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Sex-Related Outcomes in Asymptomatic Carotid Artery Stenosis Undergoing Carotid Endarterectomy

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ARTICLE INFO

Article history:
Received 19 July 2024
Received in revised form
14 October 2024
Accepted 18 November 2024
Available online xxx

Keywords:
Asymptomatic carotid artery stenosis
Carotid endarterectomy
Gender-related outcomes
Sex differences

ABSTRACT

Introduction: This study aims to retrospectively analyze the perioperative and long-term outcomes of carotid endarterectomy (CEA) performed in asymptomatic patients, stratifying the results by sex.

Methods: Data on CEAs performed from January 2009 to December 2020 at our institution were collected. A neurologic evaluation was conducted 30 d after surgery to assess the occurrence of neurological events. Instrumental evaluations using Doppler ultrasound were performed within the first 3 mo, at 12 mo, and annually thereafter. The primary endpoints were perioperative mortality, major neurological events, and major complications. Secondary endpoints included long-term overall survival, stroke-free survival, absence of neurological symptoms, and absence of significant (>70%) restenosis.

Results: Two thousand one hundred ninety-four CEAs were performed in asymptomatic patients, with 758 females and 1436 males. There were no differences in perioperative outcomes between the two groups. In the multivariate analysis, female sex was found to be a protective factor for the risk of 30-d stroke (hazard ratio: 0.2; 95% confidence interval: 0.04-0.9; $P = 0.05$). At a median follow-up of 24 mo, the estimated 10-y overall and stroke-free survival rates were 77.6% in males *versus* 62.7% in females, $P = 0.2$ and 70% in males *versus* 61% in females, $P = 0.1$, respectively. Also the rates of significant restenosis did not differ between males and females (82.2% *versus* 87.7%, $P = 0.5$).

Conclusions: This study suggests that female sex, by itself, does not represent a risk factor for adverse outcomes after carotid surgery and it appears to be protective in the first 30 d following surgery.

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0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2024.11.005

Introduction

The prevalence of stroke in individuals over 65 y of age is estimated to be over 7%, with a higher incidence among men than women.[1,2] Carotid endarterectomy (CEA) is a well-established preventive measure against stroke for both symptomatic and asymptomatic patients with severe extracranial carotid artery stenosis.[3]

Historically, female sex has been considered a predictor of poorer outcomes following CEA compared to male sex.[4-6] The current guidelines from the American Heart Association-American Stroke Association[7] suggest that female sex may be a negative predictor of CEA outcomes in symptomatic patients, while the European guidelines[8] suggest that females may be more susceptible to complications such as post-intervention restenosis and stroke. However, most studies have had a higher representation of male patients, thus making it challenging to evaluate the outcomes of the intervention specifically in female population, Furthermore, nonrandomized single or multicenter studies with a large number of patients have reported conflicting results.[9,10] Importantly, there is a scarcity of literature regarding the outcomes of the procedure in asymptomatic female patients, considering that the major trials concerning CEA in asymptomatic patients[11,12] have enrolled no more than 500 female patients each in the surgical arm.

The objective of this single-center study is to compare the perioperative and long-term results of a large number of CEAs performed in asymptomatic patients (defined as patients who had not experienced any congruent neurological symptoms in the 6 mo before surgery), with a particular focus on stratifying the cohort according to sex assigned at birth.

Materials and Methods

Study design, study group, indications for treatment and preoperative assessment

This was a single-center retrospective observational cohort study. Data on CEAs performed at our institution from January 2009 to December 2020 were prospectively collected in a dedicated database, built following suggested reporting standards.[13] A retrospective analysis of this data was conducted. At the time of the intervention, all the patients gave their informed consent for using their clinical data for future investigations. Due to the retrospective and anonymized nature of the study, local Ethical Committee approval was not mandatory. The manuscript adheres to the STROBE[14] and SAGER[15] Guidelines.

Indications that progressively changed over the course of the years have always been respected on a clinical and technical level, in agreement with the literature and cardiovascular guidelines adjustments.

All patients undergoing carotid surgery underwent a Doppler ultrasound (DUS) examination of the supra-aortic trunks. The degree of stenosis was assessed using the North American Symptomatic Carotid Endarterectomy Trial method,[16] the hemodynamic criteria were those suggested by Carpenter *et al.*[17] and the echostructure of carotid plaques were classified based on the Gray-Weale scale.[18] The exams were performed by three vascular surgeons with a certification by the Italian Society for Vascular Investigations.

