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Long-Term Survival After Carotid Endarterectomy for Asymptomatic Stenosis

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Background and Purpose—Large randomized trials have demonstrated a net benefit of carotid endarterectomy (CEA) for asymptomatic carotid artery stenosis compared with best medical treatment. However, it takes years to overcome the perioperative risk and gain the reduction in stroke or death risk. Long-term survival after CEA for asymptomatic stenosis may be an important consideration in deciding on this prophylactic procedure, but is not well documented. The aim was to analyze long-term survival after CEA for asymptomatic stenosis and the impact of risk factors in a population-based study.

Methods—The Swedish vascular registry (Swedvasc) covers all centers performing CEA. Data on all registered CEAs during 1994 to 2003 were retrieved. All patients were cross-matched with the Population-Registry for accurate data on mortality (date of death). Analyses with Kaplan-Meier curves for survival and relative odds ratio (OR) for predictors of survival were performed.

Results—A total of 6169 CEAs in 5808 patients were registered, with a median time at risk of 5.1 (range, 0.1 to 11.8) years. The indication for CEA was asymptomatic stenosis in 10.8% of the patients. Survival after CEA for asymptomatic stenosis was 78.2% after 5 and 45.5% after 10 years. Previous vascular surgery (OR, 1.8; 1.1 to 3.0), cardiac disease (OR, 1.7; 1.0 to 2.8), diabetes mellitus (OR, 2.3; 1.3 to 4.1), and age (OR, 1.5; 1.1 to 2.1 per 10 years) were predictors of decreased 5-year survival.

Conclusions—In this population-based study of patients operated on for asymptomatic stenosis, a substantial reduction in long-term survival was observed. Predictors of decreased longevity were age at operation, diabetes, cardiac disease, and previous vascular surgery. (*Stroke*. 2006;37:2886-2891.)

Key Words: asymptomatic stenosis ■ carotid endarterectomy ■ long-term survival

During the past decade carotid endarterectomy (CEA) for asymptomatic stenosis has been the focus for many reports and trials. Large randomized controlled trials have demonstrated a net benefit of CEA in addition to best medical treatment. However, because of the initial increase caused by perioperative events, it takes years to harvest that benefit in stroke or death risk. In the Asymptomatic Carotid Atherosclerosis Study (ACAS), the absolute risk reduction (ARR) for stroke or death after 5 years was estimated at 5.4% and in the Asymptomatic Carotid Surgery Trial (ACST) at 5.9%.¹⁻² Long-term follow-up after CEA for asymptomatic stenosis is not well-documented,³⁻⁴ most reports have not analyzed outcome selectively for different indications.⁵⁻⁷ Some natural history studies of patients with asymptomatic stenosis present risk factors, stroke and survival rates beyond 5 years, but differ in selection of study groups.⁸⁻¹⁰ The patients included in the majority of these studies often have a mean age of ≈70 years, and although the durability of CEA is good, the overall long-term mortality is also essential in decision-making for

this prophylactic procedure. Life expectancy is influenced not only by age but also by gender and comorbidity.

This study aimed to analyze population-based long-term survival after CEA for asymptomatic stenosis, and to assess the possible impact of various risk factors.

Subjects and Methods

The Swedish Vascular Registry (Swedvasc) started as a regional registry in 1987 and has national coverage since 1994, thus including all centers performing CEA in the country (population ≈9 million). Prospective data on basic demography and risk factors, together with details of surgical technique and postoperative outcome, are registered. Patients treated conservatively are not reported to the Registry. Degree of carotid stenosis or status of contralateral ICA are not (yet) reported.

Follow-up includes perioperative (30-day) complications and outcome, as well as overall outcome and patency at 1 year (neurological events are not registered specifically after 30 days).

Data were retrieved on all CEAs registered during a 10-year period (1994–2003), combined procedures (eg, with thoracic surgery) were also included. Procedures for restenosis were not included.

