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Long-term Survival after Carotid Endarterectomy in a Population with a Low Coronary Heart Disease Fatality: implications for Decision-Making

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Key Words: carotid endarterectomy• long-term survival • risk factors • coronary artery disease

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Abstract

Objectives - According to current guidelines, long-term survival is an important factor influencing decision-making in patients with severe asymptomatic carotid stenosis. Nevertheless data is lacking for populations with a low incidence of coronary heart disease, the main cause of death among these patients. We aimed to assess the long-term survival after carotid endarterectomy (CEA) in a Mediterranean hospital.

Materials and Methods -Retrospective analysis of 291 consecutive patients (main age 69 years, 78.7% men) who underwent a CEA for symptomatic (n=147, 50.5%) or asymptomatic (n=144, 49.5%) carotid stenosis in2005-2014 at the Hospital del Mar (Barcelona, Spain). A Kaplan-Meier life-table was done and a multivariable Cox regression model was built for the analysis of the long-term survival associated risk factors.

Results - The immediate combined mortality and/or neurological morbidity rate was 2.7%. The mean follow-up was 55 months (complete in 99.7%). During follow-up 62 patients (21.3%) died, being cancer the most frequent cause (35.5%). Cumulative 3- and 5-year survival rates were 89% and 81%, respectively. Independent risk factors (Cox regression) related to survival included: age (HR=1.09; p<.001), an ASA IV score (HR=4.04; p=.015) and the preoperative hemoglobin value (HR=0.73; p<.001). The discrimination of the resulting model was 0.719 (IC95%= 0.644-0.794). Previous symptomatic carotid stenosiswas not related to long-term survival

Conclusion - The long-term survival of patients submitted to CEA in our series lies in the lower limit of the estimated range by other groups and is markedly related to cancer. Our study suggests that predictive models for survival are influenced by regional

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Introduction

Guidelines of clinical practice support the role of carotid endarterectomy (CEA) in the management of both symptomatic and asymptomatic patients with severe carotid stenosis[1-2]. CEA is a prophylactic intervention associated with a low-moderate reduction of stroke incidence, particularly in asymptomatic cases. Therefore, both the operative risk and the long-term survival are crucial to ensure the expected benefit. With this purpose in mind, several studies from Northern Europe and United States have analyzed preoperative factors associated with long-term survival[2-5]. However, little is known about the life span and their predictive factors among patients submitted to CEA in populations with a low incidence of coronary artery disease (CAD), precisely the main cause of death within these patients[6]. The finding of markers associated with survival may determine variations in the decision-making process in patients with carotid stenosis, particularly among those without previous cerebrovascular symptoms. The aim of this study was to determine the long term survival in patients submitted to CEA at the Vascular Surgery Department of the Hospital del Mar, Barcelona (Spain), an area with a low incidence of CAD[7-8], and to develop a survival predictive score based on preoperative factors.

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Materials and Methods

Study population

A retrospective analysis of 291 consecutive patients who underwent a CEA at the Vascular Department of the Hospital del Mar (Barcelona, Spain) between 2005 and 2014 was done.

Baseline demographic and clinical data were obtained from computerized registries and hospital charts. Analyzed variables included age, gender, risk factors, associated cardiovascular diseases, other comorbidities and the American Society of Anesthesiologists risk score. Patients were classified as current smokers, former smokers > 1 year or never smokers. Hypertension, diabetes, dyslipidemia and chronic obstructive pulmonary disease were considered if previously diagnosed by a physician or under treatment. Preoperative hemoglobin and creatinine values were defined as the last measurement obtained before surgery. Coronary artery disease (CAD) was defined as any history of angina, myocardial infarction or preoperative electrocardiography changes consistent with previous myocardial ischemia. Chronic obstructive pulmonary disease (COPD) was considered if previously diagnosed by a physician and under treatment. Other comorbidities, such as atrial fibrillation, chronic heart failure or a prior cancer history, were considered if previously reported in medical records.

