Long-term survival and stroke-free survival after eversion carotid endarterectomy for asymptomatic severe carotid stenosis

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Background: **Level 1 evidence supports carotid endarterectomy (CEA) as the standard treatment for severe (>70% lumen reduction) carotid stenosis in asymptomatic patients, though its safety and efficacy in high-risk patients remain controversial. Long-term survival and stroke-free survival after CEA may guide decisions concerning this procedure for asymptomatic patients, but this outcome has only been considered in few reports outside the large randomized trial setting. This study analyzed long-term survival and stroke-free survival after CEA and the impact of risk factors in a consecutive series of asymptomatic patients, including those with medical comorbidities and particular anatomical features believed to increase the perioperative morbidity and mortality of CEA.**

Methods: **For over 10 years, data were prospectively collected for all patients who underwent CEA for asymptomatic severe carotid disease at our institution. All CEAs performed by the same surgeon involved eversion technique, with patients under deep general anesthesia and continuous perioperative electroencephalographic (EEG) monitoring for selective shunting. All patients had neurological follow-up and duplex ultrasound at 1, 6, and 12 months, and yearly thereafter. A complete follow-up (mean, 6.1 years; range, 0.1 to 10.6 years) was obtained in 348 patients (93%) with an overall 365 CEAs (93%). Survival analyses were performed using Kaplan-Meier life tables.**

Results: **Among 374 patients undergoing 391 CEAs, there were no perioperative deaths or strokes. There were 17 (4.8%) late deaths, mainly cardiac-related (70%), and 2 (0.5%) non-fatal strokes. At 5 and 10 years, survival was 96.3% and 85.7%, and stroke-free survival was 95.6% and 84.8%, respectively. At multivariate analysis, diabetes mellitus ($P = .002$) and cardiac disease ($P = .005$) were independent predictors of a shorter long-term survival.**

Conclusions: **Eversion CEA proved safe and effective in a series of patients with asymptomatic severe carotid disease representing the typical population of daily clinical practice. Although long-term results were extremely favorable, excellent stroke-free survival was not translated into a longer patient survival. (J Vasc Surg 2007;46:265-70.)**

Multicenter, randomized clinical trials (RCTs) have shown that carotid endarterectomy (CEA) significantly reduces the long-term risk of stroke due to severe (>70% lumen reduction) carotid disease in asymptomatic patients,[1,2] resulting in more CEAs being performed worldwide for asymptomatic disease, though the benefits were less striking than those seen in RCTs on CEA in symptomatic patients.[3,4] Despite RCTs providing the basis for guidelines for CEA with the assumption that the morbidity and mortality rates be better than those of the disease's natural history,[5] large institution-based studies can provide additional valuable information by recruiting patients who might not have met the specific inclusion criteria for RCTs. Indeed, asymptomatic patients with medical comorbidities (significant cardiac disease, chronic obstructive pulmonary disease, chronic kidney disease, and old age) or particular anatomical features (contralateral carotid occlusion, high carotid bifurcation, or other anticipated technical difficulties) were excluded from the RCTs, even though they account for a substantial portion of the general population seen in everyday clinical practice. Controversy remains, however, as to whether and which specific clinical or anatomical variables are associated with worse results after CEA in such patients.[6-8]

Although many authors have documented the progression of asymptomatic carotid lesions in unoperated patients[9,10] and in those who had CEA for symptomatic or asymptomatic contralateral severe lesions,[11,12] outside the RCT setting, long-term survival and stroke-free survival after CEA for asymptomatic carotid disease have been examined only partially and in a handful of studies,[13-17] most of which failed to analyze outcome selectively for different indications.[14-16]

Since long-term outcomes are an essential parameter in the evaluation of this prophylactic procedure, we designed this study to analyze long-term survival and stroke-free survival in a consecutive series of patients who underwent CEA for asymptomatic carotid disease, including those with medical comorbidities and anatomical features believed to increase the risk of CEA.[6]

PATIENTS AND METHODS

Demographic and clinical data for all patients with asymptomatic carotid disease, including those who had

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Competition of interest: none.

