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Long-Term Durability of Carotid Endarterectomy for Symptomatic Stenosis and Risk Factors for Late Postoperative Stroke

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Background and Purpose—Carotid endarterectomy (CEA) reduces the risk of stroke ipsilateral to recently symptomatic severe carotid stenosis. Other techniques such as percutaneous transluminal angioplasty with stenting are currently being compared with CEA. Thus far, case series and several small, randomized, controlled trials of CEA versus percutaneous transluminal angioplasty (with and without stenting) have focused primarily on the 30-day procedural risks of stroke and death. However, long-term durability is also important. To determine the long-term risk of stroke after CEA and to identify risk factors, we studied patients in the European Carotid Study Trial (ECST), the largest published cohort with long-term follow-up by physicians after CEA.

Methods—Risks of ipsilateral carotid territory ischemic stroke were calculated by Kaplan-Meier analysis starting on the 30th day after CEA in 1728 patients who underwent trial surgery. Risk factors were determined by Cox regression. For comparison, we also determined the “background” risk of stroke on medical treatment in the ECST in the territory of 558 previously asymptomatic contralateral carotid arteries with <30% angiographic stenosis (ECST method) at randomization.

Results—The risks of disabling ipsilateral ischemic stroke and any ipsilateral ischemic stroke were constant after CEA, reaching 4.4% [95% confidence interval (CI), 3.0 to 5.8] and 9.7% (95% CI, 7.6 to 11.7), respectively, by 10 years. The equivalent ischemic stroke risks distal to contralateral <30% asymptomatic carotid stenoses were 1.9% (95% CI, 0.8 to 3.2) and 4.5% (95% CI, 1.5 to 7.4). Presentation with cerebral symptoms, diabetes, elevated systolic blood pressure, smoking, male sex, increasing age, and a lesser severity of preoperative stenosis were associated with an increased risk of late stroke after CEA, but plaque morphology and patch grafting were not.

Conclusions—Although the risk of late ipsilateral ischemic stroke after CEA for symptomatic stenosis is approximately double the background risk in the territory of <30% asymptomatic stenosis, it is still only ≈1% per year and remains low for at least 10 years after CEA. This is the standard against which alternative treatments should be judged. Several risk factors may be useful in identifying patients at particularly high risk of late postoperative stroke. (*Stroke*. 2002;33:2658-2663.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ risk factors

Carotid endarterectomy (CEA) has been shown to reduce the risk of stroke in patients with recently symptomatic severe carotid stenosis¹⁻³ and is currently the treatment of choice. In the United States, ≈150 000 endarterectomies were performed in 1998,⁴ and rates continue to rise in Europe.⁵ Recently, however, percutaneous transluminal angioplasty (PTA) with stenting has also been promoted as a potential alternative to CEA. Several PTA case series have been reported,⁶⁻⁸ as well as 3 small, randomized, controlled trials of CEA versus PTA (with and without stenting),⁹⁻¹¹ and larger trials are underway.^{12,13} However, thus far, these studies have focused primarily on the 30-day procedural risks of stroke and

death. Although this initial procedural risk is clearly important, it is not the only consideration and may not be the main determinant of the relative efficacy of the procedures. Long-term durability is equally important but has yet to be compared. To determine the long-term risk of stroke after CEA, we studied the patients randomized to surgery in the European Carotid Study Trial (ECST), the largest published series of patients undergoing CEA with long-term follow-up by neurologists.^{1,14}

Currently, many centers routinely perform annual carotid ultrasounds to detect restenosis after CEA, although the cost-effectiveness of routine screening has been questioned.¹⁵⁻¹⁸ However, regular ultrasound screening may be warranted in

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patients at high risk of late postoperative stroke. We therefore also studied risk factors for ipsilateral ischemic stroke occurring after the 30-day postoperative period in the ECST.