Indications for CEA included patients with an ipsilateral symptomatic >50% or an asymptomatic >70% carotid stenosis [9], at average or low surgical risk as stated by a preoperative anesthesiologist evaluation, without known limiting conditions for mid-term survival and who agreed to undergo surgery. Patients excluded for CEA

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included 1) those with a stenting indication (symptomatic >50% carotid stenosis in patients with ASA class IV, redo-procedure, cervical irradiation, tracheal stoma or prior cranial nerve injury), 2) those with an asymptomatic >70% carotid stenosis and ASA class IV, and 3) in any patient with a previous disabling stroke or poor life-expectancy.

A standard CEA was performed under general anesthesia in all patients. Carotid shunt was used selectively. In all cases a distal fixation of the intima was done while endarterectomy of the external carotid artery was performed only if required. A vein or PTFE patch for closure was done in all cases. Perioperative care included observation in the recovery ward for 24 hours followed by a home discharge at the third day after the surgery. All patients were operated under antiplatelet medication and followed it indefinitely.

Follow-up and outcome

Once the patient was discharged after the operation, regular clinical and duplex surveillance were scheduled according to standard protocols. The survival status of the study population was determined from follow-up visits and hospital and Regional Health Computerized records (IMASIS and HC3). Whenever needed patients or their relatives were contacted by phone. Causes of death were considered only if obtained from reliable clinical sources.

The primary outcome was immediate and long-term survival after CEA. Secondary outcomes included 30-day neurological morbidity defined as new stroke or TIA), and the search of preoperative predictive factors. The study was conducted under the approval of the Institutional Human Research Ethics Committee (CEIC-PSMAR).

Statistical analysis

Categorical variables were expressed as cases and per cent values. Continuous variables were expressed as mean +/- standard deviation. The 3- and 5-year survival rates were assessed with the Kaplan-Meier method. Cox bivariate models were done to determine the relationship between categorical and continuous variables with long-term survival. In order to control for potential confounders, all preoperative variables significantly related to survival with a $p<0.1$ were entered into a Cox multivariate regression analysis. Statistically non-significant variables not modifying beta-coefficients were retrieved from the model to increase statistical power. The discrimination power of the model was finally assessed by the C statistic (non-time dependent). A $p<0.05$ was considered statistically significant. All analyses were done with SPSS Statistical Software (19.0 version, SPSS Inc Chicago, IL, USA) and R Statistical Software(R Development Core Team, Vienna, Austria).

Results

Population of Study

The baseline characteristics of the patients are summarized in Table 1. The mean age was 69 years and 229 (78.7%) were male. Significant comorbidities in the study group included coronary artery disease (n=80, 27.5%) and a prior malignancy history (n=35, 12%). A total of 147 patients (50.5%) had suffered an ipsilateral amaurosis fugax, transient ischemic attack or non-disabling ischemic stroke before the CEA was performed. Symptomatic patients were more likely younger (p=0.028), women (p=0.013), non-smokers (p=0.01) and with a lesser rate of coronary heart disease (p=0.013) and peripheral artery disease (p<0.001) than asymptomatic patients. Asymptomatic patients regularly came from a screening program among subjects with aneurysmal or peripheral artery disease.

Immediate and long-term survival and causes of death

Median follow-up was 55 months and was complete in 99.7% of patients. A total of 62 patients (21.3%) died during follow-up. The immediate (in-hospital or <30 days) combined mortality and neurological morbidity rate was 2.7% (4 deaths and 4 neurologic events). Causes of death in the postoperative period included 2 heart failures, 1 respiratory infection and 1 aspiration pneumonia.

The 3- and 5-year survival rates were 89% and 81%, respectively (Figure 1). The main cause of death was cancer in 22 patients (35.5%). Of these, 4 died of a neoplasia known before the CEA was performed, while in the remaining 18 a new malignancy was diagnosed at a mean time from CEA of 38 months. Other causes of late deaths included heart diseases (n=14, 22.6%), respiratory diseases (n=6, 9.7%) and stroke (n=2, 3.2%) (Table 2). The cause of death could not be ascertained properly in 4 patients (6.5%).