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non-hemispheric symptoms, eg, posterior circulatory events and non-specific symptoms ≤6 months, who underwent CEA at our institution over a 10-year period (1995-2004) were prospectively entered into a computerized database according to the recommendations of the Asymptomatic Carotid Atherosclerosis Study (ACAS).[1] Patients scheduled for CEA with concomitant coronary artery bypass grafting or with associated supra-aortic trunk lesions requiring concurrent surgery, and patients requiring procedures for recurrent disease were ruled out. Written informed consent was obtained from all patients involved in this study, which was approved by our Institutional Ethics Review Board.

The patients' demographic and clinical data were recorded on a standardized form, including potential risk factors for atherosclerosis, other anatomical and clinical variables, details of the operation and hospital stay. Smoking was defined as past (a history of smoking for at least 10 years before quitting more than 15 years ago) or current cigarette smoking (patients who had smoked for more than 10 years and continued to do so as at the time of surgery).

Hyperlipidemia was recorded for serum cholesterol levels higher than 200 mg/dL or a prior diagnosis, including the use of a lipid-lowering drug. Diabetes mellitus was diagnosed clinically before or at the time of admission for surgery: this category included both type 1 and type 2 diabetes mellitus. Hypertension was recorded on the strength of a clinical diagnosis, including the current use of antihypertensive therapy. Cardiac disease included any of the following: a history of myocardial infarction (MI), atrial fibrillation, congestive heart failure (CHF), angina pectoris, coronary artery bypass, surgery for valve disease or signs of ischemia on an electrocardiogram, and nitrate therapy. Chronic kidney disease was defined as a serum creatinine level higher than 1.5 mg/dL in either conservative or dialysis treatment. Pulmonary disease was defined as a history of chronic restrictive or obstructive disease based on pulmonary function tests, pulmonary embolism, and prior lobectomy or pneumonectomy. The diagnosis of carotid lesion was based on preoperative digital subtraction angiography (DSA) during the earlier part of this study (used with decreasing frequency over the years), while duplex ultrasound scan was the only preoperative carotid imaging study performed in most patients from mid-1998 onwards, combined in selected patients (patients who either had a pseudo-occlusion on duplex ultrasound scan or a stenosis of the internal carotid intracranial segment detected by transcranial Doppler sonography) with magnetic resonance angiography (MRA), contrast-enhanced MRA, or DSA. Stenosis was classified as 60% to 69% (peak systolic velocity [PSV] >130 cm/s; peak diastolic velocity [PDV] 40-110 cm/s; peak systolic velocity of internal carotid artery/peak systolic velocity of common carotid artery [carotid ratio] 3.2 - 4.0); 70% to 79% (PSV >210 cm/s; PDV 110-140 cm/s; ratio >4.0); or 80% to 99% (PSV >210 cm/s; PDV >140 cm/s; ratio >4.0). The velocity criteria not the features of the plaque were taken into account for CEA decision. All patients were on antiplatelet therapy. All patients with diabetes, hyperlipidemia, and/or hypoechoic plaques were on statin therapy. Preoperative patient preparation was standardized.

All CEA procedures involved eversion technique: the details of this procedure have been published elsewhere.[18] All CEAs were performed by the same surgeon with patients under deep general anesthesia and continuous perioperative electroencephalographic (EEG) monitoring for selective shunting. Shunting criteria were based exclusively on EEG changes consistent with cerebral ischemia. No completion imaging studies were performed. None of the CEA procedures considered in this series were aborted or incomplete, and none of the patients were refused CEA for technical reasons emerging during surgery.

Patients were usually monitored in the recovery room for 2 hours until their blood pressure and neurological status were considered acceptable, then they were transferred to a regular nursing unit specializing in vascular care and monitored for the next 12 to 24 hours after surgery. All patients with severe headache were observed for hyperperfusion syndrome, and hypertension was treated aggressively. Most patients were discharged 48 to 72 hours after CEA.

