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on behalf of the EVA-3S Investigators

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Original Contribution

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Jean-Louis Mas, MD; Caroline Arquizan, MD; David Calvet, PhD; Alain Viguier, MD; Jean-François Albucher, MD; Philippe Piquet, MD; Pierre Garnier, MD; Fausto Viader, MD; Maurice Giroud, MD; Hassan Hosseini, PhD; Grégoire Hinzelin, MD; Pascal Favrole, MD; Hilde Hénon, MD; Jean-Philippe Neau, MD; Xavier Ducrocq, MD; Raymond Padovani, MD; Loic Milandre, MD†; François Rouanet, MD; Valérie Wolff, MD; Denis Saudeau, MD; Marie-Hélène Mahagne, MD; Denis Sablot, MD; Pierre Amarenco, MD; Vincent Larrue, MD; Bernard Beyssen, MD; Didier Leys, PhD; Thierry Moulin, MD; Michel Lièvre, MD; Gilles Chatellier, MD; on behalf of the EVA-3S Investigators

Background and Purpose—We aimed at comparing the long-term benefit–risk balance of carotid stenting versus endarterectomy for symptomatic carotid stenosis.

Methods—Long-term follow-up study of patients included in Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S), a randomized, controlled trial of carotid stenting versus endarterectomy in 527 patients with recently symptomatic severe carotid stenosis, conducted in 30 centers in France. The main end point was a composite of any ipsilateral stroke after randomization or any procedural stroke or death.

Results—During a median follow-up of 7.1 years (interquartile range, 5.1–8.8 years; maximum 12.4 years), the primary end point occurred in 30 patients in the stenting group compared with 18 patients in the endarterectomy group. Cumulative probabilities of this outcome were 11.0% (95% confidence interval, 7.9–15.2) versus 6.3% (4.0–9.8) in the endarterectomy group at the 5-year follow-up (hazard ratio, 1.85; 1.00–3.40; P=0.04) and 11.5% (8.2–15.9) versus 7.6% (4.9–11.8; hazard ratio, 1.70; 0.95–3.06; P=0.07) at the 10-year follow-up. No difference was observed between treatment groups in the rates of ipsilateral stroke beyond the procedural period, severe carotid restenosis (≥70%) or occlusion, death, myocardial infarction, and revascularization procedures.

Conclusions—The long-term benefit–risk balance of carotid stenting versus endarterectomy for symptomatic carotid stenosis favored endarterectomy, a difference driven by a lower risk of procedural stroke after endarterectomy. Both techniques were associated with low and similar long-term risks of recurrent ipsilateral stroke beyond the procedural period.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00190398.

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Key Words: atherosclerosis ■ carotid stenosis ■ endarterectomy, carotid

Landmark studies have shown that carotid endarterectomy is effective in reducing the risk of stroke in patients with severe symptomatic carotid stenosis.[1] Compared with endarterectomy, carotid stenting has been associated with a higher risk of procedural stroke or death,[2–7] a difference mainly driven by nondisabling strokes.[6] In the first few years

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From the Hôpital Sainte-Anne, Université Paris-Descartes, INSERM U894, DHU Neurovasc-Paris Sorbonne, Paris, France (J.-L.M., D.C.); Hôpital Gui de Chauliac, Université Montpellier 1, Montpellier, France (C.A.); Hôpital Rangueil (A.V., V.L.) and Hôpital Purpan (J.-F.A.), Université Paul Sabatier, Toulouse, France; Hôpital de la Timone, Université de la Méditerranée, Marseille, France (P.P., L.M.); Hôpital Nord, Université Jean Monnet, Saint-Etienne, France (P.G.); Hôpital Côte de Nacre, Université de Caen, Caen, France (F.V.); Hôpital Général, Université de Bourgogne, Dijon, France (M.G.); Hôpital Henri Mondor, Université Paris-Val-de-Marne, Créteil, France (H. Hosseini); Nouvelles Cliniques Nantaises, Nantes, France (G.H.); Hôpital Lariboisière (P.F.) and Hôpital Bichat-Claude Bernard (P.A.), Université Paris Diderot, Paris, France; Hôpital Roger Salengro, Université du Droit et de la Santé, Lille, France (H. Hénon, D.L.); Hôpital La Milétrie, Université de Poitiers, Poitiers, France (J.-P.N.); Hôpital Saint-Julien, Université Henri Poincaré, Nancy, France (X.D.); Fondation Hôpital Saint-Joseph, Marseille, France (R.P.); Hôpital Pellegrin Tripode, Université de Bordeaux, Bordeaux, France (F.R.); Hôpital de Hautepierre, Université de Strasbourg, Strasbourg, France (V.W.); Hôpital Bretonneau, Université François Rabelais, Tours, France (D.S.); Hôpital Saint-Roch, Université Nice Sophia Antipolis, Nice, France (M.-H.M.); Hôpital Saint-Jean, Perpignan, France (D.S.); Hôpital Européen Georges Pompidou, Université Paris-Descartes, Paris, France (B.B., G.C.); Hôpital Jean Minjoz, Université de Franche-Comté, Besançon, France (T.M.); and Université Claude Bernard, Lyon, France (M.L.).

†Deceased.

