Original communication

Prognostic interaction between age and sex on outcomes following carotid endarterectomy

Mario D'Oria[1], Barbara Ziani[1], Marco Damiano Pipitone[2], Paolo Manganotti[3], Roberta Pozzi Mucelli[4], Filippo Gorgatti[1], Francesco Riccitelli[1], Francesca Zamolo[1], Maurizio Fisicaro[5], and Sandro Lepidi[1]

[1] Division of Vascular and Endovascular Surgery, Cardiovascular Department, Cattinara University Hospital ASUGI, Trieste, Italy
[2] Division of Vascular Surgery, Bolzano Regional Hospital, Bolzano, Italy
[3] Clinical Unit of Neurology, Department of Medicine Surgery and Health Sciences, Cattinara University Hospital ASUGI, Trieste, Italy
[4] Radiology Unit, Department of Medicine Surgery and Health Sciences, Cattinara University Hospital ASUGI, Trieste, Italy
[5] Cardiovascular Health Services Centre, Cardiovascular Department, Maggiore Hospital ASUGI, Trieste, Italy

Summary: *Background:* The aim of this study was to assess the prognostic interaction between age and sex on peri-operative and follow-up outcomes following elective carotid endarterectomy (CEA) for asymptomatic and symptomatic carotid stenosis. *Patients and methods:* A retrospective review of all patients admitted to a single vascular unit who underwent elective CEA between January, 2015 and December, 2019 was performed. The primary endpoints of the study were overall survival (from index operation) and cumulative stroke rate at thirty days. *Results:* A total of 383 consecutive patients were included in this study; of these 254 (66.4%) were males. At baseline, males were younger (mean age 73.4±11 vs. 76.3±10 years, p=.01) and with lower proportion of octogenarians (20.4% vs. 28.7%, p=.05). The rate of stroke in symptomatic and asymptomatic patients (males vs. females) were as follows: a) whole cohort 1.9% vs. 2% (p=1.00) and 2.7% vs. 1.3% (p=.66), respectively; b) ≥80 years old 3.7% vs. 0% (p=1.00) and 4% vs. 5.9% (p=1.00), respectively; c) <80 years old 1.2% vs. 3.3% (p=.47) and 2.5% vs. 0% (p=.55), respectively. The 3-year survival estimates were significantly lower for males (84% vs. 92%, p=.03). After stratification by age groups, males maintained inferior survival rates in the strata aged <80 years (85% vs. 97%, p=.005), while no differences were seen in the strata aged ≥80 years (82% vs. 79%, p=.92). Using multivariate Cox proportional hazards, age (HR: 2.1, 95% CI: 1.29–3.3, p=.002) and male gender (HR: 2.5, 95% CI: 1.16–5.5, p=.02) were associated with increased hazards of all-cause mortality. *Conclusions:* In this study of elective CEA for asymptomatic and symptomatic carotid stenosis, similar peri-operative neurologic outcomes were found in both males and females irrespective of age. Despite being usually older, females have superior long-term survival rates.

Keywords: Carotid endarterectomy, carotid stenosis, gender, age, outcomes, stroke, survival, cardiovascular

Introduction

Although carotid endarterectomy (CEA) remains one of the most commonly performed vascular operations, as suggested by current clinical practice guidelines for the treatment of both symptomatic and asymptomatic carotid stenosis [1], with an excellent profile of early and late neurologic outcomes [2, 3], it still continues to attract considerable debate regarding optimal patient selection to achieve satisfactory peri-operative results as well as sustained long-term benefits. Age and gender, which represent the two strongest non-modifiable risk factors for vascular surgical outputs [4], have both been linked to variations in outcomes following CEA [5, 6]. However, their combined effect is still underreported.

The aim of this study was to assess the prognostic interaction between age and sex on peri-operative and follow-up outcomes following elective CEA for asymptomatic and symptomatic carotid stenosis. We hypothesized that the impact of age on outcomes after elective CEA would differ between male and female patients.

Patients and methods

Data collection

A retrospective review of all patients admitted to the Vascular and Endovascular Surgery Division of Trieste University Hospital who underwent elective CEA between

January, 2015 and December, 2019 was performed. The unit is the only facility offering specialized vascular care in the area, thereby making local referral patterns almost exclusive.