Surveillance protocol. After discharge, visiting nurses monitored the patients' blood pressure and neurological status. All survival patients systematically underwent physical and neurological assessments by a consultant neurologist, and duplex ultrasound scans performed by two experienced technologists, 1, 6, and 12 months and then yearly after CEA. Neurological events were always classified by the consultant neurologist as transient ischemic attack (TIA); (ie, temporary hemispheric symptoms lasting no more than 24 hours, with complete recovery), amaurosis fugax (transient monocular visual loss), or stroke (minor*:* minimal, stabilized focal neurological deficit of acute onset and persisting more than 24 hours, but not causing disability or any significant impairment in activities of daily living, or major*:* a focal neurological deficit lasting more than 30 days and inducing a change in lifestyle). Brain imaging (computed tomography or magnetic resonance imaging) was performed in all patients presenting a new neurological deficit after CEA. Other complications and events observed during follow-up were recorded in accordance with the guidelines of the Ad Hoc Committee on Reporting Standards for Cerebrovascular Disease, Society for Vascular Surgery/ North American Chapter of the International Society of Cardiovascular Surgery.[19]

The study endpoints were long-term survival and stroke-free survival.

Statistical analysis. All values are expressed as mean ± SD. Continuous data were compared with the Student t test (two-tailed) and categorical variables with Pearson χ^2 test (two-tailed) or Fisher exact test, as appropriate, calculating the odds ratio (OR) with 95% confidence intervals (CIs). Cumulative life-table analyses (Kaplan-Meier) were used to assess long-term survival and stroke-free survival rates. Statistical significance was inferred for $P < .05$. A Cox proportional hazard multivariate analysis was used to deter-

Table I. Baseline characteristics of patients with asymptomatic disease who underwent CEA, patients who had complete follow-up, and those lost to follow-up

Characteristics, n (%)	*Patients who underwent CEA n = 374*	*Patients with a complete follow-up n = 348*	*Patients lost to follow-up n = 26*	*P value*
Age (yrs), mean ± SD	71.8 ± 4.9	71.1 ± 5.6	71.3 ± 4.4	1
Male	247 (66)	227 (65.2)	20 (76.9)	.225
Smoking	241 (64.4)	233 (66.9)	8 (30.7)	<.01
Hyperlipidemia	135 (36.1)	129 (37.1)	6 (23.1)	.152
Diabetes mellitus	103 (27.5)	98 (28.1)	5 (19.2)	.373
Hypertension	213 (56.9)	208 (59.7)	5 (19.2)	<.01
Cardiac disease	154 (41.2)	146 (41.9)	8 (30.7)	.264
CKD	48 (12.8)	47 (13.5)	1 (9.8)	.228
Pulmonary disease	63 (16.8)	59 (16.9)	4 (15.3)	.237
AAA/PAD	216 (57.7)	209 (60)	7 (26.9)	<.01
Contralateral CO	42 (11.2)	39 (11.2)	3 (11.5)	1
Bilateral CEA	40 (10.7)	38 (10.9)	2 (7.6)	1
Intraluminal shunting	54 (13.8)	51 (13.9)	3 (11.5)	1

SD, Standard deviation; *CEA,* carotid endarterectomy; *CKD,* chronic kidney disease; *AAA/PAD,* abdominal aortic aneurysm/peripheral artery disease; *CO,* carotid occlusion.

mine which factors with statistical or marginal significance at univariate analysis might influence long-term outcome.

RESULTS

During the study period, 391 CEA procedures were performed in 374 patients with asymptomatic severe carotid disease. Bilateral CEAs were performed in 40 (10.7%) patients with at least one asymptomatic lesion and in 17 (4.5%) for bilateral asymptomatic disease. Bilateral CEAs were planned at admission in 12 patients (correcting the carotid with the greater degree of stenosis first and leaving a mean 4 weeks between procedures), whereas contralateral CEA was indicated a mean of 25 ± 3 months after the first procedure in the other five cases. The patients' demographic data and risk factors are summarized in Table I. The mean age was 71 years (range, 40 to 93): 112 patients were under 70 years old, 223 were 70 to 79 and 39 were 80 or more. Almost two-thirds of the patients were males.

