

## ORIGINAL ARTICLE

## Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis

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## ABSTRACT

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\*Investigators and committees of the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial are listed in the Appendix.

N Engl J Med 2006;355:1660-71.

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**BACKGROUND**

Carotid stenting is less invasive than endarterectomy, but it is unclear whether it is as safe in patients with symptomatic carotid-artery stenosis.

**METHODS**

We conducted a multicenter, randomized, noninferiority trial to compare stenting with endarterectomy in patients with a symptomatic carotid stenosis of at least 60%. The primary end point was the incidence of any stroke or death within 30 days after treatment.

**RESULTS**

The trial was stopped prematurely after the inclusion of 527 patients for reasons of both safety and futility. The 30-day incidence of any stroke or death was 3.9% after endarterectomy (95% confidence interval [CI], 2.0 to 7.2) and 9.6% after stenting (95% CI, 6.4 to 14.0); the relative risk of any stroke or death after stenting as compared with endarterectomy was 2.5 (95% CI, 1.2 to 5.1). The 30-day incidence of disabling stroke or death was 1.5% after endarterectomy (95% CI, 0.5 to 4.2) and 3.4% after stenting (95% CI, 1.7 to 6.7); the relative risk was 2.2 (95% CI, 0.7 to 7.2). At 6 months, the incidence of any stroke or death was 6.1% after endarterectomy and 11.7% after stenting ( $P=0.02$ ). There were more major local complications after stenting and more systemic complications (mainly pulmonary) after endarterectomy, but the differences were not significant. Cranial-nerve injury was more common after endarterectomy than after stenting.

**CONCLUSIONS**

In this study of patients with symptomatic carotid stenosis of 60% or more, the rates of death and stroke at 1 and 6 months were lower with endarterectomy than with stenting. (ClinicalTrials.gov number, NCT00190398.)

**F**INDINGS FROM TWO LARGE RANDOMIZED, clinical trials<sup>1-3</sup> have established endarterectomy as the standard treatment for severe symptomatic carotid-artery stenosis. As compared with endarterectomy, stenting avoids the need for general anesthesia and an incision in the neck that could lead to nerve injury and wound complications. The costs may be less than those of surgery, mainly because the hospital stay is shorter. However, stenting also carries a risk of stroke and local complications, and the long-term efficacy of this technique is not well known. A systematic review<sup>4</sup> of five randomized trials comparing stenting with endarterectomy<sup>5-10</sup> concluded that the current evidence does not support a change from the recommendation of carotid endarterectomy as the standard treatment for carotid stenosis. Several more trials are in progress in Europe<sup>11-13</sup> and the United States.<sup>14</sup>

We conducted this trial, which started in November 2000, to evaluate whether stenting is not inferior to endarterectomy with regard to the risks of the procedure and its long-term efficacy in patients with symptomatic carotid stenosis. In September 2005, the safety committee recommended that enrollment in the trial be stopped. We report on the risks of stroke or death within 30 days and 6 months after treatment.

## METHODS

The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, a publicly funded, randomized, noninferiority trial, was conducted in 20 academic and 10 non-academic centers in France. The study was approved by the ethics committee of Hôpital Cochin in Paris. All patients provided written informed consent.

### CENTERS AND INVESTIGATORS

To join the trial, each center was required to assemble a team of physicians comprising at least one neurologist, one vascular surgeon, and one interventional physician. The neurologist was responsible for the initial evaluation and follow-up of the patients. The vascular surgeon had to have performed at least 25 endarterectomies in the year before enrollment. The interventional physician had to have performed at least 12 carotid-stenting procedures or at least 35 stenting procedures in the supraaortic trunks, of which at least 5 were in

the carotid artery. Centers fulfilling all requirements except those with regard to the interventional physician could join the EVA-3S study and randomly assign patients, but all stenting procedures had to be performed under the supervision of an experienced tutor (a clinician who qualified to perform stenting in this study) until the local interventional physician became self-sufficient (according to the tutor) and performed a sufficient number of procedures according to the predefined criteria.

### PATIENTS

Patients were eligible if they were 18 years of age or older, had had a hemispheric or retinal transient ischemic attack or a nondisabling stroke (or retinal infarct) within 120 days before enrollment, and had a stenosis of 60 to 99% in the symptomatic carotid artery, as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.<sup>15</sup> The degree of stenosis warranting treatment, set at 70% or more at the start of the trial, was subsequently (in October 2003) set at 60% or more because endarterectomy was shown to benefit patients with symptomatic stenosis of 50 to 69%.<sup>3</sup> The presence of an ipsilateral carotid stenosis of 60% or more had to be confirmed by means of catheter angiography or both duplex scanning and magnetic resonance angiography of the carotid artery.

Patients were excluded if one of the following was present: a modified Rankin score<sup>16</sup> of 3 or more (disabling stroke) (on a scale of 0 to 5, with higher scores indicating more severe disability); nonatherosclerotic carotid disease; severe tandem lesions (stenosis of proximal common carotid artery or intracranial artery that was more severe than the cervical lesion); previous revascularization of the symptomatic stenosis; history of bleeding disorder; uncontrolled hypertension or diabetes; unstable angina; contraindication to heparin, ticlopidine, or clopidogrel; life expectancy of less than 2 years; or percutaneous or surgical intervention within 30 days before or after the study procedure. The appearance of the stenotic lesion on angiography was not a factor in the selection of patients.

Patients who were suitable candidates for both techniques were randomly assigned to undergo endarterectomy or stenting. Randomization was carried out centrally by means of a computer-generated sequence, involving randomized blocks of

two, four, or six patients that were stratified according to study center and degree of stenosis (stenosis of  $\geq 90\%$  or  $< 90\%$ ).