Patients with both asymptomatic ≥70% and symptomatic ≥50% carotid stenosis were enrolled. The grade of stenosis was defined based on duplex ultrasound (DUS) with the North American Symptomatic Carotid Endarterectomy Trial method [7, 8]; a subsequent computed tomography angiogram of the supra-aortic and intracranial vessels was performed to corroborate DUS findings. The definition of asymptomatic was based on current clinical practice guidelines (no previous neurologic symptoms or no neurologic symptoms in the preceding 6 months) [1]. Patients with hemodynamically significant contralateral carotid stenosis or contralateral carotid occlusion were not excluded. Patients affected by carotid aneurysms or dissections, carotid body tumors, restenosis after prior carotid interventions, or CEA performed in association with other surgical procedures including coronary artery bypass grafting (CABG) and common carotid artery stenting at its origin from the arch were excluded. Patients undergoing urgent/emergent CEA within 24 hours from onset of neurologic symptoms were also excluded.

Demographic baseline characteristics, cardiovascular risk factors, preoperative medical therapy, symptoms status, operative details, and in-hospital outcomes were obtained by reviewing all available medical records at the time of operation. Any other new clinical or neurological findings after discharge and within thirty days were assessed with telephone interviews at thirty days by a dedicated doctor according to our institutional protocols.

Any acute episode requiring urgent/emergency hospitalization, as well as vital status and death information, were assessed using the Trieste University Hospital Area Intranet System (which allows for visualization of medical records of all Trieste area hospitals and outpatients clinics). If death occurred outside Trieste Area, death certificates were retrieved as permissible by the vital records statutes within the region in which the decedent passed away. A patient was considered lost to follow-up when available clinical data were older than two years, but death could not be confirmed.

An institutional review board is not available in our institution and ethical approval was not necessary in view of the retrospective nature of the study design. Local departmental structures approved the study which did not alter standard care delivered to patients. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent for clinical research was obtained from all participants involved in the study at time of index operation.

Surgical practice

At our institution, CEA is always considered as the first-line treatment for both asymptomatic and symptomatic carotid stenosis unless specific contraindications exist (previous neck surgery/radiation, contralateral laryngeal nerve palsy, high carotid bifurcation).

All CEA procedures were performed by experienced vascular surgeons (≥15 procedures/year). Our surgical protocol has been described in prior publications [9]. Briefly, two methods of CEA were considered: standard CEA with longitudinal arteriotomy of the carotid bulb and internal carotid artery (ICA) origin followed by patch or direct closure (for a straight ICA), or eversion CEA with ICA resection at the carotid bulb and its re-implantation (for an ICA with kinking or redundant coiling). Polypropilene 6.0 suture was used for all vascular anastomoses. All surgical procedures were performed under general anesthesia with neurological monitoring achieved through continuous electroencephalographic (EEG) monitoring, with selective shunt placement in case of acute deterioration of EEG waves compared to preoperative baseline measurement.

Technical success was defined as an uneventful CEA without the need for additional procedures during surgery or on waking (defined as any unplanned surgical or endovascular maneuver that was prompted by clinical or imaging evidence of technical defects or neurologic symptoms). Completion angiography was not routinely performed unless deemed necessary by the surgeon performing the operation on a case-by-case basis.

Study endpoints

The primary endpoints of the study were overall survival (from index operation) and cumulative stroke rate at thirty days. Secondary endpoints included thirty-day composite of stroke/death/myocardial infarction, post-operative local complications (bleeding requiring reoperation and peripheral nerve palsy), and major adverse cardiovascular events (MACE) during follow-up.

Stroke was defined according to the current reporting standards [10]. The National Institute of Health Stroke Scale (NIHSS) was used for preoperative neurological assessment, at patient awakening, as well as at 6 and 24 hours after the procedure by a dedicated physician. A score of ≤4 represents a minor stroke, 5 to 15 a moderate stroke, 15 to 20 a moderate-severe stroke, and 21 to 42 a severe stroke (http://www.nihstrokescale.org/). In case of altered NIHSS as compared with baseline, the patient was subsequently and independently evaluated by a neurologist for accurate evaluation and management strategy. MACE were defined as the composite of any of the following: cardiovascular death, fatal or non-fatal MI, unplanned coronary revascularization, and congestive heart failure (CHF) requiring new or recurrent hospitalization.

Statistical analysis

All data were evaluated for normality with quantile-quantile plots. Continuous variables are expressed with mean±standard deviation. Categorical variables are presented as absolute numbers and percentage. Univariable

analyses were carried out with either Student's T test or Mann-Whitney U test for continuous variables, and chi-square test or Fisher's exact test for categorical variables.

Time-dependent outcomes were reported using life tables and presented as Kaplan-Meier curves with standard error <10%; differences were determined by the log-rank test. The estimates of the cumulative incidence of MACE and death were demonstrated using a competing-risk subdistribution model with MACE and death as mutual competing risks. Survival estimates were presented with 95% confidence intervals (CI).