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Correspondence to Jean-Louis Mas, MD, Service de Neurologie, Hôpital Sainte-Anne, 1 rue Cabanis, 75014 Paris, France. E-mail jl.mas@ch-sainte-anne.fr

after treatment, both procedures seem equally effective in preventing recurrent ipsilateral strokes,[5,7–12] but little is known on the long-term efficacy of carotid stenting beyond the first few years after the procedure. As carotid stenting safety is likely to improve with better patient selection,[6,11,12] technical improvements, and additional operator experience[13] and may become a safe alternative to endarterectomy, at least in certain patient subgroups, it is crucial to know whether stenting is as effective as endarterectomy to prevent stroke recurrence in the long term.

The objectives of this study were to compare the long-term benefit–risk balance of carotid stenting versus endarterectomy in patients with severe symptomatic carotid stenosis included in EVA-3S, as well as the long-term efficacy of the 2 treatments in terms of prevention of recurrent ipsilateral stroke beyond the procedural period and incidence of severe carotid restenosis or occlusion.

Methods

EVA-3S

EVA-3S was a prospective, randomized, open, blinded end point study of carotid stenting versus endarterectomy in patients with recently symptomatic severe carotid stenosis. The design of the trial has been reported previously.[2,14] Briefly, patients aged ≥18 years were eligible if they had had a hemispheric or retinal transient ischemic attack or a nondisabling stroke (or retinal infarct) within 120 days before enrolment and had an atherosclerotic stenosis of 60 to 99% of the symptomatic carotid artery, as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.[15] Patients who were suitable candidates for both techniques were randomly assigned to undergo carotid stenting or endarterectomy. Details of inclusion criteria, randomization methods, investigator requirements, and revascularization procedures can be found in the Material in the online-only Data Supplement.

A total of 527 patients were enrolled from November 2000 to September 2005, at which time the safety committee recommended to stop enrollment for safety reasons. Patients were followed prospectively every 6 months by the study neurologists until December 2007. The study protocol included carotid ultrasound at 1 month, 6 months, and every 6 months thereafter for 3 years after revascularization or until the end of the trial (December 2007). The results of the trial up to December 2007 have been reported previously.[2,10,16]

Long-Term Follow-Up Study

The patients' subsequent outcome (from January 2008 up to December 2012) was established retrospectively between December 2011 and December 2012 using complementary methods. Vital status of all patients was ascertained through municipal death registries. Trained clinical research assistants reviewed hospital medical records of all patients and conducted a structured telephone interview with the patients or their relatives (for deceased patients and those unable to communicate effectively). The interview included questions aimed at detecting the occurrence of stroke, myocardial infarction, and performance of revascularization procedures. We used the Questionnaire for Verifying Stroke-Free Status[17] to identify stroke-free individuals. For deceased patients and those who were suspected of having had a recurrent stroke or any other vascular event, all existing clinical information and results of investigations were obtained from records held by hospitals and physicians in private practice. In addition, a neurologist (J.L.M.) contacted the patient, his or her relatives, and the physicians in charge of the patient at the time of the event.

All patients were asked in 2011 to 2012 to have an additional duplex ultrasound at their usual ultrasound laboratory, including measurement of peak systolic velocities in carotid arteries and degree of stenosis according to the NASCET method.[15] For deceased patients and those not willing to undergo carotid ultrasound, reports of the last available ultrasound examination were collected.

Two physicians blinded to study group assignments independently adjudicated outcome events (J.L.M., G.C.) and assessed the presence of carotid restenosis (C.A., J.L.M.) using the last available ultrasound report. Stroke was defined as a focal neurological impairment of sudden onset and lasting >24 hours (or leading to death) and of presumed vascular origin. Stroke was defined as ischemic or hemorrhagic based on neuroimaging. Ipsilateral stroke was defined as infarction or hemorrhage located in the territory of the randomized carotid artery. Nonipsilateral stroke was defined as stroke located in the contralateral carotid or vertebrobasilar territories. Stroke was defined as disabling if the modified Rankin scale score[18] was 3 points or more for ≥30 days after the event. Fatal stroke was defined as death from any cause within 30 days of stroke. Stroke was defined as procedural if it occurred within 30 days of treatment and postprocedural if it occurred from day 31 to the end of follow-up. Myocardial infarction was defined by ≥2 of the following: typical chest pain lasting ≥20 minutes; serum levels of creatin kinase, creatin kinase MB, or troponin at least twice the upper limit of the normal range; and new Q wave on ≥2 adjacent derivations or predominant R waves in V1 (R wave ≥1 mm >S wave in V1). Fatal myocardial infarction (MI) was defined as death from any cause within 30 days of MI.

Carotid restenosis of ≥70% was diagnosed when it was present on either velocity parameters, using a peak systolic velocity threshold of 2.1 m/s,[19] or planimetry. Carotid occlusion was established on duplex ultrasonography when no flow signal was detected within the internal carotid artery. We also assessed the rate of carotid restenosis using a peak systolic velocity threshold of 3 m/s.