Patients and Methods

The methods of the ECST have been described previously.^{1,14} Briefly, patients were randomized if they had had a carotid distribution transient ischemic attack, minor ischemic stroke, nondisabling major ischemic stroke, or a retinal infarction in the last 6 months and if, after carotid angiogram, their physician and surgeon were both uncertain whether to recommend CEA. Patients were randomized to “immediate surgery” (60%) or “avoid immediate surgery” (40%). It was strongly recommended that the surgeon performing the CEA was the trial surgeon and not a trainee or an assistant. The surgeon recorded details of the operation, including the use of specific ancillary techniques such as patching.

All patients were followed up by a neurologist or stroke physician at 4 months, at 12 months, and then annually until the end of the trial. All strokes, myocardial infarctions, and deaths were recorded. Many centers performed routine ultrasound surveillance for restenosis, but this was not a requirement of the trial, so no systematically collected data are available. Data were, however, collected on all CEAs during follow-up.

Stroke was defined as a clinical syndrome characterized by rapidly developing symptoms and/or signs of focal and at times global loss of cerebral function lasting >24 hours, with no apparent cause other than that of vascular origin. In the ECST, analysis was confined to stroke with symptoms lasting >7 days, so that very minor strokes were not given the same weight in analyses as major strokes that had caused permanent impairment.^{1,14} For this study, ipsilateral ischemic stroke was defined as a nonhemorrhagic stroke with symptoms lasting >7 days in the distribution of the operated carotid artery. Disabling stroke was defined as stroke that after 6 months was associated with a Rankin score of ≥3.

Statistical Analysis

Our analyses were restricted to patients undergoing trial surgery, defined as the first CEA performed within 1 year of randomization in a patient who was randomized to surgery.¹ Patients who died during the 30-day postoperative period were excluded, and the start of the follow-up period was defined as day 30 after surgery. Ten-year “late” stroke-free survival was calculated with Kaplan-Meier analysis.

Risk factors for “late” ipsilateral ischemic stroke were examined by univariate analysis. Ten-year actuarial risks for subgroups of each risk factor were calculated, and heterogeneity between subgroups was assessed by use of the log-rank test. In addition, risk factors were analyzed by multivariate analysis in a stepwise Cox proportional-hazards regression to determine their independent effects on postoperative ipsilateral ischemic stroke. Variables were excluded at *P*>0.1.

It is useful to assess whether the long-term post-CEA stroke risk is greater than the risk that would be expected as a result of causes other than carotid disease—eg, cardioembolic stroke and lacunar stroke. We therefore compared the late postoperative risk of ipsilateral ischemic stroke with the background risk of stroke in the territory of previously asymptomatic contralateral carotid arteries with <30% angiographic stenosis at randomization in the ECST. All analyses were performed with SAS for Windows, version 8.0 (SAS Inc).

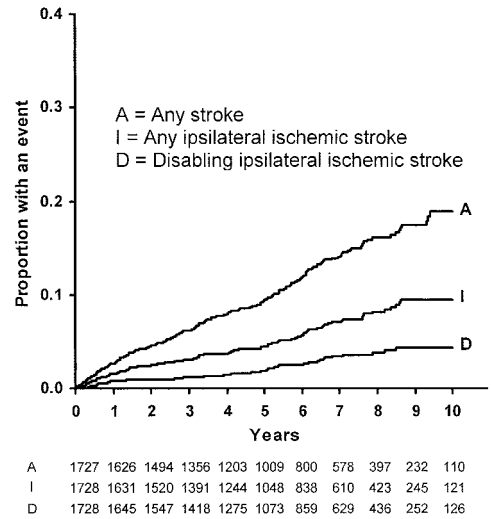


Figure 1. Kaplan-Meier curves showing risks of stroke after CEA (excluding the 30-day immediate postoperative period).