Multivariable Cox Proportional Hazards was used to assess independent predictors for all-cause mortality and MACE, with results reported as hazard ratio (HR) with 95% CI:. Covariates for these models were selected based on previously described risk factors and univariate screen of all available potential confounders and backwards selection with a criteria of 0.25 to stay in the final models; these were tested for violation of proportional hazards assumptions using Schoenfeld residuals.

To account for the potential confounding of events occurring within the first year after index CEA, sensitivity analysis with evaluation of Kaplan-Meier estimates and Cox Proportional Hazards in the restricted cohort of patients free from any adverse event (mortality and/or MACE) through the initial 12 months following index operation. Results from the sensitivity analysis confirmed the original models in all instances analyzed (data not showed).

Statistical significance was set at alpha level of 0.05. No outcome data were missing. No imputation was used to address missingness predictors variables and only covariates with missing rate <1% were used in multivariable models; therefore, the only variables excluded from the final models were body mass index and baseline hemoglobin values. All statistical analyses were conducted using R language for statistical computing software and figures were produced using the package ggplot2.

Results

Study population

A total of 383 consecutive patients were included in this study; of these 254 (66.4%) were males and 129 (33.6%) were females. At baseline, males were younger (mean age 73.4±11 vs. 76.3±10 years, p=.01) and with lower proportion of octogenarians (20.5% vs. 28.7%, p=.05) as compared with females. Also, history of past or active smoking was more frequent in males than in females, in the overall cohort as well as after stratification by age (Table I). No other major differences were found in risk factors and comorbidities between study groups but for the higher incidence of diabetes mellitus in males as compared with females (42.7% vs. 31.0%, p=.03); this difference was also significant in the subgroup of younger individuals (43.8% vs. 28.3%, p=.01) but not in those aged ≥80 years (38.5% vs. 37.8%, p=1.00).

Peri-operative outcomes

Details of CEA procedure revealed no major differences between study groups (Table II), although the total operation time that was significantly longer for males as compared with females in the whole cohort (75±29 vs. 75±26 minutes, p=.05) and in the subgroup of elderly individuals (75±24 vs. 65±35 minutes, p=.05), but not in those aged <80 years (75±29 vs. 75±20 minutes, p=.28).

Univariate analysis of thirty-day outcomes did not reveal any significant differences between genders, in the whole cohort as well as after stratification by age groups (Table III). The rate of stroke in symptomatic and asymptomatic patients (males vs. females) were as follows: a) whole cohort 1.9% vs. 2.0% (p=1.00) and 2.7% vs. 1.3% (p=.66), respectively; b) ≥80 years old 3.7% vs. 0% (p=1.00) and 4.0% vs. 5.9% (p=1.00), respectively; c) <80 years old 1.2% vs. 3.3% (p=.47) and 2.5% vs. 0% (p=.55), respectively. Out of eight peri-operative stroke events that were reported in the whole study population, five were classified as moderate-severe and three were classified as moderate according to the NIHSS scoring system.

No other differences were noted in the thirty-day rates of stroke/death and stroke/death/myocardial infarction as well as in the occurrence of post-operative local complications.

Overall survival

In the overall population, the 3-year survival estimates were significantly lower for males as compared with females (84% vs. 92%, p=.03; Figure 1). After stratification by age groups, males maintained inferior survival rates in the strata aged <80 years (85% vs. 97%, p=.005), while no differences were seen with females in the strata aged ≥80 years (82% vs. 79%, p=.92). Using multivariate Cox proportional hazards, age (HR: 2.1, 95% CI: 1.29–3.3, p=.002) and male gender (HR: 2.5, 95% CI: 1.16–5.5, p=.02) were associated with increased hazards of all-cause mortality (see electronic supplementary material [ESM] 1).

Major adverse cardiovascular events

No significant differences were seen between males and females, in the whole cohort as well as after age stratification, in freedom from MACE at 3 years (males: 81% vs. females 90%, p=.142; Figure 2). The difference in estimates of freedom from MACE remained non-significant after age stratification. Using multivariate Cox proportional hazards, no independent predictors associated with MACE were found (ESM 2).

After accounting for the competing risk of death (Figure 3), the three-year risk for MACE in the whole cohort was 0.17 in males and 0.10 in females (p=.178). After stratification by age groups, the three-year risk of MACE was not significantly different in subjects aged ≥80 years (males: 0.19 vs. females: 0.16, p=0.701), but was significantly higher in males as compared with females in subjects aged <80 years (0.17 vs. 0.07, p=.015).