Statistical Analysis

The primary end point of EVA-3S was the rate of any stroke or death within 30 days after the procedure. Analysis of this end point has been reported previously.[2] The prespecified main end point for the long-term benefit–risk analysis was a composite of any ipsilateral stroke after randomization or any procedural stroke (including retinal infarct) or death.[2,14]

This analysis was conducted in all randomized patients, irrespective of which treatment was administered (intention-to-treat population). Other end points were any stroke or procedural death, any fatal or disabling stroke or procedural death, and all-cause death.

We also conducted an efficacy analysis to compare the risks of postprocedural ipsilateral stroke, stroke in any territory, and disabling or fatal stroke in patients treated with stenting versus endarterectomy. We focused on patients who received their assigned treatment (per-protocol population) and on strokes that occurred from day 31 after treatment up to December 2012 or earlier death or withdrawal from the trial. Patients who died in the procedural period were subtracted from the total number of patients analyzed. The frequency of restenosis or occlusion was assessed from the day of the allocated treatment to the date of the most recent ultrasound examination.

We estimated the probability of events at 5 and 10 years with the Kaplan–Meier method and their 95% confidence intervals (95% CI) with the Rothman formula.[20] As the incidence and causes of death did not differ between groups, censoring was assumed to be noninformative. Cox proportional hazard models were used to calculate hazard ratios (HRs; stenting versus endarterectomy), 95% CI, and corresponding *P* values. Analyses were done with SPSS (version 19).

To assess a potential underestimation of stroke rates during the retrospective period of the study, from January 2008 (when in-person visits with the study neurologist stopped) to December 2012, we compared the 4-year cumulative probability of any stroke during the retrospective study period to that the previously reported 4-year cumulative probability of any stroke during the prospective period (up to December 2007).[10] We also compared the relative proportion of postprocedural disabling (or fatal) versus nondisabling strokes between the 2 study periods.

The study was approved by the ethics committee of Ile de France 2 (Paris, France). All patients gave informed consent.

Results

Of 527 randomized patients, 265 were assigned to stenting and 262 to endarterectomy (Figure 1). The 2 groups were well balanced with respect to the baseline characteristics of the patients, except for a greater proportion of patients with a prior history of stroke in the endarterectomy group (Table I in the online-only Data Supplement). Complete follow-up until death or the final telephone interview was obtained in 493 of the 527 patients (94%). Thirty-four patients (16 in the stenting group and 18 in the endarterectomy group) refused to participate or were lost to follow-up. For these patients, we used the last information available in medical records. A total of 3534 patient-years of follow-up were accumulated, with a median of 7.1 years (interquartile range, 5.1–8.8 years), and a maximum of 12.4 years. The duration of follow-up was similar in patients allocated to stenting (median, 7.1 years; interquartile range, 5.0–8.8) and those allocated to endarterectomy (median, 7.2 years; interquartile range, 5.2–8.7).

At the 5-year follow-up, the main end point (ipsilateral stroke after randomization or procedural stroke or death) had occurred in 29 of the 265 patients who were assigned to stenting and in 16 of the 262 patients who were assigned to endarterectomy (cumulative probability 11.0% versus 6.3%; 5-year absolute risk reduction 4.7%; number needed to treat, 21.3). The HR for stenting versus endarterectomy was 1.85 (95% CI, 1.00–3.40; P=0.04). At the 10-year follow-up, this end point had occurred in 30 patients in the stenting group and 18 in the endarterectomy group (cumulative probability 11.5% versus 7.6%; HR, 1.70; 95% CI, 0.95–3.06; P=0.07). The rates of any stroke or procedural death and of fatal or disabling stroke or procedural death did not differ significantly between groups (Tables 1 and 2; Figure 2). The 10-year cumulative rates of death were 39.0% in the stenting group and 38.7% in the endarterectomy group (HR, 1.00; 95% CI, 0.77–1.33; P=0.97), with no difference in the causes of death between groups (P=0.78; χ^2 test). The frequency of MI and revascularization procedures did not differ between groups (Table 1).

Among 527 randomized patients, 504 (247 in the stenting group and 257 in the endarterectomy group) were available for the per-protocol analysis (Figure 1). Patients excluded from this analysis did not differ from those who were included with respect to main baseline characteristics. After the procedural period, ipsilateral stroke occurred in 6 patients in the stenting group and 8 patients in the endarterectomy group (HR, 0.79; 95% CI, 0.28–2.29; P=0.67). Similarly, the rates of nonipsilateral stroke, stroke in any territory, and disabling or fatal stroke did not differ between groups (Tables 1 and 3; Figure 2). The 4-year cumulative risks of postprocedural stroke were similar in the prospective (4.8%; 95% CI, 2.6–7.0) and retrospective periods of the study (4.4%; 95% CI, 2.2–6,6), and the relative proportion of disabling (or fatal) versus nondisabling strokes did not differ between the 2 periods (P=0.29, Fisher exact test).