#### ENDARTERECTOMY AND STENTING

The goal was for endarterectomy and stenting to be performed within 2 weeks after randomization. Surgeons performed endarterectomy according to customary practice. Carotid stenting had to be carried out through the femoral route with the use of stents and protection devices approved by the accreditation committee. Interventional physicians had to have performed at least two stenting procedures with any new device before its use in the trial. In January 2003, the safety committee recommended the systematic use of stents with cerebral protection devices because of a higher risk of stroke in patients treated without cerebral protection<sup>17</sup>; centers began using them on February 1, 2003. The daily use of aspirin (100 to 300 mg) and clopidogrel (75 mg) or ticlopidine (500 mg) for 3 days before and 30 days after stenting was also recommended.

#### FOLLOW-UP AND END POINTS

The study neurologists performed follow-up evaluations at 48 hours, 30 days, 6 months after treatment, and every 6 months thereafter. The primary end point was a composite of any stroke or death occurring within 30 days after treatment. Secondary outcomes were myocardial infarction, transient ischemic attack, cranial-nerve injury, major local complications, and systemic complications within 30 days after treatment; and composites of any stroke or death within 30 days after treatment plus ipsilateral stroke, any stroke, or any stroke or death within 31 days through the end of follow-up. Neurologists assessed the degree of disability from stroke 30 days and 6 months after the event. Functional disability from cranial-nerve injury was categorized as absent, mild, moderate, or severe at the 30-day follow-up visit. Neurologists also recorded whether treatment-related outcomes were associated with a delay in discharge. The occurrence of stroke, death, and other outcomes was assessed by the events committee, which was unaware of the treatment assignments (except for patients who had local complications).

#### STATISTICAL ANALYSIS

We calculated<sup>18</sup> that we would need to enroll 872 patients for the study to have a statistical power

of 80% to assess whether stenting was not inferior to endarterectomy with regard to the 30-day incidence of stroke or death, given an expected 30-day incidence of stroke or death of 5.6% after endarterectomy<sup>19</sup> and 4% after stenting,<sup>20,21</sup> a true absolute difference between groups in the 30-day risk of stroke or death of no more than 2% (noninferiority margin), and a one-sided alpha of 0.05. A similar difference in the 30-day risk of stroke or death between endarterectomy and medical treatment was observed in NASCET.<sup>22</sup> Our protocol required that an independent safety committee review safety issues each time 10 new validated primary outcome events occurred, with no predetermined rule for stopping the trial, and reassess the number of patients required to show an effect after 30 primary outcome events had occurred. In September 2005, the safety committee recommended stopping enrollment for reasons of both safety and futility. On the basis of the observed 30-day risk of stroke or death after endarterectomy, we would have needed to enroll more than 4000 patients to test the noninferiority of stenting (assuming that the relative noninferiority limit was unchanged). Given the observed 30-day risks of stenting, the committee considered it to be extremely unlikely that the trial, should it continue with more patients, would reach its objectives.

Analyses of the 30-day outcomes were based on all patients who were randomly assigned to treatment and who underwent carotid repair. The results are presented as relative risks with 95% confidence intervals (CIs), calculated with the use of superiority analysis. We also assessed noninferiority, as initially planned. We assessed homogeneity of the relative risks of stroke or death among centers using the Breslow–Day test. For this purpose, centers were categorized into three groups, according to the numbers of patients included in the study ( $< 21$ , 21 to 40, and  $> 40$  patients). Analyses of the 6-month outcomes were based on all patients who were randomly assigned to treatment. Rates of stroke and death were estimated with the use of the Kaplan–Meier method. All data were analyzed according to the intention-to-treat principle. All P values are two-sided and were not adjusted for multiple testing. We used SAS software (version 8.2) for all analyses. The authors vouch for the completeness and veracity of the data and data analyses.

RESULTS

PATIENTS AND TREATMENTS

By September 2005, 527 patients had been randomly assigned to treatment, 7 of whom did not undergo carotid repair (Fig. 1). The remaining 520 patients were included in the analysis of the 30-day risk of stroke or death. Three strokes that occurred between randomization and treatment were not included in the analysis of the 30-day risk of stroke or death but were included in the 6-month analysis of outcomes. The two groups were similar with respect to baseline characteristics, except for a greater proportion of patients 75 years of age or older and more patients with a history of stroke in the endarterectomy group and a higher proportion of contralateral carotid occlusion in the stenting group (Table 1).

Characteristics of the endarterectomy and stenting procedures are listed in Table 2. Two patients underwent a repeated procedure within 48 hours after the initial endarterectomy owing to residual stenosis or dissection. In 13 patients, stenting was converted intraoperatively to endarterectomy owing to problems with access. Two of these patients had a stroke before endarterectomy.

END POINTS

Although the trial was intended to assess noninferiority, we observed that stenting carried a greater risk than did endarterectomy. When we analyzed the data as planned, the 95% CI of the difference in the 30-day incidence of stroke or death between stenting and endarterectomy (2.1 to 9.3%) did not include the 2% limit used to define noninferiority. The 30-day incidence of any stroke or death was 3.9% (95% CI, 2.0 to 7.2) after endarterectomy and 9.6% (95% CI, 6.4 to 14.0) after stenting, with a relative risk of 2.5 (95% CI, 1.2 to 5.1). The absolute risk increase was 5.7%, suggesting that one additional stroke or death resulted when 17 patients underwent stenting rather than endarterectomy. The 30-day incidence of disabling stroke or death was 1.5% (95% CI, 0.5 to 4.2) after endarterectomy and 3.4% (95% CI, 1.7 to 6.7) after stenting, resulting in a relative risk of 2.2 (95% CI, 0.7 to 7.2) (Table 3). A greater proportion of strokes occurred on the day of the procedure in the stenting group than in the endarterectomy group (17 of 24 vs. 3 of 9,  $P=0.05$ ).

