THERAPEUTICS

Stenting led to more stroke or death than did endarterectomy in symptomatic carotid stenosis ≥ 60%

Mas JL, Chatellier G, Beyssen B, et al. **Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis.** N Engl J Med. 2006;355:1660-71.

Clinical impact ratings: Hematol/Thrombo ★★★★★★☆ Neurology ★★★★★★★

QUESTION

In patients with severe (≥ 60%) symptomatic carotid stenosis, is stenting noninferior to endarterectomy?

METHODS

Design: Randomized, controlled, noninferiority trial (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis [EVA-3S]).

Allocation: Concealed.*

Blinding: Blinded {events, scientific, and coordinating committees}†.*

Follow-up period: 6 months.

Setting: 30 centers in France.

Patients: 527 patients ≥ 18 years of age with a hemispheric or retinal transient ischemic attack or nondisabling stroke in the past 120 days and stenosis of 60% to 99% (North American Symptomatic Carotid Endarterctomy Trial criteria) in the symptomatic carotid artery. Exclusion criteria included nonatherosclerotic carotid disease; severe tandem lesions; previous revascularization of the symptomatic stenosis; history of bleeding disorders; uncontrolled hypertension or diabetes; contraindication to heparin, ticlopidine, or clopidogrel; life expectancy < 2 years; and percutaneous procedure or surgery within 30 days of the study procedure.

Intervention: Stenting (n = 261) or endarterectomy (n = 259). Each center had to have a neurologist for initial evaluation and follow-up, a vascular surgeon who had done ≥ 25 endarterectomies in the past year, and an interventional physician who had done ≥ 12 carotid-stenting procedures or ≥ 35 stenting procedures in the supraaortic trunks, of which ≥ 5 were in the carotid artery.

Outcomes: The primary endpoint was any stroke or death at 30 days.

Patient follow-up: 520 patients (98.7%) (mean age 70 y, 75% men) (intention-to-treat analysis).

MAIN RESULTS

The study was stopped early for reasons of safety and futility. At 30 days, the incidence of any stroke or death was higher in patients who received stenting than in those who received endarterectomy (Table), and the 95% CI of the difference (2.1% to 9.3%) did not include the 2% limit used to define noninferiority. The increased risk for stroke or death with stenting was still evident at 6 months (Table).

CONCLUSION

In patients with severe (≥ 60%) symptomatic carotid stenosis, the 30-day risk for stroke or death was higher with stenting than with endarterectomy.

Source of funding: Programme Hospitalier de Recherche Clinique of the French Ministry of Health.

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*See Glossary.

†Information provided by author.

Stenting vs endarterectomy in symptomatic severe carotid stenosis‡

Outcome	Follow-up	Stenting	Endarterectomy	RRI (95% CI)	NNH (CI)
Any stroke or death	30 d	9.6%	3.9%	148% (24 to 400)	18 (10 to 68)
	6 mo	11.7%	6.1%	92% (8.5 to 240)	18 (10 to 135)

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

First the good news: Noninferiority trials can (although sometimes don't) ask clinically sensible questions. Once we are convinced that a treatment does more good than harm, if somebody comes up with a new, alternative treatment, there are 2 clinically sensible questions to be asked. First, is the new treatment better than ("superior to") the established treatment? Second, if the new treatment is not better, is it "as good as" the established treatment but preferable in some other way (e.g., safety, comfort, or cost)? To answer these 2 questions, we would carry out a "head-to-head" trial comparing the old and new treatments. At the trial's conclusion, we would want to know how confident we could be in our answers to these 2 questions; we would want any observed differences ("better than") or similarities ("as good as") to be very unlikely to be due to chance.

The bad news is that, to answer the "as good as" question, we have to stand our traditional understanding of trials and P values on its head. Alas, P values describe the probability that treatments are different by chance alone, whereas we want to know the probability that treatments are the same by chance alone. Fortunately (albeit confusingly), there is a statistical solution to this dilemma. It begins by documenting the benefit provided by the established treatment and then agreeing on a slightly less favorable ("inferior") outcome that would be acceptable if the new treatment were less risky, less painful, or preferable in some other way. This inferior outcome constitutes a lower limit of tolerability. At any worse outcome, the new treatment would be judged inferior to the established treatment. (The question of who should define this "inferiority" limit of tolerability deserves a commentary of its own; suffice it to say here that patients' definitions should dominate this determination.)

If we pose this "as good as" question in this "worse than" way, the subsequent trial's P value indicates the probability that patients receiving the new treatment have had worse ("inferior") outcomes by chance. When the P value for this inferior outcome is small, we reject the notion that the new treatment produces worse outcomes, consider it "as good as" the established treatment on a clinical level, and then risk confusing everybody by labeling it "noninferior."