A total of 2700 patient-years of follow-up were accumulated up to the date of the last ultrasound, with a median of 6.1 years (interquartile range, 2.5–7.0) and no difference between treatment groups (P=0.13; Mann–Whitney test). At the 10-year follow-up, 7 patients had carotid restenosis of ≥70% (n=6) or occlusion (n=1) after stenting, compared with 12 patients (9 with restenosis, 3 with occlusion) after endarterectomy (HR, 0.58; 95% CI, 0.23–1.48; P=0.26; Table 3). When carotid peak systolic velocities of >300 cm/s were used to define severe carotid restenosis of ≥70%, 5 patients in the stenting group versus 8 in the endarterectomy group (HR, 0.63; 95% CI, 0.21–1.93; P=0.42) were found to have carotid restenosis or occlusion. Recurrent ipsilateral stroke occurred in 1 (assigned to endarterectomy) of the 19 patients with restenosis or occlusion (3.4%) compared with 13 (6 assigned to stenting and 7 to endarterectomy) of the 478 patients (2.7%) without restenosis (P=0.33, Fisher exact test). Of the 15 patients with carotid restenosis, 7 had carotid revascularization (Table 1).

Discussion

In this long-term follow-up study of patients with symptomatic carotid stenosis included in EVA-3S, the main end point combining safety (any procedural stroke or death) and efficacy (ipsilateral stroke) favored endarterectomy. The 5-year risk of this end point was significantly higher in patients assigned to stenting than in those assigned to endarterectomy, whereas the 10-year risks differed marginally. By contrast, similar low rates of ipsilateral stroke were seen beyond the procedural period after either stenting or endarterectomy. Both techniques were also associated with low risks of carotid restenosis of ≥70% or occlusion and low rates of ipsilateral

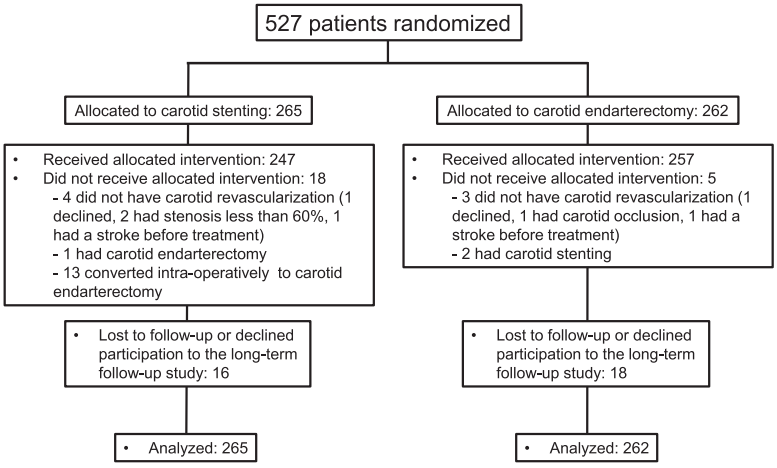

Figure 1. Flow diagram.

Table 1. Major Outcome Events

	Intention-to-Treat Population		Per-Protocol Population	
	Stenting (n=265)	Endarterectomy (n=262)	Stenting (n=247)	Endarterectomy (n=257)
Stroke (fatal, disabling, nondisabling), n patients				
Procedural (within 30 d of the procedure)	24 (1, 7, 16)	9 (2, 1, 6)	22 (1, 7, 14)	9 (2, 1, 6)
Nonprocedural				
From randomization to the procedure	2* (0, 1, 1)	1* (0, 1, 0)	1* (0, 0, 1)	0
Postprocedural (from day 31 to end of follow-up)	19†	24‡	19†	22‡
Ipsilateral	6§ (2, 2, 2)	8‖ (3, 0, 5)	6§ (2, 2, 2)	8‖ (3, 0, 5)
Nonipsilateral	14¶ (5, 3, 6)	17# (3, 7, 7)	14¶ (5, 3, 6)	15** (2, 7, 6)
Death, n patients	93	97	86	95
Procedural				
Fatal stroke	1	2	1	2
Nonstroke death	1	1	1	1
Nonprocedural				
Fatal stroke	7	6	7	5
Nonstroke vascular death	27	24	23	24
Nonvascular death	48	57	45	56
Unknown cause	9	7	9	7
Myocardial infarction, n patients	14	21	12	21
Procedural (fatal, nonfatal)	1 (1, 0)	2 (0, 2)	1 (1, 0)	2 (0, 2)
Nonprocedural (fatal, nonfatal)	13 (4, 9)	19 (5, 14)	11 (4, 7)	19 (5, 14)
Death because of MI or sudden death	11	16	10	16
Carotid revascularization, n patients	33††	28‡‡	30††	27§§
Ipsilateral (stenting, endarterectomy)	4‖‖ (4, 0)	4¶¶ (2, 2)	3‖ (3, 0)	4¶¶ (2, 2)
Contralateral (stenting, endarterectomy)	30## (5, 25)	26*** (3, 23)	28## (5, 23)	24*** (2, 22)
Other revascularization, n patients				
Coronary (stenting, surgery)	17 (15, 2)	18 (14, 4)	16 (14, 2)	18 (14, 4)
Other	12	14	11	14