The relative risk of stroke or death did not differ significantly among the centers that enrolled

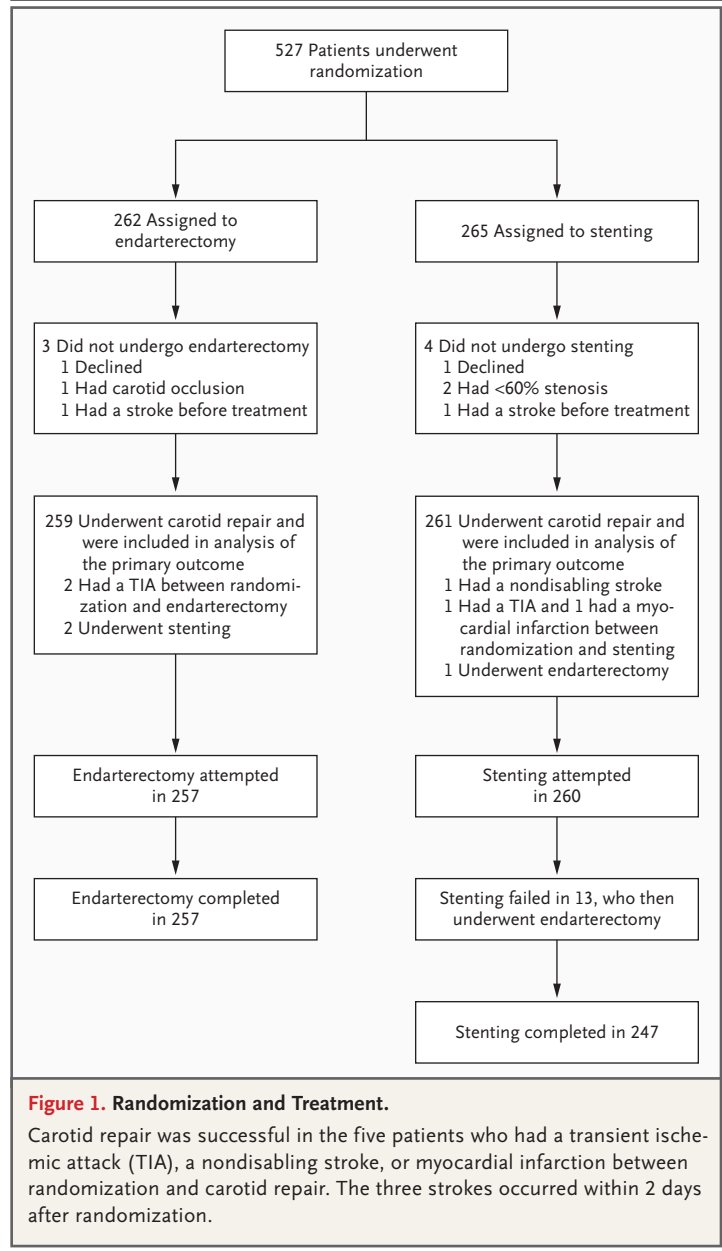


Figure 1. Randomization and Treatment.

Carotid repair was successful in the five patients who had a transient ischemic attack (TIA), a nondisabling stroke, or myocardial infarction between randomization and carotid repair. The three strokes occurred within 2 days after randomization.

fewer than 21 patients (relative risk, 1.9; 95% CI, 0.6 to 6.2), those that enrolled 21 to 40 patients (relative risk, 3.3; 95% CI, 0.7 to 15.2), and those that enrolled more than 40 patients (relative risk, 2.7; 95% CI, 0.9 to 8.1) ( $P=0.83$ ). The 30-day incidence of stroke or death was similar among patients treated by interventional physicians who were experienced (11 of 105, or 10.5%), tutored during training (7 of 98, or 7.1%), and tutored after training (7 of 57, or 12.3%) ( $P=0.54$ ; chi-square statistic, 1.25).

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Endarterectomy Group (N=259)	Stenting Group (N=261)	P Value
Age — yr	70.3±10.7	69.1±10.2	0.21
Age ≥75 yr — no. of patients (%)	105 (40.5)	84 (32.2)	0.06
Male sex — no. of patients (%)	202 (78.0)	189 (72.4)	0.16
Vascular risk factors			
Hypertension — no. of patients (%)†	188 (72.6)	192 (73.6)	0.84
Diabetes — no. of patients (%)†	66 (25.5)	58 (22.2)	0.41
Hypercholesterolemia — no. of patients (%)†	144 (55.6)	151 (57.9)	0.66
Tobacco use — no. of patients (%)‡	61 (23.6)	63 (24.1)	0.92
Systolic blood pressure — mm Hg	140.8±17.8	140.9±16.5	0.95
Diastolic blood pressure — mm Hg	77.1±10.8	77.8±9.9	0.42
Body-mass index§	26.3±4.1	26.1±4.6	0.63
History of vascular disease — no. of patients (%)			
Stroke	52 (20.1)	33 (12.6)	0.02
Transient ischemic attack	60 (23.2)	66 (25.3)	0.61
Myocardial infarction	34 (13.1)	28 (10.7)	0.42
Peripheral arterial disease	30 (11.6)	37 (14.2)	0.43
Cardiac failure leading to hospitalization	7 (2.7)	7 (2.7)	1.00
Prior surgery or angioplasty — no. of patients (%)			
Coronary artery	34 (13.1)	35 (13.4)	1.00
Carotid artery	10 (3.9)	5 (1.9)	0.20
Other artery	23 (8.9)	16 (6.1)	0.25
Medications before qualifying event — no. of patients (%)			
Antiplatelet therapy	136 (52.5)	128 (49.0)	0.43
Antihypertensive medication	177 (68.3)	179 (68.6)	1.00
Antidiabetic agents	64 (24.7)	53 (20.3)	0.25
Lipid-lowering medication	125 (48.3)	129 (49.4)	0.79
Qualifying event — no. of patients (%)			
Cerebral transient ischemic attack	78 (30.1)	95 (36.4)	
Ocular transient ischemic attack	37 (14.3)	33 (12.6)	
Ischemic stroke	139 (53.7)	127 (48.7)	
Retinal infarct	5 (1.9)	6 (2.3)	
Modified Rankin score at randomization¶			0.94
0	145 (56.0)	139 (53.3)	
1	68 (26.3)	71 (27.2)	
2	42 (16.2)	47 (18.0)	
3	4 (1.5)	4 (1.5)	