Results

In total, 1745 patients underwent trial CEA within 1 year of randomization. There were 17 deaths within 30 days of surgery [1.0%; 95% confidence interval (CI), 0.6 to 1.6], 11 as a result of stroke. There were 105 nonfatal major strokes within 30 days of surgery (6.1%; 95% CI, 5.0 to 7.3). The risk of death or major stroke was 7.1% (95% CI, 5.9 to 8.4). The stroke was in the territory of the operated artery in 105 patients (91%).

After exclusion of the 17 operative deaths, 1728 patients were alive at day 30 after surgery. The analyses of the risk of late stroke are confined to this group. Mean age was 62.5 years (SD, 8.1 years); 72% were male. The median time from last ipsilateral carotid territory cerebrovascular symptoms to randomization was 61 days. The median delay between randomization and surgery was 14 days, and 90% of operations were carried out within 52 days. The median length of follow-up was 6.0 years (maximum, 13.8 years).

Absolute Risks of Stroke

Survival free of disabling ipsilateral ischemic stroke, ipsilateral ischemic stroke, and any stroke in patients who survived beyond 30 days of their CEA is shown in Figure 1, and the 5-year and 10-year risks are summarized in Table 1. The 10-year risks of disabling ipsilateral ischemic stroke, ipsilateral ischemic stroke, and any stroke in any territory were 4.4% (95% CI, 3.0 to 5.8), 9.7% (95% CI, 7.6 to 11.7), and 19.1% (95% CI, 16.1 to 22.0), respectively.

TABLE 1. Actuarial Risks of Stroke at 5 and 10 Years After CEA (Excluding Any Stroke or Death Within 30 Days of Surgery) in 1728 Patients

Type of Stroke	5 Years			10 Years		
	Events	Risk, %	95% CI	Events	Risk, %	95% CI
Disabling ipsilateral ischemic stroke	28	1.9	1.2–2.6	46	4.4	3.0–5.8
Ipsilateral ischemic stroke	68	4.5	3.4–5.5	103	9.7	7.6–11.7
Any stroke	142	9.4	7.9–10.9	206	19.1	16.1–22.0

TABLE 2. Actuarial Risks of Stroke at 5 and 10 Years in 558 ECST Surgery Patients With an Asymptomatic Contralateral Carotid Artery With <30% Stenosis on Angiography

	5 Years			10 Years		
	Events	Risk, %	95% CI	Events	Risk, %	95% CI
Operated artery						
Ipsilateral ischemic stroke	19	3.7	2.0–5.3	30	8.5	5.2–11.9
Disabling ipsilateral ischemic stroke	7	1.3	0.4–2.3	11	3.2	1.1–5.4
Asymptomatic nonstenosed artery						
Ipsilateral ischemic stroke	10	2.0	0.8–3.2	15	4.5	1.5–7.4
Disabling ipsilateral ischemic stroke	5	1.0	0.1–1.9	7	1.9	0.4–3.4

The risks of stroke after CEA in the territory of the operated artery are compared with those in the territory of the contralateral asymptomatic carotid artery. In both cases, analyses excluded any stroke or death within 30 days of trial surgery.

There were 558 patients randomized to surgery who had an angiographic view of a previously asymptomatic contralateral carotid artery at randomization that showed <30% stenosis. Table 2 compares the risks of disabling ipsilateral ischemic stroke and any ipsilateral ischemic stroke after CEA on the symptomatic side with the equivalent risks in the territory of the contralateral <30%-stenosed carotid artery. The risks of stroke in the territory of the contralateral arteries were lower than the risks of stroke in the territory of the operated arteries, with a 1.9% (95% CI, 0.8 to 3.2) 10-year risk of disabling ipsilateral ischemic stroke and a 4.5% (95% CI, 1.5 to 7.4) risk of any ipsilateral ischemic stroke. The risks of stroke in the territory of the operated artery in these 558 patients (Table 2) did not differ significantly from those in the whole surgery group (Table 1).