Table I. Baseline characteristics

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
Mean age	73.7 (11.2)	**0.01**	82.5 (2.7)	0.41	71.3 (9.4)	0.06
	76.3 (10.3)		82.9 (2.8)		72.9 (8.2)	
Age ≥80	52 (20.5)	**0.05**	NA*	NA*	NA*	NA*
	37 (28.7)					
Symptomatic	107 (42.1)	0.51	27 (51.9)	1.00	80 (39.6)	0.25
	50 (38.8)		20 (54.1)		30 (32.6)	
Right side	129 (50.6)	0.91	28 (53.8)	0.67	101 (49.8)	0.90
	67 (51.6)		22 (59.5)		45 (48.4)	
BMI	26.2 (4.6)	0.94	25.5 (3.3)	0.98	26.3 (4.7)	0.80
	26.5 (4.9)		26 (5.6)		26.6 (4.8)	
Obesity (BMI 30 or more)	36 (18.5)	0.64	4 (10.0)	0.71	32 (20.6)	0.61
	21 (21.0)		4 (14.3)		17 (23.6)	
Smoking		**.001**		**0.05**		**0.05**
Past	84 (53.8)		13 (52.0)		71 (54.2)	
	31 (39.7)		7 (35.0)		24 (41.4)	
	49 (31.4)		7 (28.0)		42 (31.0)	
Active	20 (25.6)		2 (10.0)		18 (31.0)	
Hypertension	216 (85.0)	0.31	46 (88.5)	0.37	170 (84.2)	0.41
	104 (80.6)		30 (81.1)		74 (80.4)	
DM	109 (42.7)	**0.03**	20 (38.5)	1.00	89 (43.8)	**0.01**
	40 (31.0)		14 (37.8)		26 (28.3)	
History of CAD	59 (23.2)	0.90	12 (23.0)	0.34	47 (23.3)	0.65
	31 (24.2)		12 (33.3)		19 (20.7)	
Previous PCI/CABG	39 (15.4)	1.00	8 (15.4)	0.41	31 (15.3)	0.48
	20 (15.5)		9 (24.3)		11 (12.0)	
CHF	16 (6.3)	0.67	5 (9.6)	1.00	11 (5.4)	0.79
	10 (7.8)		4 (10.8)		6 (6.5)	
Atrial fibrillation	29 (11.4)	0.60	11 (21.2)	0.41	18 (8.9)	0.82
	12 (9.3)		5 (13.5)		7 (7.6)	
COPD	33 (12.9)	0.62	6 (11.5)	0.54	27 (13.3)	0.33
	14 (10.9)		6 (16.2)		8 (8.7)*	
CKD stage 3–5 (eGFR <60)	31 (12.2)	0.07	10 (19.2)	0.11	21 (10.4)	0.38
	8 (6.2)		2 (5.4)		6 (6.5)	
Symptomatic PAD	43 (16.9)	0.23	8 (15.4)	0.35	35 (17.2)	0.40
	15 (11.6)		3 (8.1)		12 (13.0)	
History of cancer	36 (14.1)	0.19	5 (9.6)	0.23	31 (15.3)	0.40
	25 (19.4)		7 (18.9)		18 (19.6)	
Baseline HB	13.8 (2.1)	**0.01**	13.1 (2.3)	0.35	14.05 (1.9)	**0.01**
	13.1 (2.1)		13.0 (2.4)		13.1 (1.9)	
Preoperative anemia (HB<13 in males or <12 in females)	78 (31.1)	0.29	24 (46.2)	0.13	54 (27.1)	0.67
	33 (25.6)		11 (29.7)		22 (23.9)	
Aspirin	214 (84.3)	1.00	41 (78.8)	0.26	173 (85.6)	0.49
	109 (84.5)		33 (89.2)		76 (82.6)	
Dual antiplatelet	34 (13.4)	0.75	6 (11.5)	0.37	28 (13.9)	0.25
	15 (11.6)		7 (18.9)		8 (8.7)	
Chronic anticoagulant	29 (11.5)	0.73	12 (23.1)	0.09	17 (8.5)	0.52
	13 (10.1)		3 (8.1)		10 (10.9)	
Statin	214 (84.6)	1.00	45 (88.2)	0.55	169 (83.7)	0.73
	110 (85.3)		31 (83.8)		79 (85.9)	
Diuretics	82 (32.2)	0.36	18 (34.6)	0.66	64 (31.5)	0.50
	48 (37.2)		15 (40.5)		33 (35.9)	
CCB/BB	159 (62.6)	0.91	34 (65.4)	0.82	125 (62.1)	1.00
	80 (62.0)		23 (62.2)		57 (62.0)	

(Continued on next page)

Table I. (Continued)

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
ACEi/ARB	174 (68.6) 85 (65.9)	0.64	32 (61.5) 28 (75.7)	0.18	142 (70.4) 57 (62.0)	0.18

BMI: body mass index; DM: diabetes mellitus; CAD: coronary artery disease; PCI/CABG: percutaneous coronary intervention/coronary artery bypass grafting; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PAD: peripheral artery disease; HB: hemoglobin; CCB/BB: calcium channel blockers/beta blockers; ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers. Bold numbers indicate significant p values (i.e. <.05).