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Patients operated on bilaterally were identified and one of the CEAs was selected, as the index procedure, for analysis. Because the focus of the study was the patients operated on for an asymptomatic lesion, these were primarily selected as index procedures. In case of 1 asymptomatic and 1 symptomatic carotid lesion, the CEA of the asymptomatic artery was defined as the index procedure. If both arteries were asymptomatic or symptomatic, the first operated vessel was defined as the index procedure.

In this study the definition of asymptomatic stenosis excluded all ipsilateral carotid artery events and nonhemispheric symptoms within 6 months (nonhemispheric symptoms including posterior circulation events and nonspecific symptoms).

All patients were cross-matched with the National Population-registry in November 2005 to update data on mortality and date of death. This is possible because of the fact that every Swedish citizen has a unique personal identity code. Long-term survival analyses were performed by combining these 100% accurate date of death with the date for surgery, which resulted in correct survival data for up to 11.8 years of follow-up.

Regression analyses were performed to assess factors influencing long-term survival after CEAs for asymptomatic stenosis, including all patients with 5-year data (ie, patients operated on from January 1994 to November 2000).

The retrieved Swedvasc data were extensively validated in 4 different procedures, both internal and external. In the validation process specific focus was on the asymptomatic cohort, with respect to appropriate classification of indications and perioperative complications. These results have been reported previously.¹¹

The study was ethically approved by the registry steering committee, which according to Swedish law, is the authority concerning research based on registry data.

Statistics

Analyses were performed using SPSS (12.0.1) and R (version 2.2).¹² Continuous variables were summarized by the median (and quartiles), whereas categorical variables were summarized by percentages. Continuous variables were compared with the Wilcoxon-Mann-Whitney test and categorical variables with the Pearson χ^2 test.

Logistic regression models were fitted to estimate the relative odds ratio (OR) of 5-year mortality for different risk factors, as well as for asymptomatic versus symptomatic patients adjusted for each of these risk factors one at a time. The ORs are presented with 95% CIs.

Kaplan-Meier curves were used to illustrate crude cumulative survival. Survival curve comparisons were done using log-rank test and hazard ratios, but nonproportionality of the hazards limits the ability of analysis. A statement of statistical significance implies $P < 0.05$.

Results

CEA

During the 10-year period 1994 to 2003, a total of 6169 primary carotid endarterectomies in 5808 patients were registered. In 5177 of 5808 (89.1%) patients the index CEA was for symptomatic and in 631 of 5808 (10.8%) for asymptomatic stenosis. The number of patients operated on bilaterally with CEA was 361 of 5808 (6%), and among patients with an asymptomatic stenosis 152 of 631 (24%). Operations for bilateral asymptomatic lesions were performed in 35 of 631 (6%). Bilateral operations were staged.

The indications for the symptomatic patients were minor stroke in 41%, transient ischemic attack in 37%, amaurosis fugax in 20%, and nonhemispheric symptoms in 2%.

Median age was 70 years (quartiles 64; 75), equal for the symptomatic and asymptomatic cohort. Baseline characteristics are presented in Table 1.

TABLE 1. Baseline Characteristics Among Patients With Asymptomatic and Symptomatic Stenosis as Indication for Their Index CEA

Baseline Characteristics	Asymptomatic Stenosis, N=631	Symptomatic Stenosis, N=5177	P*
Male	63.8% (402)	66.6% (3440)	0.168
Cerebrovascular disease	62.1% (379)	98.4% (5094)	<0.001
Diabetes mellitus	19.2% (115)	18.9% (886)	0.856
Hyperlipidemia	54.2% (206)	49.6% (1303)	0.096
Hypertension	65.1% (394)	60.1% (2888)	0.017
Cardiac disease	48.2% (290)	44.3% (2127)	0.072
Previous vascular surgery	36.8% (222)	13.5% (636)	<0.001
Bilateral CEA	24.1% (152)	4.0% (209)	<0.001
Renal insufficiency	6.1% (36)	3.6% (167)	0.004
Pulmonary disease	9.0% (54)	8.6% (401)	0.711
Smoking	41.7% (237)	42.2% (1845)	0.83

*Pearson χ^2 test.