There were 460 deaths during follow-up after the 30-day postoperative period. The causes of death were as follows: stroke (n=46), definite myocardial infarction (n=61), sudden death considered likely to have resulted from ischemic heart disease (n=102), other vascular causes (n=96), nonvascular causes (n=141), and unknown cause (n=14). There were also 92 nonfatal myocardial infarctions during follow-up.

Risk Factors for Stroke After CEA

A univariate analysis of risk factors for ipsilateral ischemic stroke at 10 years is summarized in Figure 2. Cerebral symptoms as the presenting event, the presence of diabetes, peripheral vascular disease and elevated systolic blood pressure were significantly associated with an increased risk of stroke at 10 years. Male sex, smoking, and increasing age approached significance as positive risk factors. The severity of preoperative angiographic stenosis, plaque morphology, and use of a patch graft were not associated with stroke risk. We included in the analysis the 105 patients who had had a nonfatal operative stroke within 30 days of trial surgery. The 10-year actuarial risk of a further ipsilateral ischemic stroke during follow-up in these patients was nonsignificantly lower than that in patients who had not had an operative stroke: 3 of 105 (2.9%; 95% CI, 0.1 to 6.0) versus 100 of 1623 (10.1%; 95% CI, 7.9 to 12.2; $P=0.19$).

Table 3 shows the results of the Cox regression analysis of the same risk factors. Again, diabetes, age, and elevated systolic blood pressure were significantly associated with an increased stroke risk over the 10-year follow-up period. Peripheral vascular disease was not an independent predictor

of late stroke, but smoking became more significant in the multivariate analysis. Interestingly, when entered as a continuous variable, the degree of preoperative stenosis was negatively associated with the risk of late stroke. A stepwise Cox regression was performed to produce a model that might be used to identify patients at increased risk of late stroke (Table 4). An increased stroke risk was associated with diabetes, elevated systolic blood pressure, smoking, increasing age, presentation with cerebral symptoms, male sex, and lesser severe preoperative stenosis.

CEA During Follow-Up

Only 9 patients had a second CEA on the operated side. The mean time from initial surgery to reoperation was 36 months. There were no strokes or deaths within 30 days of reoperation. Five patients were reoperated because of symptomatic restenosis (ipsilateral events during the 6 months before surgery: transient ischemic attack in 3, stroke in 2), and 4 were reoperated because of restenosis detected on routine ultrasound surveillance. Risk factors for reoperation included male sex [odds ratio (OR), 3.1; 95% CI, 0.4 to 24.7], diabetes (OR, 3.9; 95% CI, 1.0 to 15.8), and peripheral vascular disease (OR, 4.2; 95% CI, 1.1 to 15.6), but there was no association with any of the other risk factors listed in Table 3.

Fifty-four patients had a CEA on the contralateral nonoperated side during follow-up. Of these, 20 were reoperated because of symptomatic carotid stenosis. The mean time from randomization to surgery was 34 months. There were 6 strokes (11.1%) within 30 days of surgery, but all occurred in the territory of the recently operated artery (contralateral to the artery that had had initial trial surgery).

Discussion

The risks of stroke reported here exclude early postoperative strokes and deaths (ie, events that occurred within 30 days of CEA) to allow estimation of the long-term risk of "late" stroke in patients who survive CEA. However, all patients who survived the 30-day postoperative period were followed up and included in our analysis, including those patients who had a nonfatal operative stroke during the initial 30-day period. The data in Table 1 and Figure 1 show that CEA is a highly durable operation, with a risk of subsequent ipsilateral ischemic stroke of only $\approx 1\%$ per year up to 10 years. Late postoperative ipsilateral ischemic strokes accounted for only half of the overall risk of any stroke.