Factors associated with survival

Preoperative variables significantly associated with a reduced long term survival in the bivariate analysis included age (HR 1.091; p<.001), an ASA IV class (HR 4.130; p=.012), COPD (HR 2.031; p=.023) and the preoperative hemoglobin value (HR 0.710; p<.001). The preoperative hemoglobin value was both related to cancer (HR 0.678, p=.002) and non-cancer long term mortality (HR 0.713, p=.001). No significant differences in the long-term survival were seen between patients with symptomatic or asymptomatic carotid stenosis.

In the multivariate analysis (Table 3) age (HR per year 1.092; p<.001), an ASA IV status (HR 4.037; p=.015) and the preoperative hemoglobin value (HR per additional g/dl 0.734; p<.001) were all independently associated with long-term reduced survival. The addition of previous symptomatic carotid stenosis status to the model neither became predictive of long-term survival nor modified the β coefficient of the other variables. A survival predictive score was generated from the Cox regression model, which showed a good discrimination capacity (C statistic=0.719; 95%CI 0.644-0.794).

Neurological and Coronary events during follow-up

During follow-up 14 neurological events (including 4 postoperative) were recorded, of which 2 (14.3%) were transient ischemic attacks and 12 (85.7%) strokes. The 1- and 5-year free-survival from a neurological event was 97.1% and 94.2%, respectively. Stroke was the cause of late death in 3 patients (one of them postoperative). Acute coronary events occurred in 15 patients (5.2%), of which 3 were postoperative and the remaining 12 all over the follow-up. Seven patients required a coronary stenting intervention while 2 were submitted to coronary bypass. The 1- and 5-year free survival from an acute coronary event was 99% and 95%, respectively.

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Discussion

Stroke remains the third cause of death and the leading cause of long-term disability and institutionalization in the USA[1]. Carotid artery stenosis is thought to be the cause of 20-30% of strokes[10] while it is known that 80% of strokes are not preceded by transitory symptoms[1, 11]. These data together with a well-documented low-moderate benefit of CEA in stroke prevention support the role of this prophylactic intervention in current vascular practice[12] since two decades. However to ensure the expected benefit, some current guidelines have stated that asymptomatic patients selected for CEA should have a minimum life expectancy of 3 years[2]. To address properly this issue the long-term survival and predictive factors of patients currently submitted to CEA has been recently analyzed. Accordingly several groups from USA and Northern European countries have reported 5-year mortality rates among these patients ranging from 3,8% to 18%[3-4, 13-14], a better prognosis than the observed in our series (19%). To understand why among our intervened patients, who live in a setting with a low incidence of CAD[15-16], the 5-year survival rate is in the lower limit of the estimated range by other studies, the characteristics of our study population, the main causes of late deaths and the predictive factors of long-term survival have been taken in consideration.

In the last decade several studies have identified preoperative variables related to long-term survival in patients submitted to CEA[3-4, 6, 13-14, 17]. Among them, COPD, chronic heart failure, CAD, chronic kidney disease and increasing age have been the most frequently reported. Some of them, such as COPD and dialysis[2, 4], were found to have a powerful relationship with survival. COPD appeared to be related to survival in our univariate analysis, although this relationship was not confirmed in the multivariate analysis. In our study group a low prevalence of CAD and heart disease related fatality were observed as compared with previous studies[3-4, 13-14] and, additionally, very few patients under dialysis treatment were submitted to carotid surgery. The small number of cases in both subgroups may have accounted for the lack of significant relationships between these factors and survival among our patients. Consistent with other studies, a previous stroke did not contribute significantly to late mortality among patients submitted to CEA[14, 18-19]. However it is a limitation of the present study the analysis of predictive factors of survival in a mixed series of symptomatic and asymptomatic subjects undergoing carotid surgery.

A low preoperative hemoglobin value was found to be a strong predictive factor of long-term survival in our study and to our knowledge this is the first study reporting this finding among patients submitted to carotid endarterectomy. In patients undergoing cardiac surgery the impact of preoperative hemoglobin value on outcome has been well documented[20-24]. Higher rates of postoperative morbidity and mortality have been reported among anemic patients, especially in elderly population. Although much less reported, anemia has also been shown to increase the risk of cardiac events and postoperative mortality in non-cardiac surgical patients, including those submitted to a mix of vascular interventions[25-28]. However, the relationship between preoperative anemia and long-term survival has only been established by Stratenet al[29] in cardiac interventions. A low preoperative hemoglobin value might thus be indicating some sort of frailty, poor nutritional status, underlying malignancy or a chronic disease status among patients submitted to surgery.