Patch closure was performed in 34.4% of patients with asymptomatic versus 31.6% with symptomatic lesions ($P=0.15$). Eversion CEA was used in 3.3% for asymptomatic versus 1.9% for symptomatic stenosis ($P=0.01$).

The perioperative combined stroke or death rate was 2.2% for the asymptomatic versus 4.4% for symptomatic cohort ($P=0.010$). There were 2 fatal strokes (of 3 deaths) among patients operated on for asymptomatic and 19 strokes (of 70 deaths) for symptomatic stenosis.

Long-Term Survival

In total, 5808 patients with a median (range) time at risk of 5.1 (0.1 to 11.8) years, were studied. The Kaplan-Meier curves in Figure 1 display the crude cumulative survival rate with respect to indication for CEA. The median survival for the asymptomatic cohort was estimated to 10.2 (9.0 to *) years and for the symptomatic 10.8 (10.5 to 11.6) years (*the upper limit of the 95% CI for the curve has not yet crossed the 0.5 level). The average hazard did not differ statistically significantly between the symptomatic and asymptomatic groups ($P=0.12$; hazard ratio=0.89; 0.76 to 1.03).

Patients operated on for asymptomatic stenosis had a perioperative mortality of 0.5%, an ARR of 0.9% compared with the symptomatic cohort (0.5% versus 1.4%; $P=0.07$), but this was reduced at 1 year to an ARR of 0.3% (3.8% versus 4.1%, $P=0.71$). After 1 year the survival curves crossed, and at 10 years the asymptomatic cohort had a negative ARR of -8.3% (46.2% versus 54.5%; $P=0.11$). These differences were further explored by analyzing the annual mortality after CEA, which are presented in Table 2. The mortality changed over time periods and between the asymptomatic and symptomatic cohorts.

The 5-year and 10-year survival after CEA were also calculated, the numbers followed up at 5 years were 3734 of 5808, and at 10 years 948 of 5808. The survival was at 5 years

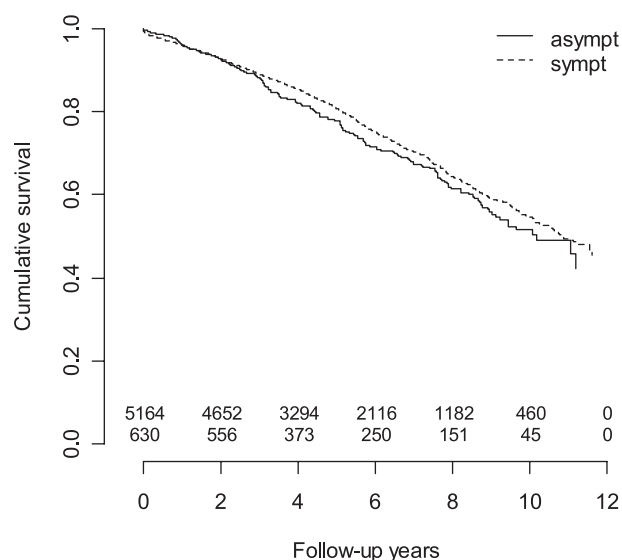


Figure 1. Kaplan-Meier curve for crude cumulative survival of the asymptomatic (solid line) and symptomatic (dotted line) cohort. Numbers of patients at risk listed for every second year of follow-up.

for the group with asymptomatic stenosis 78.2% versus 81.1% for the symptomatic group ($P=0.353$), and at 10 years 45.5% versus 53.8% ($P=0.114$).

Risk Factors and 5-Year Survival

The analyzed data on all patients with a completed 5-year follow-up, with respect to the risk factors registered at baseline, are presented in Figure 2. Previous vascular surgery (OR, 1.8; 1.1 to 3.0), cardiac disease (OR, 1.7; 1.0 to 2.8), diabetes mellitus (OR, 2.3; 1.3 to 4.1), and age (OR per 10 years, 1.5 1.1 to 2.1) were predictors of decreased 5-year survival.