Perioperative (30-day) events. There were no perioperative deaths or strokes in this series. Three patients (0.8%) had perioperative CHF, including two with a history of CHF, and one of them also had a postoperative nonfatal MI. No hyperperfusion syndrome was observed in any of the patients. Other surgical complications included 19 (4.8%) nerve injuries, and 18 (4.6%) neck hematomas requiring surgical evacuation, with no further sequelae. Injuries involved the cranial nerves in 3.3% of cases (13/391) and the cervical nerves in 1.5% (6/391). There were 8 hypoglossal nerve injuries, 4 recurrent laryngeal nerve injuries, 1 superior laryngeal nerve injury, 2 marginal mandibular nerve injuries, 3 greater auricular nerve injuries, and 1 transverse cervical nerve injury. All nerve dysfunctions were transient, and all recovered completely within 6 months of CEA.

Long-term results. Long-term follow-up (mean, 6.1 years; range, 0.1 to 10.6 years) was obtained in 348 of 374 (93%) patients with an overall 365 (93.3%) CEAs (Table I). Seventeen (4.8%) late deaths occurred, mainly of cardiac-

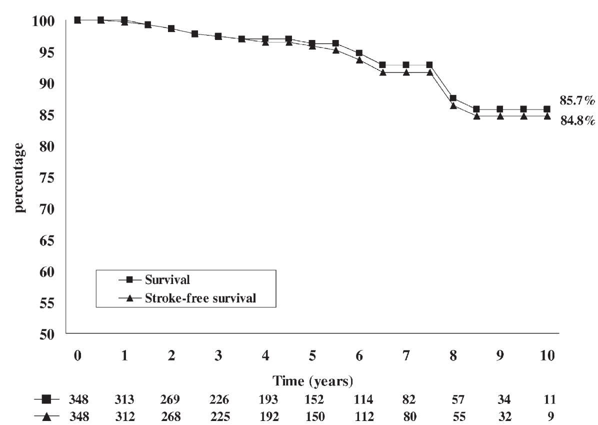

Fig. Kaplan-Meier curves show long-term survival and stroke-free survival of asymptomatic patients with complete follow-up. Percentages on the right represent rates of survival and stroke-free survival at 10 years. The standard error is less than 10% at each time point in each curve. Range of standard errors is 0% to 4.6% for survival and 0% to 4.7% for stroke-free survival, respectively. Raw numbers of the patients at risk analyzed in each subset at each time point are provided below the figure.

related causes (cardiac disease, 12; cancer, 3; pancreatitis, 1; car accident, 1). Kaplan-Meier analysis showed survival rates at 1, 3, 5, and 10 years of 100%, 97.4%, 96.3%, and 85.7%, respectively (Fig).

Two (0.5%) late non-fatal strokes occurred: both were clinically diagnosed as minor strokes and contralateral to the revascularized hemisphere. Kaplan-Meier analysis identified a stroke-free survival at 1, 3, 5, and 10 years of 99.7%, 97.1%, 95.6%, and 84.8 %, respectively (Fig).

Table II shows a list of baseline characteristics with the corresponding frequencies of late deaths and associated univariate probabilities. Diabetes mellitus (OR, 5.1; 95% CIs = 1.84-14.3; $P = .001$), cardiac disease (OR, 4.8; 95%

Table II. Univariate analysis of the association between baseline demographic and clinical variables and long-term risk of death after CEA