For patients with carotid stenosis exceeding 60%, a computed tomography angiography of the neck and intracranial vessels, along with the study of cerebral parenchyma, was routinely performed. Additionally, a preoperative assessment of global cardiovascular and anesthetic risks was conducted. Before 2018, the indication for surgery was based solely on the presence of stenosis exceeding 60% in patients with low-to-intermediate surgical risk.[19] Following the publication of the new European Society for Vascular Surgery guidelines,[8] immediately transposed to the Italian national level as well,[19] surgery was only recommended for patients with a life expectancy greater than 3 y and the presence of a >60% plaque with characteristics considered at high risk of embolization.

Anesthetic and surgical details

For patients undergoing general anesthesia, cerebral perfusion monitoring was conducted through somatosensory evoked potential, with the insertion of a selective shunt in case of critical modifications in the potentials. In patients receiving loco-regional anesthesia or cooperative patient general anesthesia (CoPaGeA),[20] any neurological changes observed during clamping were considered criteria for selective shunt insertion. In cases where somatosensory evoked potential was not assessable or patients were unresponsive or intolerant to local anesthesia or CoPaGeA, a shunt was immediately placed. Before clamping, all patients received intravenous heparin prophylaxis at the dosage of 30 IU/kg.

The surgical procedure followed a standardized technique, including the early distal clamping of the internal carotid artery, an extensive overpass of the lesion and polyurethane patch closure. In selected cases, the eversion technique was preferred. Completion study with angiography or DUS was routinely performed. At discharge, postoperative medical management consisted of indefinite single antiplatelet treatment, along with high-dose statins. In patients requiring oral anticoagulation for comorbidities, antiplatelet treatment with 100 mg acetylsalicylic acid was prescribed for the first postoperative month.

Follow-up strategy and endpoints

At 30 d after the procedure, all patients underwent a comprehensive neurological assessment conducted by a consulting neurologist. Instrumental follow-up program consisted of DUS examinations within the third postoperative month, at 12 mo, and annually thereafter. Any clinical events that occurred during the designated period were recorded, along with information on the patency of the internal carotid artery and on the status of the contralateral internal carotid artery. In cases where patients did not attend scheduled controls, direct phone call consultations or examination of available digitalized medical records were utilized. The analysis of follow-up data ceased at December 2022.

Perioperative outcomes were mortality, major neurological events, and major complications. Among major neurological events we considered transient ischemic attacks (TIAs), defined as a single episode of focal neurological dysfunction and/or amaurosis fugax, not associated with cerebral infarction and spontaneously resolved within few minutes to hours, minor strokes (defined as any neurological event lasting more than 24 h with recovery in several days without residual functional impairment) and major strokes (any neurological event lasting more than 24 h with residual stabilized neurologic deficit). Complications were defined as local or systemic conditions requiring reintervention or significantly prolonging the length of hospital stay. Follow-up outcomes included overall survival, stroke-free survival, absence of any neurological symptoms, and absence of significant (>70%) restenosis of the operated carotid. The criteria for significant restenosis were those suggested by the Italian Guidelines, namely, a peak systolic velocity greater than 180 cm/s indicated the presence of a >70% restenosis.[21]

Statistical analysis

Statistical analysis was performed with the SPSS 28.0 for Windows program (SPSS Inc., Chicago). Statistical significance was considered for a P value < 0.05.

Clinical, demographic, and anatomical characteristics were analyzed. Continuous variables were tested for normality and quantitative variables were compared through Student's t-test. The chi-squared test was used to compare qualitative variables. Univariate analysis was used to identify potential predictors of 30-d stroke and death, and when association yielded P values < 0.2, a binary logistic regression analysis was performed using the Wald's backward stepwise model.

Follow-up results were analyzed using life-table analysis and Kaplan–Meier curves. Comparisons between the two groups were conducted using the log-rank test. For statistics, we followed the methodology suggested by Hickey *et al.*[22] Missing data were managed with a complete case analysis.

Results

Study cohort

During the study period, 2821 consecutive CEAs were performed. Among these, 2194 (77.8%) were conducted for asymptomatic carotid stenosis and comprised the subjects of our study, whereas the 627 CEAs performed in symptomatics were excluded. Out of the asymptomatic cases, 758 (34.5%) were performed on female patients, while 1436 (65.5%) were performed on male patients.

Demographic characteristics, risk factors and comorbidities

Male patients had a higher prevalence of smoking history (62% and 41%, respectively, $P < 0.001$, odds ratio [OR], 1.7) and multilevel atherosclerotic manifestations (peripheral artery disease and coronary artery disease) compared to females. Conversely, female patients had a higher predisposition to hypertension (89% and 85%, respectively, $P = 0.03$, OR 0.7). Further details and definitions can be found in Table 1.