In the model comparing the patients with asymptomatic and symptomatic stenosis there was no difference regarding the relative risk of 5-year mortality and the (known) con-

TABLE 2. Incremental Deaths After CEA for Asymptomatic and Symptomatic Stenosis

Time After CEA	Patients With Asymptomatic Stenosis		Patients With Symptomatic Stenosis	
	N Risk/N Dead	Mortality	N Risk/N Dead	Mortality
0–30 days	630/3	0.5%	5164/70	1.4%
30 days–1 year	627/21	3.3%	5097/147	2.9%
1–2 years	606/23	3.8%	4950/165	3.3%
2–3 years	556/24	4.3%	4652/175	3.8%
3–4 years	458/31	6.8%	3949/149	3.8%
4–5 years	373/19	5.1%	3294/165	5.0%
5–6 years	315/24	7.6%	2692/179	6.6%
6–7 years	250/13	5.2%	2116/122	5.8%
7–8 years	200/16	8.0%	1626/121	7.4%
8–9 years	151/11	7.3%	1182/83	7.0%
9–10 years	92/6	6.5%	790/47	5.9%

Numbers at risk at the beginning of each year and annual mortality after CEA.

founding risk factors did not statistically significantly influence the difference (Figure 3).

Perioperative Complications and 5-Year Survival

An analysis of the asymptomatic cohort was performed to evaluate if perioperative complications were predictive of late mortality. Patients with a cardiovascular event after CEA demonstrated a statistically significant decreased 5-year survival (2.2% among those alive versus 11.4% among those dead; $P<0.001$), but not those with a perioperative stroke (2.5% versus 3.4%; $P=0.658$).

Discussion

In this long-term follow-up, the median survival after carotid endarterectomy for patients with an asymptomatic stenosis was 10.2 years. Although the perioperative mortality was low (0.5%), the increasing annual mortality negatively affects longevity when compared with expected survival for this age group.¹³

Although if the plot of survival curves gives a visual impression of difference between the 2 curves, with decreased long-term survival for the asymptomatic cohort (Figure 1), it was not demonstrated by the statistical analyses performed. However, although the late crude survival for the asymptomatic cohort was not significantly different from the symptomatic cohort, this in itself was a somewhat unexpected finding.

The survival in this population-based study, with half of the patients having had a CEA for an asymptomatic stenosis being dead after 10 years, causes some concerns about the long-term overall benefit of this increasingly performed prophylactic procedure. In Sweden the number of CEAs for asymptomatic stenosis has been stable over the years (11% to 12% of all CEAs), until recently when the numbers increased after the results of the ACST were made public (20% in 2004 and increasing).¹⁴ The same effect was seen in Northern America after the publication of ACAS, with an up to 10-fold increase.¹⁵

Most series on outcome after CEA neither report long-term follow-up (survival) nor analyze results specifically depending on the indication for surgery. When late survival is reported, it is commonly demonstrated at 5 and 10 years. In the present study the 5-year survival was 78.2% and the 10-year survival was 45.5% for the asymptomatic cohort.

In a study on long-term survival after CEA for asymptomatic stenosis, Branchereau et al³ demonstrated survival after 5 years of 74.6%, and after 10 years of 59.4%, when including patients with combined procedures and nonhemispheric symptoms, and when excluding the latter 2 groups the 5-year survival was 82.0%. Cao et al⁴ analyzed late survival after CEA for asymptomatic lesions and correlated it to the presence of silent brain infarctions, with a 5-year survival of 86.0% without versus 78.3% with silent brain infarctions, and a 10-year survival of 69.3% versus 60.6%, respectively.