Characteristic	*Category*	*Death* n/N (%)	P *value*
Age (years)			
<70	Yes	5/103 (4.8)	1
	No	12/245 (4.9)	
70 −79	Yes	11/208	.863
	No	6/140	
≥ 80	Yes	2/37	.699
	No	15/311	
Gender	Female	6/121 (4.9)	.830
	Male	11/227 (4.8)	
Smoking	Yes	8/233 (3.4)	.127
	No	9/115 (7.8)	
Hyperlipidemia	Yes	7/129 (5.4)	.918
	No	10/219 (4.5)	
Diabetes mellitus	Yes	11/98 (11.2)	.001
	No	6/250 (2.4)	
Hypertension	Yes	12/208 (5.7)	.450
	No	5/140 (3.6)	
Cardiac disease	Yes	13/146 (8.9)	.004
	No	4/202 (1.9)	
CKD	Yes	3/47 (6.3)	.712
	No	14/301 (4.6)	
Pulmonary disease	Yes	2/59 (3.3)	.747
	No	15/289 (5.1)	
AAA/PAD	Yes	14/209 (6.7)	.073
	No	3/139 (2.1)	
Contralateral CO	Yes	5/39 (12.8)	.040
	No	12/309 (3.9)	
Bilateral CEA	Yes	1/38 (2.6)	.706
	No	16/310 (5.1)	
Intraluminal shunting	Yes	2/51 (3.9)	1
	No	15/297 (5.0)	

CEA, Carotid endarterectomy; *CKD*, chronic kidney disease; *AAA/PAD*, abdominal aortic aneurysm/peripheral artery disease; *CO*, carotid occlusion.

CIs = 1.5-15.1; *P* = .004) and contralateral carotid occlusion (OR, 3.6; 95% CIs = 1.2-10.9; *P* = .040) were significantly associated with a higher risk of death at 10 years. A history of abdominal aortic and/or peripheral aneurysmal/atherosclerotic disease (AAA/PAD), either conservatively or surgically treated, was marginally significant as a positive risk factor for late death (OR, 3.2; 95% CIs = 0.9-11.5; *P* = .073). Male gender, older age, smoking, hyperlipidemia, high systolic blood pressure, chronic kidney or lung diseases, bilateral CEA, and intraluminal shunting were unassociated with late mortality. By Cox proportional hazard multivariate analysis of the variables considered (diabetes mellitus, cardiac disease, contralateral carotid occlusion, and AAA/PAD), only diabetes mellitus (*P* = .002) and cardiac disease (*P* = .005) revealed a significant influence on long-term survival.

Univariate and multivariate analyses for stroke and stroke-related death were inappropriate because the number of outcome events was too small and the number of potential variables was relatively large.

DISCUSSION

In this study, 374 consecutive patients with baseline characteristics typical of the general population, including those with comorbid conditions or particular anatomical features underwent CEA for asymptomatic severe carotid disease with no perioperative stroke or death. This outcome correlates well with recently-published, large institution-based studies report 30-day major stroke and death rates ranging from 0.9% [20] to 1.9% [21] for patients undergoing CEA for asymptomatic disease, and compares favorably with the results of previous RCTs, such as the 2.3% of the ACAS [1] and the 2.8% of the Asymptomatic Carotid Surgery Trial (ACST).[2]

Although many authors have documented the durability of the CEA procedure, showing an acceptably low incidence of restenoses and late occlusions,[14,15,22-24] outside the RCT setting, long-term survival and stroke-free survival after CEA in asymptomatic patients have only been examined in a few studies,[13-17] usually with providing any information on outcome vis-à-vis indications for surgery.[13-15] Data from the RCTs on long-term survival have yet to become available, however: in the ACAS, the mean follow-up was 2.6 years, and the ACST is still pursuing a long-term follow-up.[1,2]