As opposed to previous studies, cancer was the main cause of death in our cohort of patients. This finding, together with the significant relationship seen between the preoperative hemoglobin value and long-term survival, raises the question of whether an occult malignancy might be present among these patients at the time the CEA was performed. Against this assumption, however, it is the fact that the preoperative hemoglobin value was both associated with cancer related and non-related mortality and that the median interval from CEA to cancer diagnosis among patients dying of this cause was long. Additionally neither a preoperative history of malignancy was associated with long-term survival or cancer recurrence of malignancies already known before CEA contributed significantly to late deaths. Further research is needed however to explore prospectively the influence of anemia in the long-term survival after carotid surgery.

This study has several limitations including its retrospective design which, among others, has limited our ability to explore more deeply the relationship between the preoperative hemoglobin value and long-term survival, and a relatively small sample size which may have decreased the power to evaluate properly the influence of several risk factors on long-term survival, particularly those with a low prevalence at baseline. Additionally it has not been possible to provide data about patients with significant carotid stenosis managed medically or subjects treated with carotid stenting during the period of study. Although very few patients (<5 cases per year) are regularly submitted to carotid stenting at our Department, both conditions may have resulted in a potential selection bias. Furthermore the cause of late death was not possible to ascertain in a small group of patients. The ASA IV score appeared to be significantly related to survival although only a small group of patients were

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categorized in this group, thus raising the risk of committing an alpha error. Finally, the data used to create our prediction model was taken from a single-center registry, and therefore, may not be generalized to other regions or countries with a low incidence of CAD. Indeed selection of patients from screening programs for other diseases, which may vary among institutions, can modify the prevalence of risk factors as compared with symptomatic cases and result in changes in the life expectancy of intervened patients.

Conclusion

The long-term survival of patients submitted to a CEA in our study lies in the lower limit of the estimated range by other groups despite living in a region with a low CAD fatality rate. Cancer is the most frequent cause of late death while a low preoperative hemoglobin value was a strong predictor of long-term survival.

Recently many groups have stated the importance in selecting patients for asymptomatic EA intervention, focusing the decision making on the presence of certain risk factors influencing long-term survival. Our study however suggests that predictive models for long-term survival after CEA may be influenced by regional characteristics of the intervened population and that this effect should be taken in consideration in the decision-making in these patients.

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Tables

Table 1. Characteristics of patients undergoing carotid endarterectomy

	Asymptomatic N=144	Symptomatic N=147	p
Age (years)*	69(8, 49-81)	70(8.3, 48-81)	0.028
Male gender	122 (84.7)	107 (72.8)	0.013
Smoking			
Never	21 (14.6)	43 (29.3)	
Former (>1 year)	79 (54,8)	68 (46.2)	
Current	44 (30.6)	36 (24.5)	0.01
Hypertension	111 (77)	112 (76.2)	n.s.
Diabetes Mellitus	46 (31.9)	60 (40.8)	n.s.
Dyslipidemia	115 (79.8)	109 (74.1)	n.s.
Chronic Obstructive Pulmonary Disease	18 (12.5)	18 (12.2)	n.s.
Prior Cancer History	17(11.8)	18(12.3)	n.s.
American Society of Anesthesiologists score			
ASA II	23 (16)	30 (20.4)	
ASA III	117 (81.2)	109 (74.1)	
ASA IV	4 (2.8)	8 (5.4)	n.s.
Hb (g/dl)*	13.6(1.7, 10.2-16.5)	13.6(1.7, 9.6-16.2)	n.s.
Creatinine (mg/dl)*	1.1 (0.4, 0.61-1.89)	1.1(0.53, 0.54-1.99)	n.s.
Coronary Artery Disease	49 (34)	31 (21.1)	0.013
Peripheral Artery Disease	88 (61.1)	39 (26.5)	<0.001
Previous cerebrovascular events			
Amaurosis fugax		18 (6,2%)	
Transient ischemic attack		47 (16,2%)	
Non-disabling stroke		82 (28,5%)	