Other recent series on survival after CEA, without information regarding outcome depending on indication for surgery but with more than one-third of patients operated on for asymptomatic stenosis (33% to 64%), the reported late survival varies considerably. In a study of CEA with two-

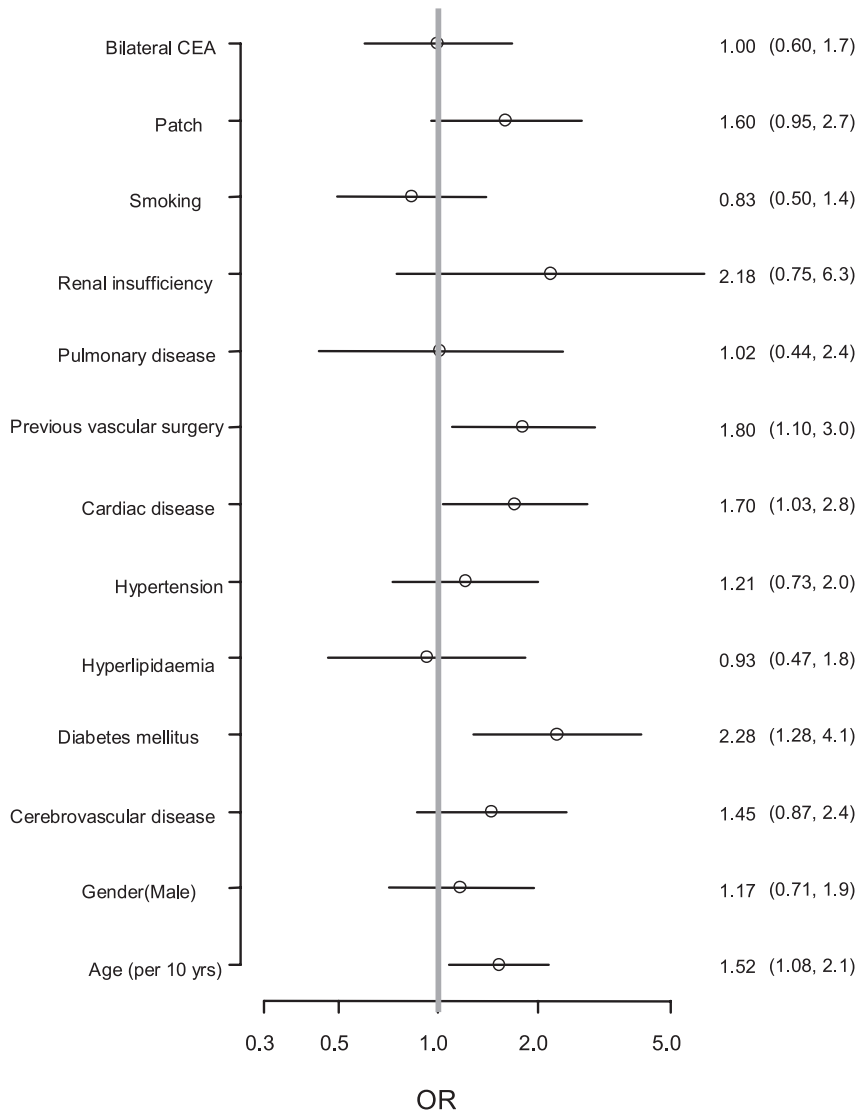


Figure 2. Risk factors for 5-year mortality in asymptomatic patients. The circles and lines represent crude relative odds ratios and 95% CIs.

thirds having asymptomatic stenosis as indication for the procedure, the long-term survival was similar to the findings of this study, with 72.4% at 5 years and 44.7% at 10 years.⁶ However, other studies with at least one-third of the patients operated on for an asymptomatic stenosis demonstrated far better survival with 92% to 93% at 5 years and 87% to 89% at 10 years.^{5,7}

Long-term survival in the randomized trials is not yet available, in ACAS mean follow-up was 2.6 years and in ACST there is an ongoing long-term follow-up.^{1,2} These awaited results will probably provide further information on this matter, including the stroke-free survival, which was not possible to assess in this study, because stroke >30 days after surgery is not reported to the Swedvasc. However, it will take years before the follow-up of the trial is completed.