Among our 348 patients with a complete follow-up after CEA for asymptomatic disease, the 5- and 10-year risk of death was 3.7% and 14.3%, respectively, while the 5- and 10- year stroke-free survival rates were 95.6% and 84.8%, respectively. These findings confirm what we already reported in a previous experience[15] on 1150 CEAs (302 CEAs with patching and 848 eversion CEAs) performed in 1000 patients (only a third of them asymptomatic) with a 5- and 10- year risk of death of 7.2% and 12.8%, respectively. These findings also correlate well with the 3- and 5-year risk of death of 10% and 18% demonstrated by AbuRhama et al,[11] related to the natural history of the asymptomatic carotid disease in a series of 420 patients who underwent contralateral CEA for symptomatic or asymptomatic severe carotid lesions. The outcome of our series contrasts, instead, with the far worse results reported by other authors.[16,17] In a series of 631 CEAs (3.3% of them eversion CEAs) performed for asymptomatic disease over a 10-year period, Kragsterman et al[17] recorded a 5- and 10-year risk of death of 21.8% and 54.5%, respectively. They explained the substantial drop in the long-term survival of their patients, despite extremely low perioperative mortality (0.5%), with an increasing annual mortality that negatively affected longevity when compared with the expected survival for general population of the same age. No information was available on stroke-free survival, however. Similar results were reported by LaMuraglia et al[16] in a series of 2236 CEA procedures (1987 patients; no eversion CEAs), more than 60% of them performed for asymptomatic disease, with a 5- and 10-year risk of death of 27.6% and 55.3%, respectively. Here again, no information on long-term stroke-free survival was forthcoming.

Although the impact of age on long-term survival was reported in many series, and this has negatively influenced decisions concerning CEA in asymptomatic older patients, we found no such influence of older age in our study. The mean age of our series was somewhat higher than in the ACAS[1] (67 years) or ACST [2] (68 years), but was comparable with most of the series considered in reports on long-term outcome after CEA.

Likely because diabetic patients comprised almost one third of our asymptomatic cohort (28%), in agreement with other studies,[16,17] diabetes mellitus ($P = .002$) resulted an independent predictor of late mortality. Another predictor of reduced longevity was cardiac disease ($P = .005$), which is hardly surprising since cardiac disease has commonly been identified as a risk factor with a significant impact on long-term survival in such patients.[16,17] These risk factors, thus, should be taken into account when deciding whether to perform this prophylactic procedure.

Our findings should be interpreted bearing in mind the study's limitations, however. First, although the data were collected prospectively, the analysis is retrospective in nature. Second, the globally-high incidence of prior major vascular surgery and bilateral CEA, AAA, and PAD, and occlusion of the contralateral carotid among our patients probably reflects how most of them were identified and recruited, ie, during assessment or follow-up for other procedures and atherosclerotic lesions. These patients may, therefore, represent a selected group with multiple atherosclerotic manifestations and this might alter the outcome, though the potentially negative bias introduced clearly has not affected the perioperative or long-term results. Third, because our study population was limited to a group of 348 patients drawn from the initial set of 374, we cannot exclude the possibility of the incidence of late fatal or adverse events being higher, or confined to patients lost to follow-up. Baseline risk factors comparison between our cohort and the other patients showed, however, that the patients with a complete follow-up were not healthier than the others. Indeed, the higher prevalence of diabetes mellitus and high systolic blood pressure, and the preponderance of cardiac and peripheral artery diseases and smokers in our study cohort produced a bias towards a worse prognosis than for those without a complete follow-up, so the patients lost to follow-up were unlikely to have experienced a higher incidence of long-term adverse events. Fourth, our study would have benefited from a comparison of the long-term outcome in patients with asymptomatic severe carotid disease followed up without CEA, but we believed it would have been unethical to continue to follow patients up clinically if CEA was indicated. Finally, we are aware that the nil perioperative stroke/mortality incidence and the small number of late fatal or adverse events limit the reliability of our results, but these are our results nonetheless.

CONCLUSION

Eversion CEA for asymptomatic severe disease proves a safe and effective procedure in the general population, including patients who would probably have been excluded from RCTs, with better perioperative results than those achieved in the RCTs. Long-term survival and stroke-free survival after CEA are important issues to consider when deciding whether to recommend this prophylactic procedure and, in this series, the results were extremely favorable. The excellent long-term stroke-free survival was not translated into a longer patient survival, however, because none of late deaths were related to neurological adverse events.

AUTHOR CONTRIBUTIONS

Conception and design: EB, CB
Analysis and interpretation: RM
Data collection: GM
Writing the article: EB, CB
Critical revision of the article: EB, CB
Final approval of the article: EB, GM, RM, CB
Statistical analysis: RM
Obtained funding: Not applicable
Overall responsibility: EB, CB

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