Table II. Procedural details

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
Ipsilateral ICA stenosis >70%	205 (85.4) 100 (83.3)	0.64	41 (83.7) 27 (77.1)	0.57	164 (85.9) 73 (85.9)	1.00
Ipsilateral CCA stenosis >70%	7 (3.1) 0 (0)	0.10	3 (6.2) 0 (0)	0.26	4 (2.2) 0 (0)	0.32
Contralateral ICA stenosis >70%	42 (19.6) 22 (19.3)	1.00	15 (32.6) 6 (18.8)	0.20	27 (16.1) 16 (19.5)	0.59
Contralateral CCA stenosis >70%	5 (2.4) 2 (1.8)	1.00	3 (6.4) 1 (3)	0.64	2 (1.2) 1 (1.3)	1.00
Bilaterally patent VA	146 (82.5) 74 (90.2)	0.18	30 (85.7) 17 (85)	0.86	116 (81.7) 57 (91.9)	0.16
Shunt	22 (8.6) 10 (7.8)	0.85	8 (15.4) 4 (10.8)	0.75	14(6.9) 6 (6.5)	1.00
Operation time (minutes)	75 (29.2) 75 (26.0)	0.06	75 (24.2) 65 (35.0)	0.06	75 (29.2) 75 (20.0)	0.30
Clamp time (minutes)	22 (11.0) 20 (9.5)	0.06	21 (14.5) 18 (12.0)	0.20	22 (11.0) 20 (9.0)	0.24
Eversion CEA	37 (14.5) 26 (20.2)	0.31	11 (21.2) 9 (24.3)	0.47	26 (12.8) 17 (18.5)	0.44

CCA: common carotid artery; ICA: internal carotid artery; VA: vertebral artery; EEG: electroencephalogram; CEA: carotid endarterectomoy.

Discussion

Atherosclerosis of the supra-aortic vessels and especially of the carotid bifurcation is a well-recognized cause of recurrent ischaemic stroke and there is evidence that stroke risk be related to the degree of carotid stenosis [11]. The CEA operation is widely acknowledged as the gold standard surgical approach for prevention of major cerebral events in patients with significant carotid stenosis, with landmark trials from the 1990s that favoured CEA plus best medical therapy (BMT) over BMT alone in the management of patients with significant carotid atherosclerotic disease [12, 13]. Both octogenarians and females were initially underrepresented categories in these major trials, while in real-world clinical practice both advanced age and female sex are not usually regarded as formal contraindications to carotid surgery. Furthermore, while isolated effects of age and gender on outcomes of CEA have been explored in previous studies [5, 6], their combined interaction remains almost unexplored. In that sense, the main novelty of our study is represented by the analysis of the combined prognostic effect that age and gender (which remain the two most important non-modifiable risk factors for surgical interventions) may have on peri-operative and follow-up outcomes, including survival and MACE, after CEA in a large contemporary real-world cohort of patients with symptomatic and asymptomatic carotid stenosis.

In our study, we found that males and females undergoing elective CEA for asymptomatic and symptomatic carotid stenosis share almost comparable distribution of cardiovascular risk factors irrespective of age. However, females were generally older with a mean age of 76 years (vs 73 years in males), and a higher proportion of females were octogenarians with almost 29% being aged ≥80 years (vs 20% in males). Despite these dissimilarities, we were unable to find any significant differences in the overall risk of adverse peri-operative neurologic events. These data demonstrate that perioperative risks are similar for males and females, and that sex should not be a factor when candidacy for CEA is sought in both asymptomatic and symptomatic patients. Nevertheless, our study highlighted that males undergoing CEA had lower long-term survival