*All patients had ipsilateral ischemic stroke.
†One patient had a nondisabling ipsilateral stroke, then a fatal nonipsilateral stroke.
‡One patient had a disabling nonipsilateral stroke, then a fatal ipsilateral stroke.
§Five patients had an ischemic stroke, 1 patient had a hemorrhagic stroke. Three patients also had a procedural ipsilateral stroke.
‖Seven patients had an ischemic stroke, 1 patient had a hemorrhagic stroke. One patient also had a procedural ipsilateral stroke.
¶Nine patients had an ischemic stroke, 5 patients had a hemorrhagic stroke.
#Fifteen patients had ischemic stroke, 2 patients had hemorrhagic stroke.
**Fourteen patients had ischemic stroke, 1 patient had hemorrhagic stroke.
††One patient had ipsilateral stenting (asymptomatic stenosis), then contralateral endarterectomy (asymptomatic stenosis).
‡‡One patient had ipsilateral stenting (asymptomatic stenosis), then contralateral stenting (asymptomatic stenosis). Another patient had ipsilateral endarterectomy (asymptomatic stenosis), then contralateral endarterectomy (asymptomatic stenosis).
§§One patient had ipsilateral endarterectomy (asymptomatic stenosis), then contralateral endarterectomy (asymptomatic stenosis).
‖‖One patient had symptomatic stenosis.
¶¶All patients were asymptomatic.
##Four patients had symptomatic stenosis.
***Three patients had symptomatic stenosis.

carotid revascularization. The long-term prognosis of patients did not differ between groups with regard to rates of death, myocardial infarction, and revascularization procedures.

Our results are in line with previous randomized clinical trials of stenting versus endarterectomy for symptomatic stenosis. These studies showed that the excess risk of stroke associated with stenting compared with endarterectomy was mainly driven by a significant increased risk of procedural nondisabling strokes whereas there was no significant difference in the occurrence of postprocedural ipsilateral strokes.[5,7–10] Previous studies, however, only reported on outcomes that occurred during the first few years after revascularization. In our study, the similar protection against postprocedural ipsilateral stroke conferred by both techniques extended over ≥10 years after the procedures. Taken together, randomized clinical trials strongly suggest that stenting is as effective as surgery to prevent postprocedural ipsilateral stroke, although none of these randomized clinical trials was powered to show

Table 2. Cumulative Probability of Stroke and Death ≤10 Years*

	5-Year Risk (95% CI)					10-Year Risk (95% CI)				
	n	Stenting	n	Endarterectomy	HR (95% CI) *P* Value	n	Stenting	n	Endarterectomy	HR (95% CI) *P* Value
Main outcome										
Any ipsilateral stroke or procedural stroke or death	29	11.0 (7.9–15.2)	16	6.3 (4.0–9.8)	1.85 (1.00–3.40) *P*=0.04	30	11.5 (8.2–15.9)	18	7.6 (4.9–11.8)	1.70 (0.95–3.06) *P*=0.07
Other outcomes										
Any stroke or procedural death	38	14.7 (11.0–19.5)	28	11.4 (8.1–15.8)	1.40 (0.86–2.29) *P*=0.17	43	17.4 (13.3–22.5)	34	15.4 (11.1–21.1)	1.31 (0.84–2.06) *P*=0.24
Any fatal or disabling stroke or procedural death	17	6.7 (4.3–10.5)	12	4.9 (2.9–8.3)	1.43 (0.68–2.98) *P*=0.35	22	9.4 (6.4–13.7)	17	8.5 (5.4–13.4)	1.30 (0.69–2.46) *P*=0.41
Death	58	22.1 (17.5–27.5)	54	20.8 (16.4–26.1)	1.08 (0.74–1.56) *P*=0.69	92	39.0 (32.5–45.9)	93	38.7 (32.5–45.3)	1.00 (0.75–1.33) *P*=0.97

CI indicates confidence interval; and HR, hazard ratio.

*Analyses were conducted in the intention-to-treat population using the first occurrence of the relevant outcome event from randomization ≤5 and 10 y.

a difference between treatments (≥9000 patients would be needed to show a 33% relative difference between stenting and surgery, assuming a 10-year risk of ipsilateral stroke of 5%, a 2-sided type 1 error risk of 5% and a power of 80%).

On the basis of experience with coronary bare-metal stenting, concerns have been raised that carotid stenting could be associated with higher rates or carotid restenosis compared with endarterectomy. A meta-analysis of previous randomized trials[7] showed no significant increase in severe restenosis after primary stenting compared with endarterectomy, albeit with both a wide confidence interval around the effect estimate and evidence of substantial heterogeneity. The heterogeneity between studies may be partly explained by differences in ultrasound criteria used for the diagnosis of restenosis. Reduction of compliance of stented carotid arteries could increase peak systolic velocities, leading some authors[21,22] to recommend a threshold of 3 m/s instead of 2.1 m/s to define carotid restenosis of ≥70% to avoid overestimation of carotid restenosis in patients who received stents. In the most comprehensive analysis of restenosis after carotid revascularization reported by the

