results are combined, the case for operating on women is poor.9 There are important age differences. Patients >75 years who develop TIAs are at high risk and the NNT to prevent an ipsilateral stroke is only 5.8 Whereas in ACST,2 evidence suggested that asymptomatic patients >75 years should not be offered intervention.

Informed consent and patient choice are crucial issues. If asymptomatic patients are told that a procedure will halve the risk of stroke, then most would choose to have it. If further information is provided that the absolute risk of stroke is small, perhaps 12% over 5 years, that it is reduced by enthusiastic medical therapy, that there is a 3% upfront risk of stroke, MI or death and that it takes four years before benefit is derived, many would choose conservative therapy.

Just because an attractive procedure is available does not mean it should be recommended. Even if a procedure has been shown to work in certain situations performed by skilled operators using particular devices or techniques, it does not mean that it is as applicable to other patient groups, other operators, other devices and other techniques.

The very fact that stenting is perceived to be a lesser procedure than surgery raises the concern that it will be performed more frequently and more readily than surgery, particularly for asymptomatic disease. A further worry is that with the wide availability of catheter techniques and expertise in using them in other medical areas, especially cardiology, stenting will be offered to neurologically unselected patients who may not need it. In some cases, patients will be assessed and guided by physicians, at risk of financial gain, who may not be neurosurgeons and not have the same insight into the special problems of having the unforgiving brain distal to an arterial stenosis.

**Conclusion**

SAPPHIRE’s main finding that stenting with protection does not appear to be inferior to carotid endarterectomy is not a license for the widespread use of stenting, but it should indicate that patients, before stenting, need to be assessed as thoroughly and appropriately as those being considered for endarterectomy.

In testing the benefits and risks of new treatments in different patient groups, registries are not acceptable because of their risks of bias. These difficulties will not be overcome by a meta-analysis of registries, randomized trials are required. Randomized stenting trials in symptomatic carotid patients are in progress10 and a trial in asymptomatic patients is imminent. Patients should be entered rapidly into these trials so that answers to the important questions on how patients should be managed will be available as quickly as possible. For the moment asymptomatic patients should not be offered protected stenting outside a controlled randomized trial.

**References**


**Key Words:** carotid stenosis | endarterectomy | randomized controlled trials | stents
Protected Carotid Artery Stenting Versus Endarterectomy in High-Risk Patients
Reflections From SAPPHIRE
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