Table III. Thirty-day outcomes

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
Stroke						
Overall	6 (2.4)	0.72	2 (3.8)	1.00	4 (2.0)	1.00
	2 (1.6)		1 (2.7)		1 (1.1)	
Symptomatic	2 (1.9)	1.00	1 (3.7)	1.00	1 (1.2)	0.47
	1 (2.0)		0 (0)		1 (3.3)	
Asymptomatic	4 (2.7)	0.66	1 (4.0)	1.00	3 (2.5)	0.55
	1 (1.3)		1 (5.9)		0 (0)	
Stroke/Death						
Overall	6 (2.4)	0.72	2 (3.8)	1.00	4 (2.0)	1.00
	2 (1.6)		1 (2.7)		1 (1.1)	
Symptomatic	2 (1.9)	1.00	1 (3.7)	1.00	1 (1.2)	0.47
	1 (2.0)		0 (0)		1 (3.3)	
Asymptomatic	4 (2.7)	0.66	1 (5.9)	1.00	3 (2.5)	0.55
	1 (1.3)		1 (4.0)		0 (0)	
Stroke/Death/MI						
Overall	6 (2.4)	1.00	2 (3.8)	1.00	4 (2.0)	1.00
	3 (2.3)		1 (2.7)		2 (2.2)	
Symptomatic	2 (1.9)	1.00	1 (3.7)	1.00	1 (1.2)	0.47
	1 (2.0)		0 (0)		1 (3.3)	
Asymptomatic	4 (2.7)	1.00	1 (5.9)	1.00	3 (2.5)	1.00
	2 (2.5)		1 (4.0)		1 (1.6)	
Return to OR for bleeding	11 (4.3)	0.07	5 (9.6)	0.07	6 (3.0)	0.44
	1 (0.8)		0 (0)		1 (1.1)	
Peripheral nerve palsy	34 (13.3)	0.41	8 (15.4)	0.35	26 (12.8)	0.70
	13 (10.1)		3 (8.1)		10 (10.9)	
Hospital LoS (days)	3 (1.0)	0.95	3 (1.0)	0.72	3 (1.0)	0.73
	3 (1.0)		3 (1.0)		3 (1.0)	

MI: myocardial infarction; OR: operating room; LoS: length of stay.

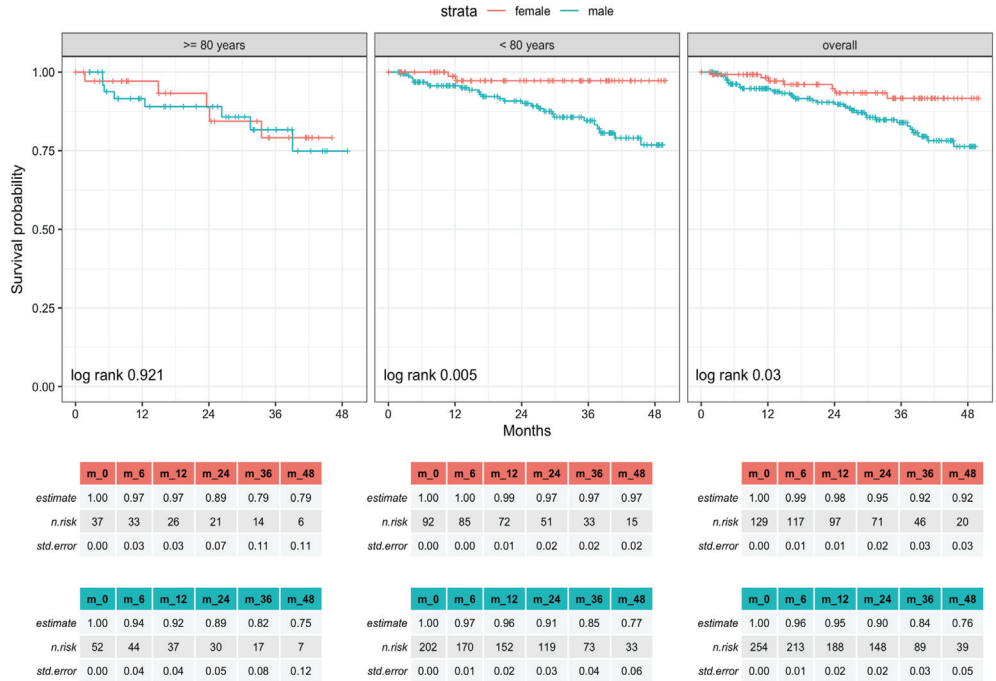

Figure 1. Kaplan Meier estimates of overall survival (males vs. females). Left box: age 80 years or more; middle box: age less than 80 years; right box: whole study cohort.