Cases (percentage)
** Mean (Standard Deviation, Confidence Interval 95%)*

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Table 2. Causes of late death among patients submitted to carotid endarterectomy

	Patients (%)
Cancer	22 (35,5)
Heartdisease	14 (22,6)
Respiratorydisease	10 (16,1)
Dementia	4 (6,5)
Stroke	2 (3,2)
Sepsis	2 (3,2)
Kidneyfailure	1 (1,6)
Cirrhosis	1 (1,6)
Aneurysmrupture	1 (1,6)
Trauma	1 (1,6)
Unknown	4 (6,5)
Overall	62 (21,3%)

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Table 3. Predictive factors (multivariate analysis) of long-term reduced survival after carotid endarterectomy.

	Hazard Ratio	*P value*
Age (per year)	1,092	<0,001
American Society of Anesthesiologists score		
ASA II	Referent	-
ASA III	1,158	0,690
ASA IV	4,037	0,015
Hemoglobin value (per mg/dl)	0,734	<0,001

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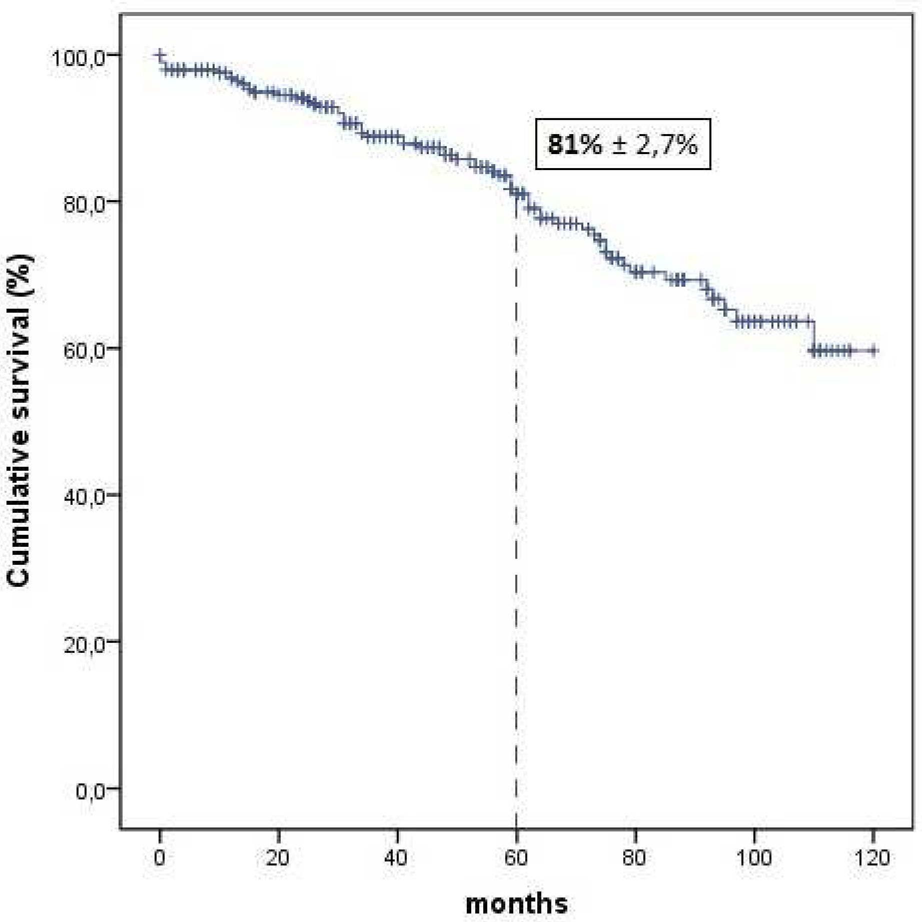
Figures

Figure 1. Kaplan-Meier estimated long-term survival of patients submitted to carotid endarterectomy



Time (months)	20	40	60	80	100
Patients at risk	238	183	129	72	32
Survival (%)	94.5	88.8	81	70.4	63.7
Standard D.	1.4	2.0	2.7	3.6	4.3

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