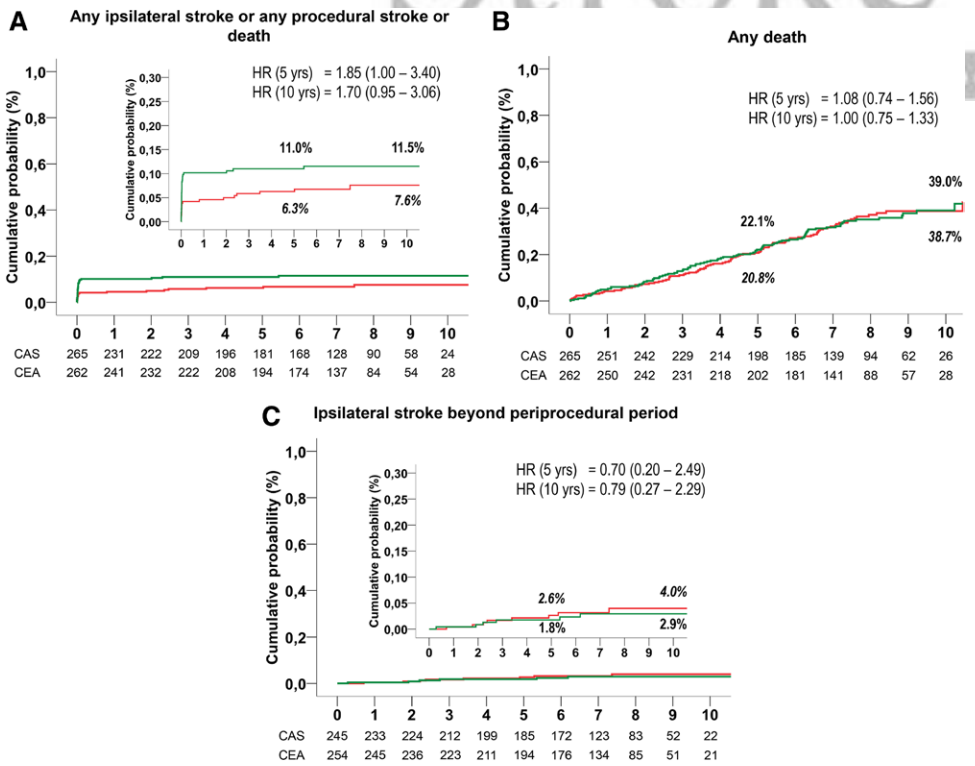

Figure 2. Kaplan–Meier cumulative probability of major outcomes. **A** and **B** are analyzed from the day of randomization in the intention-to-treat population, whereas **C** is analyzed from day 31 after completed treatment in the per-protocol population. Of 504 patients available for the per-protocol analysis, 5 died with 30 days of treatment, leaving 499 patients at risk (245 in the stenting group and 254 in the endarterectomy group). The numbers below the panels are the numbers of patients in each group who were event free and still at risk during each year of follow-up. Also shown are cumulative probabilities of end points at 5 and 10 years (in italics for endarterectomy). CAS indicates carotid artery stenting (curves are in green); and CEA, carotid endarterectomy (curves in red).

Table 3. Cumulative Probability of Postprocedural Stroke and Carotid Restenosis or Occlusion ≤10 Years*

	5-Year Risk (95% CI)					10-Year Risk (95% CI)				
	n	Stenting	n	Endarterectomy	HR (95% CI) *P* Value	n	Stenting	n	Endarterectomy	HR (95% CI) *P* Value
Ipsilateral stroke†	4	1.8 (0.9–4.4)	6	2.6 (1.3–5.5)	0.70 (0.20–2.49) *P*=0.58	6	2.9 (1.5–6.1)	8	4.0 (2.2–7.6)	0.79 (0.27–2.29) *P*=0.67
Nonipsilateral stroke†	11	5.1 (3.0–8.8)	11	4.9 (2.9–8.3)	1.07 (0.46–2.46) *P*=0.88	14	6.9 (4.3–11.2)	15	7.7 (4.8–12.4)	0.99 (0.48–2.06) *P*=0.99
Any stroke†	14	6.4 (3.9–10.5)	17	7.4 (4.8–11.4)	0.87 (0.43–1.77) *P*=0.71	19	9.3 (6.1–10.4)	22	10.7 (7.1–15.9)	0.91 (0.50–1.69) *P*=0.77
Fatal or disabling stroke†	8	3.7 (2.0–7.0)	8	3.6 (2.0–6.6)	1.06 (0.40–2.82) *P*=0.91	12	5.8 (3.7–10.2)	11	6.1 (3.3–10.2)	1.15 (0.51–2.62) *P*=0.73
Carotid restenosis ≥70% or occlusion‡	5	2.3 (1.2–5.0)	10	4.2 (2.4–7.4)	0.52 (0.18–1.51) *P*=0.23	7	5.0 (2.5–11.2)	12	8.3 (4.4–16.0)	0.58 (0.23–1.48) *P*=0.26

CI indicates confidence interval; and HR, hazard ratio.

*Analyses were conducted in patients who received their assigned treatment (per-protocol population) using outcomes that occurred from day 31 after completed treatment ≤10 y for stroke outcomes or from completed treatment ≤10 y for carotid restenosis or occlusion.

†Of 504 patients available for the per-protocol analysis, 5 died within 30 d of treatment, leaving 499 patients at risk (245 in the stenting group and 254 in the endarterectomy group).

‡Of 504 patients available for the per-protocol analysis, 7 did not have carotid duplex ultrasonography after revascularization (3 in the stenting group and 4 in the endarterectomy group), leaving 497 patients at risk (244 in the stenting group and 253 in the endarterectomy group).

Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) investigators,[22] both procedures were associated with similar 2-year rates of restenosis. Our results provide reassurance that carotid stenting is as durable as carotid endarterectomy, by showing similar low rates of severe restenosis in both groups ≤10 years after revascularization, whatever the threshold used to define carotid restenosis. We found no association between restenosis and recurrent events, which is difficult to interpret because of the small numbers of recurrent events and restenosis seen in our study.

Procedural myocardial infarction has been reported to be more common after endarterectomy than after carotid stenting[5,23] and has been associated with higher late mortality in different settings.[24] Whether procedural myocardial infarction adds further to the risk of late mortality or (only) identifies a population of patients at greater risk of death in longer-term follow-up is unclear. In EVA-3S, there was no indication that the risk of late mortality, vascular mortality, or mortality because of MI was higher after endarterectomy versus carotid stenting.

To improve the risk–benefit profile of stenting, there is a need to establish which factors among characteristics of patients, operator experience, and the procedure itself are associated with a high risk of stroke after carotid stenting. In this respect, there is strong evidence that both procedures carry similar risks of procedural stroke or death in patients <70 years, whereas in older patients, the risk with stenting is about twice that with endarterectomy.[6,11] The severity of white matter damage on neuroimaging has been associated with an increased risk of procedural stroke after stenting.[12] We also reported that the risk of stenting is lower when the procedure is performed by operators with annual volume ≥6 procedures per year.[13] Technical aspects of stenting including stent systems and use of cerebral protection devices[25] also have an impact on the procedural complication rate. Finally, the increase in risk of stenting compared with surgery seems to be greatest in patients treated within 7 days of the onset of symptoms.[26]

The strengths of this study include the randomized design with blinded assessment of clinical outcomes, the long-term follow-up of patients and the low and similar dropout rates in the 2 groups. Our study has potential limitations. First, the retrospective methods used for ascertaining events during the second study period may have underestimated rates of stroke, in particular of minor stroke. However, underestimation of stroke rate (if any) is likely to have been minimal because the rates of (postprocedural) stroke were similar (≈1% per year) in both study periods and close to the rates reported after carotid revascularization in recent randomized trials.[5,27] In addition, there was no difference in the relative proportion of nondisabling strokes between the 2 study periods, suggesting no or limited under-reporting of minor events. Moreover, under-recognition of stroke is unlikely to differ between the 2 treatment groups. Second, final Doppler ultrasound exams were done at local ultrasound laboratories, which may have induced some heterogeneity in measurements. However, our long-term results on severe restenosis or occlusion are consistent with our previous findings at 3 years based on a standardized evaluation.[16] Third, difference in risk factor management and antithrombotic treatment between groups may introduce a bias in the evaluation of outcome. We previously reported[10] that at the 4-year follow-up, the 2 groups were well balanced with regard to management of risk factors and use of antiplatelet drugs. We did not investigate this in the second study period, but it is unlikely that preventive measures differed between the 2 groups when in-person visits with the study neurologist stopped. Fourth, the number of patients included in EVA-3S was lower than expected because of early discontinuation of the study and the rate of postprocedural ipsilateral stroke

was low, leading to large confidence intervals around the point estimate.

Conclusions

The long-term benefit–risk balance of carotid stenting versus endarterectomy in patients with severe symptomatic carotid stenosis included in EVA-3S favors endarterectomy. The difference is mainly driven by a significant increased risk of procedural stroke while both techniques were associated with low and similar long-term risks of recurrent ipsilateral stroke beyond the procedural period. In view of the low rate of ipsilateral stroke after successful carotid revascularization either by stenting or surgery, stenting could become an alternative to endarterectomy in patients with symptomatic stenosis who have similar procedural risk after stenting or endarterectomy (eg, patients <70 years), at centers in which procedures are performed by board-certified endovascular specialists.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Supplemental 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 nonacademic centers in France.

Inclusion/Non-Inclusion Criteria

- 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 randomisation, and if they had an atherosclerotic stenosis of 60 to 99% in the symptomatic carotid artery, as determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. The presence of a 60% or more ipsilateral carotid stenosis had to be confirmed by conventional digital subtraction angiography or the combination of carotid duplex scanning and magnetic resonance angiography, provided the results of these noninvasive techniques were concordant.
- Patients were excluded if one of the following was present: a modified Rankin score of 3 or more (disabling stroke) (on a scale of 0 to 5, with higher scores indicating more severe disability); non-atherosclerotic 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; percutaneous or surgical intervention within 30 days before or after the study procedure.

Randomisation.

- Patients who were considered suitable candidates for both techniques were randomly assigned to undergo carotid 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 ≥90% or <90%).

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 study neurologists did the initial and follow-up evaluations at 48 h, 30 days, and 6 months after treatment and then every 6 months thereafter. He or she had to document experience in the care of stroke patients (including the use of stroke scales) and prior participation in randomized clinical trials.
- The vascular surgeons had to have performed at least 25 endarterectomies in the year preceding the entry into the study.
- The interventional physicians 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 (no operator joined the trial based on this latter criterion).

Investigators who did not fulfill the requirements with regard to experience were in procedural training and had to do all stenting procedures together with and under the supervision of experienced tutors (nominated by an accreditation committee) until they had done at least 12 carotid stenting procedures and were considered self-sufficient by their tutor.