There are some recent natural history studies on long-term survival in patients with asymptomatic carotid artery stenosis, but because of differences in study population and definition of stenosis, comparisons are difficult. Inzitari et al⁹ published a study of patients from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) with a (contralateral) asymptomatic stenosis (>60%) and the 5-year survival

was 79%. In a report by AbuRahma et al⁸ of patients with asymptomatic stenosis (>60%) and contralateral occlusion, the 5-year survival was 83%, and after 10 years was 67%. These series on late survival for patients with asymptomatic stenosis, not undergoing CEA, compares favorably with the results in the present study.

However, as the baseline risk factors indicate, this is a selected group with many patients (37%) having undergone previous vascular interventions (ie, contralateral CEA, aneurysm repair or interventions for peripheral artery disease [PAD]). When comparing longevity for patients operated on for other vascular procedures, a published series of revascularization for PAD with claudication a 10-year survival of 54% was demonstrated,¹⁶ and for elective repair of an infrarenal aortic aneurysm the overall survival was 75% and 49% at 5 years and 10 years, respectively.¹⁷

Because almost half (48%) of the asymptomatic cohort had cardiac disease registered, comparisons with longevity after coronary artery bypass grafting may also be of interest, and in a large study of coronary artery bypass grafting the 10-year survival was 70%.¹⁸