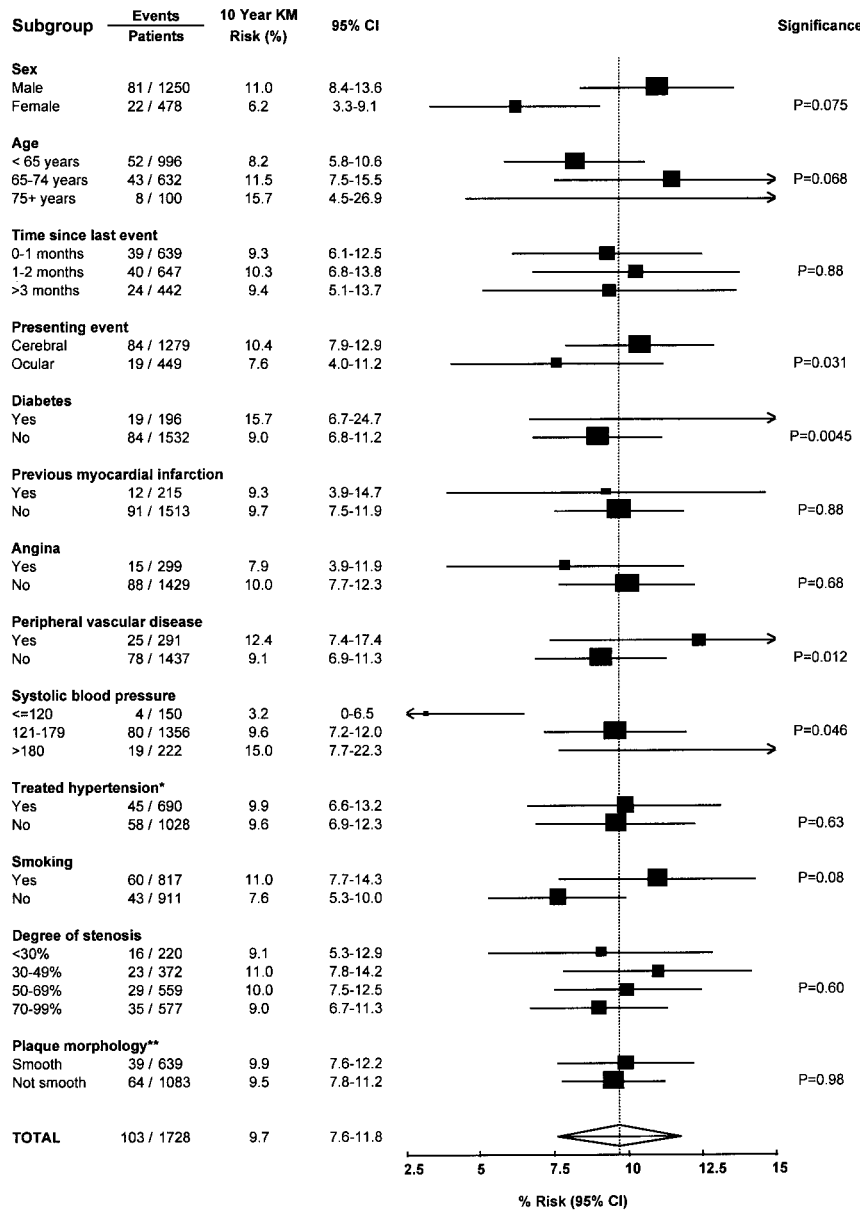


Figure 2. Univariate analysis of the association between baseline clinical and radiographic variables and 10-year ipsilateral ischemic stroke risk after CEA (excluding any stroke or death within 30 days of surgery). Percentage risks are derived from Kaplan-Meier (KM) analysis and will therefore differ from the risks that would be derived from the crude number of events. Statistical significance of the effect of risk factors was obtained with a log-rank test based on the full duration of follow-up and therefore will not equate exactly with the 95% CIs of the observed risks at 10 years. *Data not available for 10 cases; **data not available for 6 cases.

The only other large, published study of the durability of CEA with long-term follow-up by a neurologist or stroke physician was from the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Among the 326 surgical patients in NASCET with severe stenosis, the 8-year risks of disabling ipsilateral stroke, any ipsilateral stroke, and any stroke (excluding events within 30 days of CEA) were 4.6%, 9.4%, and 23.6%, respectively.¹⁹ These risks are slightly higher than those in the ECST, but they include hemorrhagic strokes and minor strokes with symptoms lasting <7 days. Overall, these risks are highly consistent with those from the ECST.