As with other issues in "statistical significance," sense and comprehension are better conveyed with confidence intervals than P values, and examples of these are shown in the Figure. The dotted line labeled MIH indicates the "minimally important harm" limit of tolerability, to the right of which the new treatment is inferior to the old one. Similarly, the line labeled MIB indicates the "minimally important benefit," to the left of which the new treatment is superior. Example A describes an inferior treatment (e.g., the EVA-3S trial) and B an "as-good-as," or noninferior, one. Example C is an all-too-familiar example of an "indeterminate" trial that may have been stopped before it could tell us whether the new treatment was worse than (inferior to) or as good as (noninferior to) the established treatment (e.g., the SPACE trial).

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Noninferiority was not shown between stenting and endarterectomy in severe symptomatic carotid stenosis

Ringleb PA, Allenberg J, Bruckmann H, et al. **30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial.** Lancet. 2006;368:3239-47.

Clinical impact ratings: Neurology ★★★★★★★

QUESTION

In patients with severe symptomatic carotid stenosis, is stenting noninferior to endarterectomy?

METHODS

Design: Randomized, controlled, noninferiority trial (Stent-Supported Percutaneous Angioplasty of the Carotid Artery verus Endarterectomy [SPACE]).
Allocation: Concealed.*
Blinding: Blinded (data safety and monitoring committee).*
Follow-up period: 24 months.
Setting: 35 centers in Germany, Austria, and Switzerland.
Patients: 1200 patients > 50 years of age who had symptomatic stenosis (amaurosis, transient ischemic attack, or stroke) in the past 180 days and severe ipsilateral carotid artery stenosis (≥ 50% according to North American Symptomatic Carotid Endarterectomy Trial criteria or ≥ 70% according to European Carotid Surgery Trial criteria). Exclusion criteria included intracranial bleeding in the past 90 days; uncontrolled hypertension; intracranial arteriovenous malformation or aneurysm; life expectancy < 2 years; coagulation abnormality; contraindication to heparin, aspirin, clopidogrel, or contrast media; occlusion of the common or internal carotid artery; and other causes of stenosis.
Intervention: Stenting (n = 605) or endarterectomy (n = 595). Neurologists had to be experienced in duplex sonography and stroke treatment, interventionalists had to have done ≥ 25 successful percutaneous transluminal angioplasty or stent procedures, and vascular surgeons had to have done ≥ 25 carotid endarterectomy procedures and provide mortality and morbidity rates.
Outcomes: Any ipsilateral stroke (ischemic stroke, intracerebral bleeding, or both, with symptoms lasting > 24 h) or death from any cause at 30 days. Secondary 30-day outcomes included disabling ipsilateral stroke or death, any stroke, and procedural failure.
Patient follow-up: 1183 patients (98.6%) (mean age 68 y, 72% men) (intention-to-treat analysis).

MAIN RESULTS

Stenting and endarterectomy did not differ for any ipsilateral stroke or death from any cause (primary endpoint), and the criterion for noninferiority was not met (Table). Groups did not differ for disabling ipsilateral stroke or death (4.7% vs 3.8%; odds ratio [OR] 1.25, 95% CI 0.71 to 2.22), any stroke (7.5% vs 6.2%; OR 1.24, CI 0.79 to 1.95), or procedural failure (3.2% vs 2.1%; OR 1.56, CI 0.71 to 3.56).

CONCLUSION

In patients with severe symptomatic carotid stenosis, noninferiority was not shown between stenting and endarterectomy.

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*See Glossary.

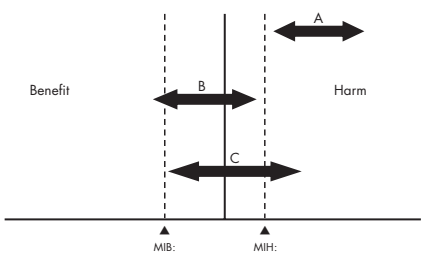
Stenting vs endarterectomy for severe symptomatic carotid stenosis at 30 days†

Outcome	Stenting	Endarterectomy	Difference (90% CI)
Any ipsilateral stroke or death from any cause	6.84%	6.34%	0.51% (–1.89 to 2.91)†

†The criterion for noninferiority was an upper limit of < 2.5% for the 90% CI, so noninferiority was not shown.

COMMENTARY *(continued from page 32)*

For the present, carotid stenting should be recommended only for patients at high risk for cardiovascular complications after endarterectomy based on the results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial (1). Based on the results of EVA-3S and SPACE and a recent Cochrane review (2), any other patient should receive maximum medical therapy and have endarterectomy if clinically indicated or be enrolled in ongoing trials comparing stenting with endarterectomy.



Minimally important benefit (MIB) and minimally important harm (MIH) boundaries for trial results in noninferiority trials. The EVA-3S trial is illustrated by A, and the SPACE trial by C.

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2. **Coward LJ, Featherstone RL, Brown MM.** Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomized evidence. Stroke. 2005;36:905-11.