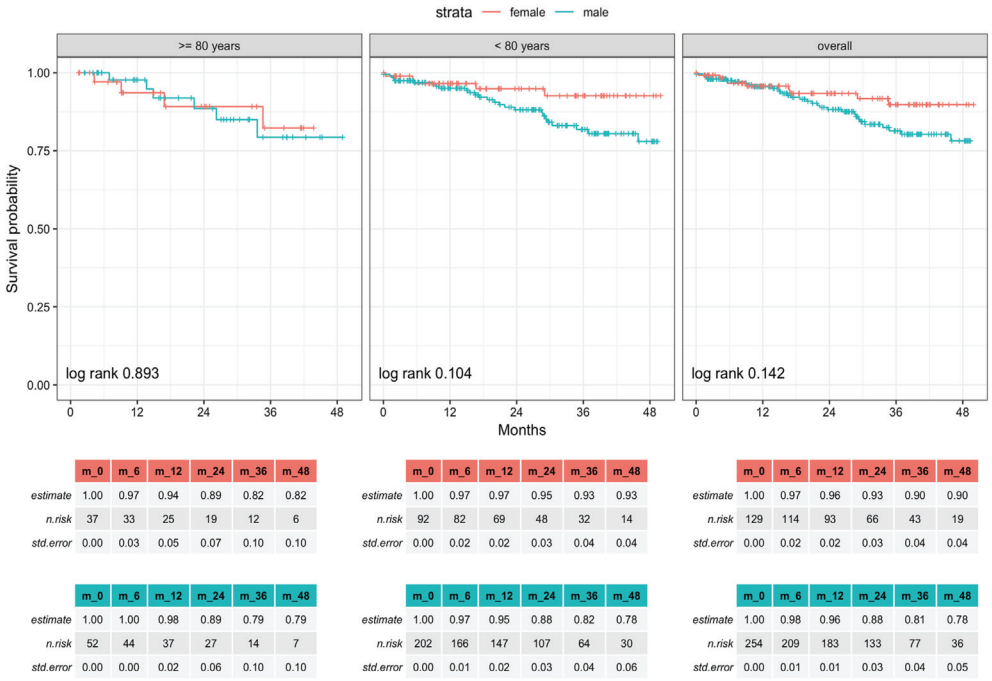

Figure 2. Kaplan Meier estimates of freedom from major adverse cardiovascular events (males vs. females). Left box: age 80 years or more; middle box: age less than 80 years; right box: whole study cohort.

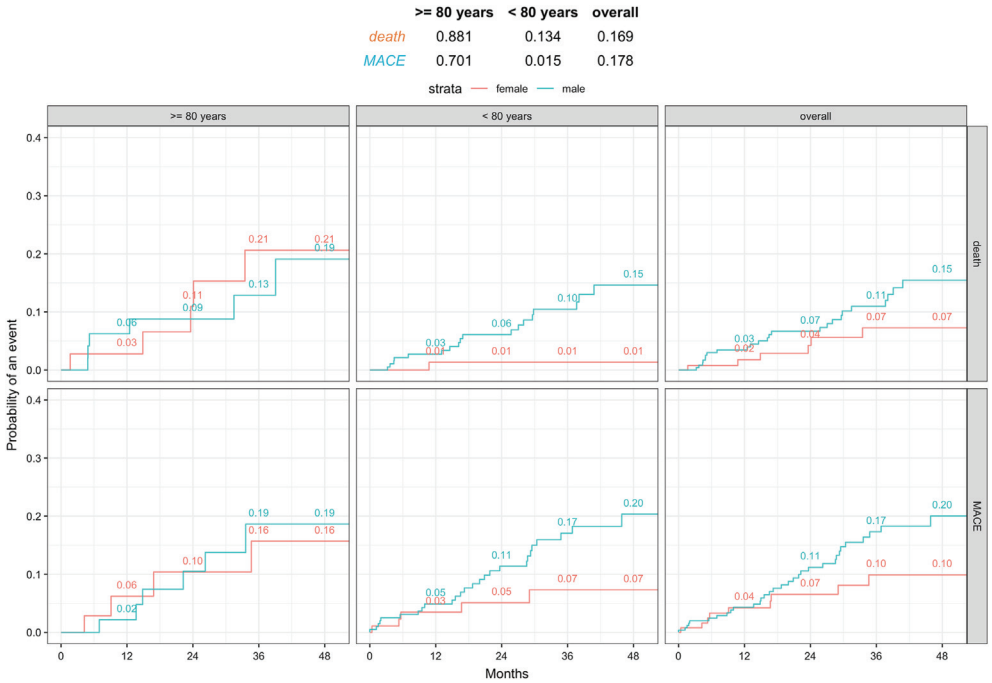

Figure 3. Cumulative incidence of mortality and major adverse cardiovascular events (MACE) with competing-risk subdistribution (males vs. females). Left box: age 80 years or more; middle box: age less than 80 years; right box: whole study cohort.

as compared with females, and the difference remained significant in those aged <80 years although survival rates were not significantly different in elderly individuals. Furthermore, multivariable analysis confirmed that age and male sex were both independently associated with higher odds of mortality, which may underline the presence of a combined age-gender effect on death risk in CEA patients.