Data on the long-term stroke risk after carotid PTA and stenting are very limited. In the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS),¹¹ there was no difference between PTA and CEA in the 3-year risk of ipsilateral stroke lasting >7 days. However, mean follow-up was <2 years, and only ≈15% of patients had 3-year follow-up. One case series of carotid PTA and stenting has reported follow-up

data at 3 years in 528 patients.²⁰ However, only 10% of patients had 3-year follow-up data. More long-term follow-up data are required, and it is essential that the randomized trials of PTA and stenting versus CEA produce reliable comparisons of stroke risk to at least 5 years of follow-up, preferably longer.

Many ipsilateral ischemic strokes that occur late after CEA or angioplasty will be unrelated to the previous surgery. The background risk of lacunar stroke and cardioembolic stroke in this population is likely to be higher than in the general population. The risk of stroke in the territory of the previously asymptomatic contralateral carotid arteries with <30% stenosis on the prerandomization angiogram is probably a reasonable estimate of this risk. The fact that the risk was lower than the late postsurgery risk of ipsilateral stroke partly reflects the fact that, although the cut point was set at <30% stenosis, most of these asymptomatic carotid arteries had no angiographically visible carotid disease at all. The background stroke risk in the territory of these arteries would

TABLE 3. Multivariate Analysis of the Relationship Between Baseline Characteristics and the 10-Year Risk of Ipsilateral Ischemic Stroke Risk After CEA (Excluding Any Stroke or Death Within 30 Days of Surgery)

Risk Factor	Wald χ^2	<i>P</i>	Hazard Ratio	95% CI
Stenosis (per 10%)	4.47	0.03	0.93	0.86–0.99
Male sex	2.60	0.1	1.50	0.92–2.41
Age (per year)	2.423	0.019	1.03	1.00–1.06
Time since last event	0.006	0.94	1	0.97–1.03
Cerebral presenting event	2.50	0.11	1.81	0.87–3.77
Diabetes	9.30	0.002	2.24	1.35–3.74
Irregular/ulcerated plaque	0.14	0.71	0.92	0.61–1.40
Previous myocardial infarction	0.16	0.90	0.96	0.50–1.83
Angina	0.013	0.91	0.97	0.54–1.74
Peripheral vascular disease	1.96	0.16	1.43	0.87–2.35
Systolic blood pressure (per 10 mm Hg)	5.14	0.02	1.10	1.00–1.30
Treated hypertension	0.006	0.94	0.98	0.66–1.47
Smoking	3.35	0.06	1.50	0.97–2.31
Patch graft	0.41	0.5	1.16	0.75–1.79

The analysis included the 1716 patients with 103 events for whom all risk factors were available.

account for $\approx 50\%$ of the residual stroke risk in the territory of the operated arteries. Thus, the number of strokes that are likely to have been attributable to restenosis, or other consequences of surgery, is relatively low (ie, 0.5% per year).

The reported rates of restenosis after CEA vary from 1% to 35% but depend on the definition of restenosis and both the method and length of follow-up.²¹ A recent systematic review of the published literature concluded that restenosis of $>50\%$ occurs in $\approx 10\%$ of patients during the first year after CEA but that the rate then falls to $\approx 1\%$ in the third year and remains stable thereafter.²¹ Therefore, although only 9 patients (0.5%) had CEA for restenosis during follow-up in the ECST, the rate of restenosis is likely to have been higher. Follow-up ultrasound scanning data were not collected in the ECST, and we do not know what proportion of centers performed routine follow-up imaging. Nevertheless, the low risk of late ipsilateral ischemic stroke during follow-up suggests that most of these restenoses remain asymptomatic and probably do not require reoperation. These results call into question the cost-effectiveness of routine annual surveillance ultrasound after CEA.