The 30-day incidence of stroke or death was lower among patients who underwent stenting with cerebral protection (18 of 227, or 7.9%) than among those treated with stenting alone (5 of 20, or 25%;  $P=0.03$ ). However, the relative risk of stroke

or death for stenting over endarterectomy did not differ significantly before systematic use of a cerebral protection device was recommended (2.0; 95% CI, 0.8 to 5.0) or after (3.4; 95% CI, 1.1 to 10.0;  $P=0.50$ ).

**Table 1. (Continued.)**

Characteristic	Endarterectomy Group (N=259)	Stenting Group (N=261)	P Value
Brain imaging — no. of patients (%)			
Computed tomography	217 (83.8)	230 (88.1)	0.17
Magnetic resonance imaging	161 (62.2)	156 (59.8)	0.59
Infarct corresponding to the qualifying event	133 (51.4)	117 (44.8)	0.16
Previous infarct	70 (27.0)	68 (26.1)	0.84
Diagnostic carotid angiography — no. of patients (%)			
Catheter angiography	110 (42.5)	113 (43.3)	0.86
Magnetic resonance angiography	163 (62.9)	161 (61.7)	0.79
Ultrasonography	245 (94.6)	253 (96.9)	0.20
Degree of symptomatic carotid stenosis — no. of patients (%)			0.68
60–69%	21 (8.1)	15 (5.7)	
70–79%	55 (21.2)	56 (21.5)	
80–89%	77 (29.7)	86 (33.0)	
90–99%	106 (40.9)	104 (39.8)	
Contralateral carotid occlusion — no. of patients (%)	3 (1.2)	13 (5.0)	0.02
Contralateral stenosis of 60–99% — no. of patients (%)	44 (17.0)	31 (11.9)	0.11
Time from qualifying event to treatment — no. of patients (%)			0.62
<2 wk	41 (15.8)	53 (20.3)	
2–4 wk	68 (26.3)	66 (25.3)	
4–12 wk	124 (47.9)	118 (45.2)	
>12 wk	26 (10.0)	24 (9.2)	
Time from randomization to treatment			
Median — days	6.0	6.0	0.52
Interquartile range — days	2–10	3–9	
<2 wk — no. of patients (%)	240 (92.7)	249 (95.4)	0.26

\* Plus-minus values are means ±SD. Proportions, means, and medians were compared with the use of Fisher's exact test, Student's t-test, and the Wilcoxon nonparametric test, respectively.

† This condition was diagnosed before the qualifying event.

‡ Tobacco use was defined as the smoking of one cigarette or more per day.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The modified Rankin score ranges from 0 to 5, with higher scores indicating more severe disability.

|| The degree of stenosis was measured with the use of digital subtraction angiography or magnetic resonance angiography, according to the NASCET method.

The relative risk of stroke or death adjusted for age was 2.4 (95% CI, 1.2 to 4.8) and adjusted for the presence or absence of a history of stroke was 2.6 (95% CI, 1.3 to 5.2). More patients in the stenting group had contralateral carotid occlusion; none of them had a stroke after stenting. The 30-day incidence of stroke or death after stenting did not differ significantly between patients who received dual antiplatelet therapy (19 of 211, or 9.0%) and those who received single antiplatelet therapy (4 of 36, or 11.1%; P=0.75).

There were more systemic complications (mainly pulmonary) after endarterectomy and more severe local complications after stenting than after endarterectomy, but these differences were not significant. Cranial-nerve injury was significantly more common after endarterectomy than after stenting (7.7% vs. 1.1%, P<0.001). The median duration of the hospital stay was shorter after stenting (3 days; interquartile range, 2 to 5) than after endarterectomy (4 days; interquartile range, 3 to 5; P=0.01).