Several factors may explain the higher risk of death in male patients following CEA, especially in non-octogenarians, when compared with females. Previous literature had already suggested that differences might exist in the pathophysiology of atherosclerosis owing to hormonal responses [14, 15]. In that sense, it might be hypothesized that elderly patients could share a similar long-term mortality risk due to accumulation of several comorbidities, while

in younger individuals the impact of cardiovascular disease (s) would play a major role, as suggested by the competing-risk analysis. The observation of more elderly females undergoing CEA in our study might also reflect less intensive cardiovascular screening in this specific population, which may merit further investigation. In fact, previous research has described that females are less likely to be diagnosed with coronary disease [16]; in turn, this may result in suboptimal management and contribute to an increase in mortality which, however, was not observed in the current study. Although this study cannot definitely support any of these arguments, it suggests that additional research is needed to determine what other factors may be driving this discrepancy between female and male patients.

Although no significant differences were found in the long-term rate of MACE between study groups, using a competing-risk subdistribution model we were able to find that risk of MACE was significantly higher for males as compared with females in subjects younger than 80 years. This observation, coupled with the lower long-term survival in this subset of patients, might indicate that cardiovascular events be the main driver of mortality. These findings may deserve further attention as they may be relevant to design patient-specific tailored approaches for follow-up and cardiovascular risk factors management. Interestingly, we did not find any significant differences in the medical management strategy between males and females although as many as 15% of study subjects were not on any statins at time of surgery. Therefore, medical optimization of patients undergoing CEA should be regarded as an unmet priority for cardiovascular specialists as well as primary care physicians.

Findings from this study must be interpreted in light of recommendations from current clinical practice guidelines, which recommend invasive treatment of carotid stenosis if reasonable life expectancy (5 years or more) can be anticipated [1]. The association between older age and increasing risk of mortality has already been described and the general concept that age predicts life expectancy still applies to this analysis. To date, only few scores have been proposed and have not become routine in clinical practice due to their limitations. Future studies should focus on external validation of existing score systems to predict mortality risk in CEA patients [17]. Therefore, the findings in the current study would provide further evidence that the treating physician should consider declining life expectancy with advancing age when making treatment recommendations to patients with carotid atherosclerotic disease.

However, age in itself should not be the sole criterion used for preoperative risk-stratification and risk scoring systems may be a valuable adjunctive tool for predicting long-term mortality. Indeed, recent research has focused on the impact of frailty on surgical outcomes. Frailty is defined as the accumulation of multisystem physiologic deficits that leads to decreased reserves and vulnerability to stressors, and that is known to increase the risk of adverse outcomes after surgery [18, 19]. The use of frailty index scores is based on the theory that the total accumulation of deficits, rather than the specific characterization of deficits that describe the phenotype, is an accurate descriptor of frailty [20]. Although frailty is a complex entity still difficult to assess in reproducible way, advanced age may be seen as a valid surrogate marker in many clinical instances [21]. On the basis of large epidemiologic studies, women tend to be more frail compared to men of similar age [22]. However, in the general geriatric population, they tend to live longer on average and may be able to tolerate frailty better, a phenomenon referred to as the sex frailty paradox [23]. How these considerations will apply to patients undergoing CEA may represent another area of future research endeavors.

Limitations

Findings from this study must be interpreted within the context of its limitations. First, this was a single-center retrospective study, thereby intrinsically prone to bias. Also, the number of males was almost twice as the number of females undergoing CEA in the study cohort. However, the relatively large sample size and long follow-up duration, coupled with the stability of surgical practice during the study timeframe, would make the results clinically reasonable. Furthermore, the recording of death events was highly accurate given the local referral patterns of treated patients. Indeed, the duration of follow-up was similar between males and females (mean 29.8 months, 95% CI: 27.6–32.0 vs. mean 28.6 months, 95% CI: 25.5–31.6; p=.43) as was the number of lost to follow-up (males: 8.7% vs. females: 4.7%; p=.21). Furthermore, retrieval of clinical data for the in-hospital phase was highly reliable, with no missing data on neurologic and mortality outcomes following CEA. Although we tried to account for significant confounders using robust multivariate analyses and confirmed the robustness of the main results with use of sensitivity analyses, it is still possible that some unmeasured confounders have remained.

Conclusions

In this study of elective CEA for asymptomatic and symptomatic carotid stenosis, similar peri-operative neurologic outcomes were found in both males and females irrespective of age. Despite being usually older, females have superior long-term survival rates. Cumulative risk of major adverse cardiovascular events during follow-up is higher in males than in females below 80 years of age.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000957

ESM 1. Multivariate Cox Proportional Hazards for predictors of all-cause mortality [Figure].

ESM 2. Multivariate Cox Proportional Hazards for predictors of major adverse cardiovascular events (MACE) [Figure].

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ORCID
Mario D'Oria
https://orcid.org/0000-0002-7156-7827

Correspondence address
Dr Mario D'Oria
Division of Vascular and Endovascular Surgery
Cardiovascular Department
Cattinara University Hospital ASUGI
Strada di Fiume 447
34149 Trieste
Italy

mario.doria88@outlook.com