Risk Factors for Ipsilateral Stroke After CEA

Several baseline variables were associated with an increased risk of late postoperative ipsilateral stroke. Interestingly, these were

mostly the risk factors usually associated with an increased risk of stroke on medical treatment alone, ie, male sex, increasing age, hypertension, diabetes, and presentation with cerebral ischemic events rather than ocular events only.^{22,23} Of particular interest, female sex, which is associated with an increased risk of stroke within 30 days of surgery,²⁴ was associated with a reduced risk of late postoperative stroke.

The degree of preoperative angiographic stenosis and plaque surface morphology are both important risk factors for stroke on medical treatment in patients with symptomatic carotid stenosis.²⁵ The lack of an association between plaque morphology and late postoperative risk of ipsilateral ischemic stroke is consistent with the fact that the plaque has been removed and suggests that the relationship between plaque surface morphology and stroke risk on medical treatment are causal. The negative association between degree of preoperative angiographic stenosis and stroke risk in the multivariate analyses is interesting. It may be due to the fact that, in patients who initially present with a TIA or stroke and lower degrees of stenosis, the cause of their symptoms is more likely to be unrelated to the carotid disease (eg, intracerebral small-vessel disease). In this case, CEA might be expected to be less effective in preventing recurrent events.

TABLE 4. Stepwise Cox Regression Analysis of Risk Factors for Ipsilateral Ischemic Stroke Occurring >30 Days After CEA

Risk Factors	χ^2	<i>P</i>	Hazard Ratio	95% CI
Diabetes	9.85	0.0017	2.25	1.36–3.71
Systolic blood pressure (per 10 mm Hg)	5.74	0.016	1.11	1.02–1.19
Age (per year)	5.72	0.016	1.03	1.01–1.06
Smoking	4.53	0.03	1.58	1.04–2.42
Degree of stenosis (per decile)	4.10	0.04	0.93	0.87–0.99
Male sex	2.84	0.09	1.51	0.94–2.43
Cerebral presenting event	2.68	0.10	1.83	0.98–8.85

The analysis included the 1716 patients with 103 events for whom all risk factors were available.

Of the risk factors that were significantly associated with an increased risk of late stroke, 3 have implications for preventive treatment: systolic hypertension, smoking, and diabetes. Although these are only observational associations and we cannot prove a causal link, our results highlight the importance of continuing active preventive treatment after CEA. It is important that patients understand that the risk of stroke has not been removed completely by surgery and that they also have a high risk of death resulting from ischemic heart disease and other vascular causes.

Screening for restenosis after CEA might be worthwhile if it were possible to target individuals at higher risk of stroke.^{15–18} The risk model in Table 4 requires independent validation but may be useful in identifying patients who require more frequent follow-up after surgery.

The use of a patch graft was not associated with the risk of late postoperative stroke. The rationale for patching the internal carotid artery during CEA is that the additional luminal diameter provided by the patch limits restenosis, but there are no convincing data on the effectiveness of the technique.^{26,27} Although we did not measure postoperative carotid stenosis, our nonrandomized analysis provides no evidence to support the use of patching in the prevention of late postoperative stroke.

In conclusion, CEA for symptomatic carotid stenosis is a highly durable procedure with a late postoperative stroke risk of only $\approx 1.0\%$ per year and a disabling ipsilateral stroke risk of $<0.5\%$ per year. Moreover, half of these strokes are probably unrelated to any residual carotid disease. However, there are several risk factors for late postoperative stroke, and these might be useful in targeting screening for restenosis. Finally, ongoing randomized, controlled trials of PTA and stenting versus CEA must have sufficiently long follow-up to determine whether PTA has better, equivalent, or worse long-term durability than CEA. Comparisons of immediate procedural risks will not be a sufficient basis on which to justify routine use of PTA or other alternatives to CEA.

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