**Table 2. Characteristics of Treatment for 257 Patients Who Completed Endarterectomy and 247 Patients Who Completed Stenting.\***

Treatment Group	Value
<b>Endarterectomy</b>	
Anesthesia — no. of patients (%)†	
General	187 (73.0)
Locoregional	69 (27.0)
Cerebral monitoring — no. of patients (%)†	66 (25.8)
Surgical technique — no. of patients (%)	
Endarterectomy	
With the use of a patch	129 (50.2)
Without the use of a patch	53 (20.6)
Eversion	63 (24.5)
Carotid-carotid bypass	11 (4.3)
Transposition	1 (0.4)
Shunt	50 (19.5)
Duration of surgery — min	
Median	80
Interquartile range	60–110
Medical treatment — no. of patients (%)	
Preprocedure‡	
Antiplatelet therapy	168 (69.1)
Anticoagulant therapy	30 (12.3)
Both	45 (18.5)
During procedure§	
Heparin	253 (99.2)
Postprocedure¶	
Antiplatelet therapy	97 (38.2)
Anticoagulant therapy	16 (6.3)
Both	141 (55.5)
<b>Stenting</b>	
Anesthesia — no. of patients (%)	
General	16 (6.5)
Neuroleptanalgesia	56 (22.7)
Local	175 (70.9)
Mean length of lesion— mm	15.6±7.9
Femoral route — no. of patients (%)	238 (96.4)
Predilatation of stenosis — no. of patients (%)	42 (17.0)
Number of stents — no. of patients (%)	
0	1 (0.4)
1	236 (95.5)
2 or more	10 (4.0)
Stent across external carotid artery — no. of patients (%)**	202 (82.1)

**Table 2. (Continued.)**

Treatment Group	Value
<b>Stenting</b>	
Duration of procedure (min)	
Median	70
Interquartile range	50–90
Type of stent used — no. of patients (%)**	
Carotid Wallstent Monorail (Boston Scientific)	140 (56.9)
Acculink (Abbott)	70 (28.5)
Precise RX (Cordis)	26 (10.6)
Carotid Wallstent OTW (Boston Scientific)	5 (2.0)
Zilver (Cook)	5 (2.0)
Cerebral protection — no. of patients (%)	
Before systematic use of protection devices recommended by safety committee	58 (78.4)††
After systematic use of protection devices recommended by safety committee	169 (97.7)††
Device used	
GuardWire Plus (Medtronic)	67 (29.5)
FilterWire EZ (Boston Scientific)	61 (26.9)
Spider RX (ev3)	30 (13.2)
EmboShield (Abbott)	24 (10.6)
Angioguard RX (Cordis)	21 (9.3)
Spider (ev3)	19 (8.4)
AccUNET (Abbott)	5 (2.2)
Medical treatment — no. of patients (%)	
Preprocedure†	
Dual antiplatelet therapy	204 (82.9)
Single antiplatelet therapy	42 (17.1)
During procedure	
Heparin	241 (97.6)
Atropine	192 (77.7)
Postprocedure	
Dual antiplatelet therapy	211 (85.4)
Single antiplatelet therapy	36 (14.6)

\* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

† Data are missing for one patient.

‡ Data are missing for 14 patients.

§ Data are missing for two patients.

¶ Data are missing for three patients.

|| Anticoagulant therapy consisted of low-molecular-weight heparins at prophylactic doses for a few days.

\*\* The stent could not be implanted in one patient.

†† Among the 247 patients who completed stenting, 74 underwent stenting before the recommendation was given and 173 underwent stenting afterward.

**Table 3. Risk of Stroke or Death and Other Treatment-Related Outcomes within 30 Days after Endarterectomy or Stenting.\***

Outcome Event	Endarterectomy (N=259)	Stenting (N=261)	Unadjusted Relative Risk (95% CI)	P Value
	no. of patients (%)			
Nonfatal stroke	7 (2.7) <sup>†</sup>	23 (8.8) <sup>‡</sup>	3.3 (1.4–7.5)	0.004
Symptoms lasting 7 days or more	6 (2.3)	20 (7.7)		
Nondisabling	6 (2.3)	16 (6.1)		
Disabling <sup>§</sup>	1 (0.4)	7 (2.7)		
Death	3 (1.2)	2 (0.8)	0.7 (0.1–3.9)	0.68
Fatal stroke	2 (0.8) <sup>†</sup>	1 (0.4) <sup>‡</sup>		
Other cause	1 (0.4) <sup>¶</sup>	1 (0.4) <sup>  </sup>		
Any stroke or death	10 (3.9)	25 (9.6)	2.5 (1.2–5.1)	0.01
Any disabling stroke or death	4 (1.5)	9 (3.4)	2.2 (0.7–7.2)	0.26
Transient ischemic attack	2 (0.8)	6 (2.3)	3.0 (0.6–14.6)	0.28
Myocardial infarction**	2 (0.8)	1 (0.4)	0.5 (0.04–5.4)	0.62
Bradycardia or hypotension <sup>††</sup>	0	11 (4.2)	Not computable	<0.001
Systemic complications	8 (3.1) <sup>‡‡</sup>	5 (1.9) <sup>§§</sup>	0.6 (0.2–1.9)	0.42

Table 4 lists the incidence of primary outcome events at 6 months. The three composite outcomes were significantly more common after stenting than after endarterectomy.

#### DISCUSSION

This trial was stopped early for reasons of both safety and futility. The 30-day risk of any stroke or death was significantly higher after stenting (9.6%) than after endarterectomy (3.9%), resulting in a relative risk of 2.5 (95% CI, 1.2 to 5.1). Although early stopping of randomized clinical trials carries a risk of the overestimation of treatment effects (i.e., analyzing the data at a “random high”),<sup>23</sup> the excess of primary outcome events after stenting was considered large enough (one additional stroke or death among each 17 patients treated by stenting) for the safety committee to recommend stopping the trial. In addition, the observed rates of the primary outcome made it very unlikely that the trial would show the noninferiority of stenting.