Procedures

- 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. In January 2003, the safety committee recommended the systematic use of cerebral protection devices because of a higher risk of stroke in patients treated without cerebral protection. Patients had to be given aspirin (100–300 mg) and clopidogrel (75 mg) or ticlopidine (500 mg) for at least 3 days before and for 30 days after stenting. A special committee of the study decided on the stents and distal protection devices that could be used in the study. As regards new devices that were approved by the committee, interventionalists had to document at least 2 cases of patients treated with the new device outside the trial, before using it in the trial.
- The goal was for endarterectomy and stenting to be performed within 2 weeks after randomization.

Committees and investigators

Committees
Scientific Committee — J.-L. Mas (chair), G. Chatellier (co-chair), 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.

Investigators
The following investigators (with the number of patients randomly assigned at each center given in parentheses) participated in the EVA-3S trial:
Hôpital Purpan, Toulouse (52) — J.-F. Albucher, 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. Carluer, 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. Domigo, 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. Berthoumieu;
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 Minjoz, Besançon (1) — T. Moulin, J.-F. Bonneville, J.Y. Huart;
Fondation Saint-Joseph, Paris (1) — C. Gauthier, J.M. Pernes, C. Laurian.

Supplemental Table I: Baseline characteristics of the patients

	Intention-to-treat population			Per-protocol population		
	Stenting N = 265	**Endarterectomy** N = 262	**p**	**Stenting** N = 247	**Endarterectomy** N = 257	**p**
Age (years)	69.1 ±10.3	70.2 ± 10.7	0.20	69.0 ± 10.1	70.2 ±10.7	0.21
Male	193 (72.8%)	204 (77.9%)	0.18	180 (72.9%)	200 (77.8%)	0.20
Vascular risk factors						
Hypertension*	193 (72.8%)	190 (72.5%)	0.94	181 (73.3%)	187 (72.8%)	0.90
Diabetes mellitus*	59 (22.3%)	67 (25.6%)	0.37	56 (22.7%)	64 (24.9%)	0.56
Hypercholesterolemia*	154 (58.1%)	146 (55.7%)	0.58	144 (58.3%)	143 (55.6%)	0.55
Tobacco use†	61 (23.3%)	65 (24.5%)	0.74	60 (24.3%)	61 (23.7%)	0.88
Prior history of vascular disease						
Stroke	35 (13.2%)	52 (19.8%)	0.04	31 (12.6%)	51 (19.8%)	0.03
Transient Ischemic attack	68 (25.7%)	60 (22.9%)	0.46	62 (25.1%)	59 (23.0%)	0.57
Myocardial infarction	28 (10.6%)	35 (13.4%)	0.32	28 (11.3%)	34 (13.2%)	0.52
Peripheral arterial disease	40 (15.1%)	30 (11.5%)	0.22	35 (14.2%)	30 (11.7%)	0.40
Cardiac failure leading to hospitalization	7 (2.6%)	7 (2.7%)	0.98	7 (2.8%)	7 (2.7%)	0.94
Prior surgery or angioplasty						
Coronary artery	35 (13.2%)	35 (13.4%)	0.96	35 (14.2%)	34 (13.2%)	0.76
Contralateral carotid artery	6 (2.3%)	10 (3.8%)	0.30	5 (2.0%)	10 (3.9%)	0.22

Qualifying event			0.45			0.48
Cerebral TIA	97 (36.6%)	79 (30.2%)		90 (36.4%)	78 (30.4%)	
Ocular TIA	34 (12.8%)	37 (14.1%)		29 (11.7%)	36 (14.0%)	
Ischemic stroke	128 (48.3%)	141 (53.8%)		122 (49.4%)	138 (53.7%)	
Retinal infarct	6 (2.3%)	5 (1.9%)		6 (2.4%)	5 (1.9%)	
Rankin score at randomization ‡			0.96			0.86
0	142 (53.6%)	146 (55.7%)		131 (53.0%)	144 (56.0%)	
1	72 (27.2%)	69 (26.3%)		68 (27.5%)	68 (26.5%)	
2	47 (17.7%)	43 (16.4%)		45 (18.2%)	41 (16.0%)	
3	4 (1.5%)	4 (1.5%)		3 (1.2%)	4 (1.6%)	
Degree of symptomatic carotid stenosis reported by investigators§			0.68			0.67
60 – 69%	15 (5.7%)	21 (8.0%)		15 (6.1%)	21 (8.2%)	
70 – 79%	58 (21.9%)	56 (21.4%)		53 (21.5%)	55 (21.4%)	
80 – 89%	87 (32.8%)	78 (29.8%)		83 (33.6%)	76 (29.6%)	
90 – 99%	105 (39.6%)	107 (40.8%)		96 (38.9%)	105 (40.9%)	
Contralateral carotid (70 – 99%) stenosis or occlusion	28 (10.6%)	25 (9.5%)	0.68	27 (11.0%)	25 (9.8%)	0.65

Data are n (%), or mean (±SD), or %.
* diagnosed before qualifying event
† one cigarette or more per day
‡ the scale runs from 0-6, from perfect health without symptoms to death; 3 or more indicates at least moderate disability, with the need for some help in daily affairs.
§ the degree of stenosis was measured on digital subtraction angiography or magnetic resonance angiography, according to the NASCET method.