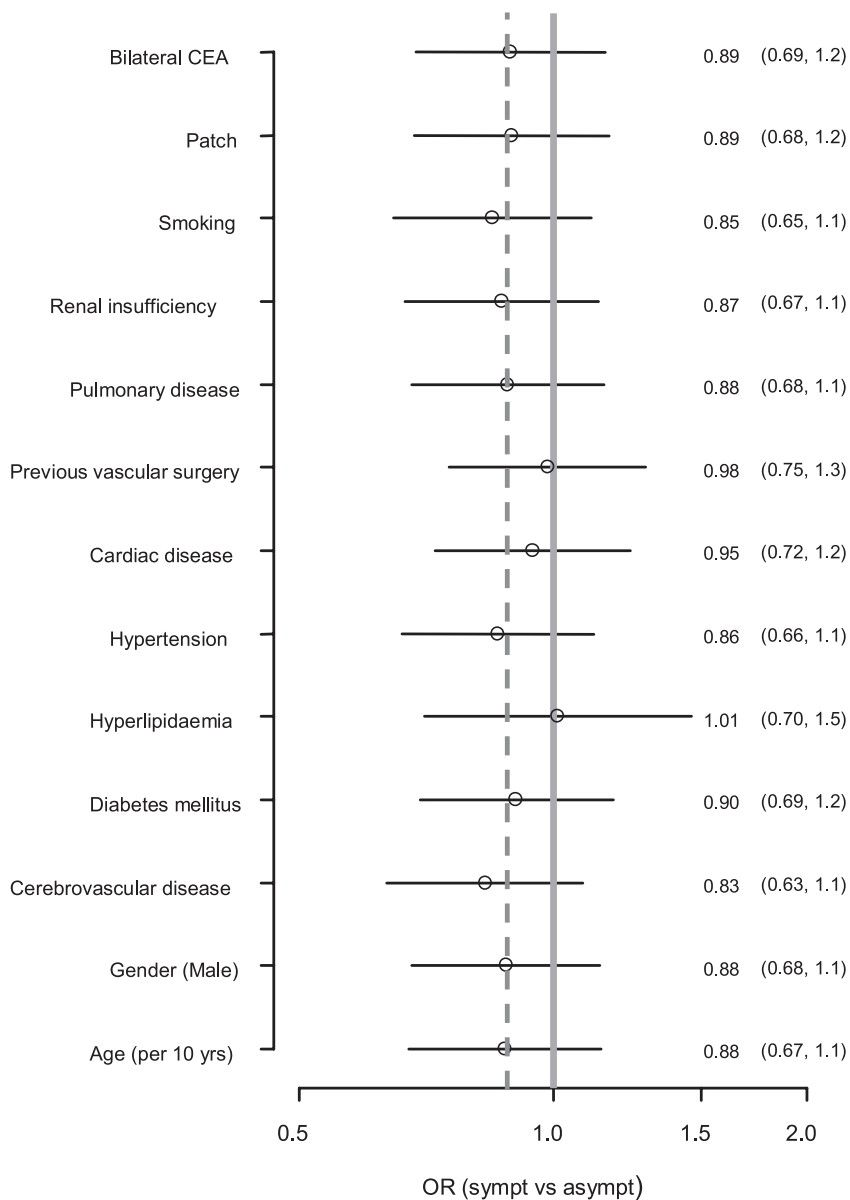


Figure 3. Adjusted relative odds ratios of 5-year mortality for symptomatic versus asymptomatic patients (adjusted for each of the listed variables one at a time). Dashed line represents OR=0.89 (0.76 to 1.03).

Altogether, it is clear that the patients operated on for asymptomatic stenosis in this population-based analysis had a high late mortality, and the predictors of decreased longevity were age, diabetes, cardiac disease, and previous vascular surgery.

The impact of age on late survival is not surprising. However, it is a factor to consider when deciding on CEA for asymptomatic lesions. The mean age (70 years) in this series is somewhat higher than in the ACAS (67 years) and the ACST (68 years), but similar to most series on survival after CEA. Life expectancy for an average 70-year-old person in Sweden was 12.3 years for men versus 15.4 years for women in 1995, and has increased to 13.7 years for men versus 16.5 years for women in 2004.¹³ We could not find any gender influence on late survival in the present study.

In one of the few studies of long-term survival after CEA for asymptomatic stenosis, Cao et al⁴ found age >70 years, lacunar infarction, and diabetes to be independent predictors

of late mortality. The correlation of diabetes with decreased late survival is in agreement with the present findings, and also with the results from a recent large review of patients having CEA, which included 64% with asymptomatic indication.⁶ Coronary artery disease was another negative predictor of long-term survival, also in agreement with our findings of cardiac disease and cardiovascular perioperative complication as risk factors for decreased late survival.

Previous vascular surgery correlated with decreased longevity in this study and was present in 37% of the patients with asymptomatic lesions. This reflects how these patients were often identified, namely when investigated and followed after surgery for a contralateral carotid artery stenosis, aneurysm, or PAD. In one-quarter (24%) of the patients operated on for asymptomatic stenosis bilateral CEA had been performed, but this was not a predictor of late mortality. This consequently indicates that the remaining patients (13%) who had undergone other peripheral vascular procedures (ie,

operations for PAD or aneurysms) had an even higher late mortality. In contrast, in other studies patients operated on only for PAD or isolated aneurysms seem to have a better long-term survival.^{16–17}

It is noteworthy that almost two-thirds (63%) of the patients operated on for asymptomatic stenosis in the present study had cerebrovascular disease registered at baseline as a preoperative risk factor. These registrations may be explained by the presence of symptomatic contralateral carotid artery disease (stenosis or occlusion) or by previous (>6 months ago) cerebrovascular events of various causes. It is important to bear in mind that these patients represent a highly selected group with often multiple atherosclerotic manifestations that may influence the long-term results. This may explain the similar mortality among the patients with symptomatic and asymptomatic stenosis.

Conclusion

Long-term survival after carotid endarterectomy for an asymptomatic stenosis is an important consideration when deciding on this prophylactic procedure. In this population-based study a substantial reduction in long-term survival was observed. Predictors of decreased longevity were age at operation, diabetes, cardiac disease, and previous vascular surgery.

However, it is important to consider that these patients represent a selected group and not to make general conclusions for all patients with asymptomatic stenosis based on these results. Randomized studies on population-based screening for asymptomatic carotid artery stenosis seem highly motivated to further define which patients with asymptomatic stenosis benefit most from prophylactic carotid endarterectomy.

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Disclosures

None.

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