The 30-day incidence of stroke or death after endarterectomy was lower in our trial than in previous trials of endarterectomy in symptomatic patients.<sup>1,2</sup> The lower surgical risk in our study is

unlikely to be explained by the selection of surgeons with a very high level of expertise. Indeed, the surgeons worked in academic and nonacademic centers in various areas of France and had only to have performed 25 endarterectomies in the year before enrollment; there was no upper limit for perioperative stroke and death. The baseline characteristics of our patients were similar to those included in other trials of endarterectomy,<sup>2,5</sup> which makes it unlikely that our findings are explained by the inclusion of patients at low risk for perioperative stroke or death. Moreover, to prevent the underreporting of minor strokes in patients who underwent surgery under general anesthesia and then were returned to surgical wards, all patients were examined 2 days after the procedure. Therefore, the most likely explanation for the low rate of complications from endarterectomy in our trial is that the risks of this procedure have decreased since the pivotal trials<sup>1,2</sup> were conducted.

The combination of results of previous trials<sup>4</sup> yielded a 30-day incidence of stroke or death after endovascular repair of the carotid artery of 8.1% (51 of 632 patients; range, 0.0 to 12.1%). There was significant heterogeneity among these trials, which may have resulted from the use of differ-

Table 3. (Continued.)

Outcome Event	Endarterectomy (N = 259) <i>no. of patients (%)</i>	Stenting (N = 261)	Unadjusted Relative Risk (95% CI)	P Value
Major local complications	3 (1.2)	8 (3.1) ¶¶¶	2.6 (0.7–9.9)	0.22
Cervical or groin hematoma ¶¶	2 (0.8)	1 (0.4)		
Infection***	1 (0.4)	1 (0.4)		
Femoral pseudoaneurysm or arteriovenous fistula at puncture site †††	—	4 (1.5)		
Lower-limb arterial occlusion or thrombosis ‡‡‡	—	4 (1.5)		
Cranial-nerve injury	20 (7.7) §§§	3 (1.1) ¶¶¶¶	0.15 (0.04–0.49)	<0.001

- \* Proportions were compared with the use of Fisher’s exact test. Relative risks were calculated with endarterectomy as the reference group.
- † Among patients who underwent endarterectomy, stroke was caused by cerebral infarction in six patients (including one who had a disabling nonfatal stroke and none who had a fatal stroke) and cerebral hemorrhage in three (including two who had a fatal stroke). All but one of the strokes were ipsilateral to the treated artery. Of the nine strokes, three occurred on the day of the procedure. Cerebral hemorrhage occurred 1 hour after the procedure in one patient and the day after in the two other patients. At the time of cerebral hemorrhage, the first patient had received intravenous heparin during the procedure (0.5 mg per kilogram of body weight) and the two other patients were receiving prophylactic doses of low-molecular-weight heparin.
- ‡ Among patients who underwent stenting, stroke was caused by cerebral infarction in 21 patients (including 5 who had disabling nonfatal strokes and 1 who had a fatal stroke) and cerebral hemorrhage in 3 (2 who had disabling nonfatal strokes and none who had a fatal stroke). All but two of the strokes were ipsilateral to the treated artery. Of the 24 strokes, 17 occurred on the day of the procedure. Cerebral hemorrhage occurred 24 hours, 7 days, or 10 days after the procedure. At the time of cerebral hemorrhage, the three patients were receiving dual antiplatelet therapy.
- § Stroke was defined as disabling if the modified Rankin score (on a scale of 0 to 5, with higher scores indicating more severe disability) was 3 or more for at least 30 days after the event, with an increase of 2 points or more over the prestroke score.
- ¶ This patient committed suicide 17 days after endarterectomy.
- ¶¶ This patient died suddenly 30 days after stenting.
- \*\*\* Myocardial infarction was defined by at least two of the following criteria: typical chest pain lasting 20 minutes or more; serum levels of creatine kinase, creatine kinase MB, or troponin at least twice the upper limit of the normal range; and new Q wave on at least two adjacent derivations or predominant R waves in V<sub>1</sub> (R wave ≥1 mm >S wave in V<sub>1</sub>).
- †† Bradycardia or hypotension was listed if it required treatment or prolonged monitoring.
- ‡‡ Systemic complications in the endarterectomy group were infection (mainly pulmonary) in five patients, unstable angina in one, gastrointestinal bleeding in one, and subdural hematoma in one. Six of the eight events were associated with a delay in discharge.
- §§ Systemic complications in the stenting group were infection in two patients, pacemaker implantation in one, thrombocytopenia in one, and venous thrombosis in one. Four of these five events were associated with a delay in discharge.
- ¶¶ Two patients had two major local complications each.
- ¶¶¶ Hematoma was listed if it required surgery or blood transfusion.
- \*\*\* Infection was listed if it required surgery or parenteral antibiotic therapy.
- ††† Femoral pseudoaneurysm or arteriovenous fistula was listed if it required surgery.
- ‡‡‡ Occlusion or thrombosis was listed if it required percutaneous or surgical treatment.
- §§§ Nerve injury in the endarterectomy group was hypoglossal-nerve palsy in 10 patients, palsy of the marginal mandibular branch of the facial nerve in 7, recurrent laryngeal-nerve palsy in 2, and glossopharyngeal-nerve palsy in 1. At the 30-day follow-up visit, two of the cranial-nerve injuries (hypoglossal-nerve palsy in one patient and recurrent laryngeal-nerve palsy in one patient) were categorized as severe, one of them leading to delayed discharge.
- ¶¶¶¶ Nerve injury in the stenting group was hypoglossal-nerve palsy in two patients and Horner’s syndrome in one patient. The patient with Horner’s syndrome had carotid dissection during angioplasty. The other two patients had aborted angioplasty with conversion to surgery. At the 30-day follow-up visit, no cranial-nerve injury was categorized as severe.

**Table 4. Incidence of Primary Outcome Events at 6 Months.**

Event	Endarterectomy Group N = 262 <i>no. of patients (%)</i>	Stenting Group N = 265	P Value*
Any stroke or death at 30 days† plus ipsilateral stroke between 31 days and 6 mo	11 (4.2)	27 (10.2)	0.008
Any stroke or death at 30 days† plus any stroke between 31 days and 6 mo	12 (4.6)	29 (10.9)	0.007
Any stroke or death within 6 mo†	16 (6.1)	31 (11.7)	0.02

\* P values were obtained with the use of the log-rank test.

† Any stroke or death included a stroke in one patient between randomization and planned endarterectomy (which was canceled) and strokes in two patients between randomization and planned stenting (which was canceled in one patient).

ent endovascular techniques or different criteria for patient selection. The 30-day incidence of stroke after stenting in our study (9.2%) was higher than that in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial<sup>10</sup> (3.6%), despite the use of similar endovascular techniques. However, most patients (70%) included in the SAPPHIRE trial had asymptomatic stenosis, which carries a lower risk of stroke during carotid repair than does symptomatic stenosis.<sup>20,24</sup> Patients in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)<sup>5</sup> were similar to those in our trial, but the majority (77%) underwent carotid angioplasty without stenting, and procedures were not performed with the use of cerebral protection devices.

A potential bias in the comparison of a relatively new procedure such as stenting with an established procedure such as endarterectomy is the effect of the learning curve. Our trial involved centers with staff members who had various degrees of experience in carotid stenting, including centers in which investigators treated enrolled patients under the supervision of a tutor. We tried to limit the effect of the learning curve through the careful training and supervision of interventional physicians. We did not find any significant differences in outcome related to the number of stenting procedures performed in individual centers or to the experience of the interventional physicians, although these analyses were able to detect only large differences. There may also be a learning

curve related to changes in technique. Centers in our trial were not required to use a device from a particular manufacturer for stenting or cerebral protection, but experience with any new device was required before its use in the trial.

Cerebral-protection devices have been developed to reduce embolization of plaque fragments during stenting. Uncontrolled studies<sup>11,20,21</sup> suggest that these devices may reduce the risk of procedural stroke. However, one could argue that protection devices may cause additional adverse events in some patients and increase costs.

In summary, our results indicate that in patients with symptomatic carotid stenosis of 60% or more, treatment with endarterectomy results in lower rates of stroke or death at 30 days and 6 months than does stenting. Long-term follow-up is ongoing to determine whether the advantage of endarterectomy is sustained. A larger number of patients are required to provide definite answers about the risk–benefit profile of stenting, as compared with endarterectomy, and to permit meaningful subgroup analyses.

Supported by a grant from the Programme Hospitalier de Recherche Clinique of the French Ministry of Health (AOM 97066), Assistance Publique–Hôpitaux de Paris.

Dr. Beyssen reports having received lecture fees from ev3 and Guidant; and Dr. Becquemin, lecture fees from Cordis, Guidant, and Cook. No other potential conflict of interest relevant to this article was reported.

We are indebted to Véronique Favret, Ouafia Lakat, and Christine Mandet for their outstanding efforts in data management; to Ludovic Trinquart for statistical help; and to Joël Ménard and Nicolas Best for their constant support.

#### APPENDIX

The following investigators (with the number of patients randomly assigned at each center given in parentheses) and committees participated in the EVA-3S trial: **Hôpital Purpan, Toulouse (52)** — J.-F. Albuher, F. Chollet, H. Rousseau, C. Cognard, M. Degeilh, A. Barret, J.P. Bossavy; **Hôpital Rangueil, Toulouse (52)** — A. Viguier, V. Larrue, H. Rousseau, P. Arrué, P. Tall, Y. Glock; **Hôpital Sainte-Marguerite, Marseille (47)** — B. Denis, S. Cohen, F. Nicoli, J.M. Bartoli, P. Piquet; **Hôpital Nord, Hôpital de Bellevue, Saint-Etienne (43)**

— P. Garnier, C. Veyret, F.G. Barral, J.P. Favre, X. Barral; **Hôpital Côte de Nacre, Caen (40)** — F. Viader, A. Duretête, L. Carlier, J. Théron, P. Courthéoux, O. Coffin, D. Maïza; **Hôpital Sainte-Anne, Hôpital Cochin, Hôpital Georges Pompidou, Paris (29)** — E. Touzé, C. Arquizan, C. Lamy, D. Calvet, V. Domingo, B. Beyssen, J.F. Méder, D. Trystram, P.O. Sarfati, P. Julia, J.N. Fabiani; **Hôpital Général, Hôpital du Bocage, Dijon (28)** — M. Giroud, G.V. Osseby, O. Rouaud, I. Benatru, D. Krause, J.P. Cercueil, R. Brenot, M. David; **Hôpital Henri Mondor, Créteil (26)** — H. Hosseini, H. Kobeiter, J.-P. Becquemin, P. Desgranges; **Nouvelles Cliniques Nantaises, Nantes (21)** — G. Hinzelin, A. Bouyssou, J.-C. Pillet; **Hôpital Lariboisière, Paris (20)** — P. Favrole, K. Berthet, C. Gobron, M.G. Bousser, R. Chapot, E. Houdart, C. Petitjean; **Hôpital Roger Salengro, Lille (20)** — C. Lucas, H. Hénon, C. Lefebvre, D. Leys, M.A. Mackowiak-Cordoliani, X. Leclerc, J.-P. Pruvo, M. Koussa; **Hôpital La Milétrie, Poitiers (17)** — J.P. Neau, G. Godenèche, H. Moumy, J. Drouineau, J.B. Ricco; **Hôpital Central, Nancy, Hôpital Brabois, Vandoeuvre les Nancy (15)** — X. Ducrocq, J.C. Lacour, S. Bracard, C. Amicabile, O. Hassani, G. Fiévé; **Hôpital Charles Nicolle, Rouen (12)** — Y. Onnient, B. Mihout, E. Clavier, J. Thiebot, J. Watelet, D. Plissonnier; **Clinique Pasteur, Toulouse (11)** — J.R. Rouane, J.C. Laborde, B. Escude, F. Berthoumiou; **Fondation Hôpital Saint-Joseph, Marseille (12)** — R. Padovani, O. Bayle, P. Bergeron, J.M. Jausseran; **Hôpital La Timone, Marseille (10)** — L. Milandre, J.M. Bartoli, G. Moulin, A. Branchereau, P.E. Magnan; **Hôpital Pellegrin Tripode, Bordeaux (10)** — F. Rouanet, J. Berge, X. Barreau, D. Midy, J.C. Baste; **Hôpital Privé Beauregard, Marseille (10)** — H. Guinot, P. Commeau, F. Houel; **Hôpital Civil, Strasbourg (10)** — V. Wolff, J.M. Warter, R. Beaujeux, C. Jahn, J.G. Kretz; **Hôpital Bretonneau, Tours (9)** — D. Saudeau, I. Bonnaud, D. Herbreteau, P. Lermusiaux, R. Martinez; **Polyclinique, Essey-les-Nancy (8)** — I. Masson, M. Amor, J.P. Carpena, C. Amicabile; **Hôpital Saint-Roch et Hôpital Pasteur, Nice (6)** — M.H. Mahagne, J. Baque, J. Sedat, M. Dib, R. Hassen-Khodja, M. Batt; **Hôpital Saint-Jean, Perpignan (5)** — D. Sablot, J.L. Bertrand, M. Beaufigeau, G.A. Pelouze; **Hôpital Bichat-Claude Bernard, Paris (4)** — P. Amarenco, O. Simon, E. Meseguer, P. Lavallée, H. Abboud, E. Houdart, M. Mazighi, G. Lesèche; **Polyclinique du Bois, Lille (3)** — M. Combelles, V. Courteville, G. Gozet, C. Depriester, I. Lambert, J. Pommier; **Hôpital E. Muller, Mulhouse (3)** — G. Rodier, D. Weisse, J. Aventin, G. Dalcher; **Clinique du Belvédère, Nice (2)** — P. Marcel, P. Maillet, J.M. Gagliardi; **Hôpital Jean Minjot, Besançon (1)** — T. Moulin, J.-F. Bonneville, J.Y. Huart; **Fondation Saint-Joseph, Paris (1)** — C. Gauthier, J.M. Pernes, C. Laurian; **Scientific Committee** — J.-L. Mas (chair), G. Chatellier (cochair), J.-P. Becquemin, J.-F. Bonneville, A. Branchereau, D. Crochet, J.C. Gaux, V. Larrue, D. Leys, J. Watelet; **Events Committee** — T. Moulin (chair), S. Bracard, M. Hommel, J.L. Magne, F. Mounier-Vehier, S. Weber; **Accreditation Committee** — B. Beyssen (chair), J.-F. Bonneville, L. Boyer, J.P. Favre, M. Giroud, K. Hassen-Kodja, J.B. Ricco; **Imaging Committee** — J.-P. Pruvo (chair), J.F. Meder (cochair), C. Arquizan, F. Becker, F. Cattin, J.M. Debray, J.M. Jausseran, A. Long, O. Naggara, P.J. Touboul; **Safety Committee** — M. Lièvre (chair), J.P. Beregi, J. Bogousslavsky, M. Testart.

REFERENCES

1. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-87.
2. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415-25.
3. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107-16.
4. 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.
5. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729-37.
6. 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;38:1589-95.
7. Brooks WH, McClure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery* 2004;54:318-24.
8. Naylor AR, Bolia A, Abbott RJ, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg* 1998;28:326-34.
9. Alberts MJ. Results of a multicenter prospective randomized trial of carotid artery stenting versus carotid endarterectomy. *Stroke* 2001;32:325. abstract.
10. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493-501.
11. EVA-3S Investigators. Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial. *Cerebrovasc Dis* 2004;18:62-5.
12. Featherstone RL, Brown MM, Coward LJ. International Carotid Stenting Study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. *Cerebrovasc Dis* 2004;18:69-74.
13. Ringleb PA, Kunze A, Allenberg JR, et al. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy Trial. *Cerebrovasc Dis* 2004;18:66-8.
14. Hobson RW. CREST (Carotid Revascularization Endarterectomy versus Stent Trial): background, design, and current status. *Semin Vasc Surg* 2000;13:139-43.
15. North American Symptomatic Carotid Endarterectomy Trial: methods, patient characteristics, and progress. *Stroke* 1991;22:711-20.
16. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.
17. Mas JL, Chatellier G, Beyssen B. 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-e20.
18. Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials* 1982;3:345-53.
19. Rothwell PM, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. *Stroke* 1996;27:260-5.
20. Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. *Catheter Cardiovasc Interv* 2003;60:259-66.
21. 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;34:813-9.
22. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-53.
23. Pocock SJ. When (not) to stop a clinical trial for benefit. *JAMA* 2005;294:2228-30.
24. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 2003;34:2290-301.

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