Anatomical and clinical features of extracranial carotid disease

Among females, 36 (4.7%) had silent ischemic cerebral lesions ipsilateral to the internal carotid artery requiring intervention at the preoperative brain computed tomography examination. In males, this condition was present in 73 (5%) patients ($P = 0.9$). The carotid plaque exhibited hypoechoic characteristics on DUS in 451 (60%) cases from females and 860 (60%) cases from males ($P = 0.9$). Six females and 22 males suffered more than 6 mo before surgery from a contralateral carotid artery symptom ($P = 0.1$, OR 1.3). Contralateral carotid occlusion was more

Table 1 – Demographics and comorbidities.

Examined factor	Females ($n = 758$)	Males ($n = 1436$)	P	OR
Age, mean ± SD	74.2 ± 7	73.7 ± 7	0.3	0.9
Octogenarians, *n* (%)	159 (21)	288 (20)	0.6	0.8
Smoking history, *n* (%)	309 (41)	897 (62)	<0.001	1.7
Hypertension, *n* (%)	674 (89)	1222 (85)	0.03	0.7
Diabetes, *n* (%)	174 (23)	332 (23)	0.9	1
Ischemic heart disease, *n* (%)	150 (20)	391 (27)	<0.001	1.5
Peripheral arterial obstructive disease, *n* (%)	116 (15)	269 (19)	0.04	1.3
Hypercholesterolemia, *n* (%)	560 (74)	1017 (71)	0.1	0.8
Chronic renal failure, *n* (%)	168 (22)	357 (25)	0.3	0.9

Hypertension: arterial hypertension in medical treatment.
Diabetes: Need for specific antidiabetics drugs.
Ischemic heart disease: Prior myocardial infarction or surgical or percutaneous revascularization.
Peripheral arterial obstructive disease: ankle brachial index value lower than 0.9 and higher than 1.4.
Hypercholesterolemia: Hypercholesterolemia in medical treatment.
Chronic renal failure: estimated glomerular filtration rate <60 mL/min/1.73 m^2.

commonly observed in males (83 cases, 5.7% *versus* 28 cases, 3.6%, $P = 0.03$). Carotid restenosis prompted the intervention in 15 (2%) patients in females and 34 (2.3%) patients in males ($P = 0.8$). Additionally, the procedure was performed concurrently with a cardiac intervention in 6 (0.9%) cases in females and 9 (0.6%) cases in males ($P = 0.6$).

Surgical details

The majority of procedures in both groups were performed under CoPaGeA, with 614 (81%) cases in females and 1164 (80%) cases in males ($P = 0.8$). Pure local anesthesia was used in 40 (5.3%) cases in females and 86 (6%) cases in males ($P = 0.7$). General anesthesia with instrumental monitoring was utilized in the remaining cases. Selective shunt insertion was required in 70 (9.2%) cases in females and 100 (6.9%) cases in males ($P = 0.05$). The rate of primary shunt insertion was 7.2% (55 cases) in females and 9.2% (133 cases) in males ($P = 0.1$). Overall, the rate of shunt insertion was 16.4% in females and 16.2% in males ($P = 0.8$). Patch angioplasty was the most common type of internal carotid reconstruction performed (95.2%), with the eversion technique being more frequently employed in female patients (Table 2).

Perioperative results (<30 d)

Six deaths occurred within 30 d of the surgery, one in females (0.1%) and five in males (0.3%; $P = 0.3$). One female patient experienced postoperative cerebral hemorrhage. In male patients, two patients died due to respiratory complications, two due to cardiac reasons, and one due to septic shock following aspiration pneumonia. Four patients (three in females and one in males) presented with congruent TIA with the operated carotid, seven (two in female patients and five in males) experienced minor stroke, while five cases (all males) had a major stroke. No fatal strokes were recorded in either group. Overall, the rate of stroke and death was 0.4% in females and 1% in males ($P = 0.1$). The perioperative rate of acute myocardial infarction was similar between the two groups ($P = 0.7$), with four cases (0.5%) in females and nine cases (0.6%) in males. No significant differences were observed in terms of local complications, such as hematoma requiring surgical revision (9 cases in female patients, 1.1%, and 13 cases in males, 0.9%, $P = 0.5$), and cranial nerve injuries (2.1% and 1.8%, respectively, $P = 0.6$). Nonfatal systemic complications occurred in 1% of patients in females and 1.6% of patients in males ($P = 0.2$). The combined outcome of perioperative stroke, death, acute myocardial infarction, local complications, and systemic complications was similar between the two groups, with a trend toward better results among females (5.9% *versus* 4.8%, $P = 0.2$). Table 3 provides the results of the univariate and multivariate analysis for the 30-d stroke and death in the entire study group.

Follow-up results

The adherence to follow-up was 90.5% (1943 patients), with a median duration of 24 mo (range 1-176 mo). During the follow-up period, 105 deaths were recorded with 31 among females and 74 among males ($P = 0.2$). The primary causes of death in both groups were neoplastic and cardiac conditions. The estimated 10-y survival rate was 62.7% in females (standard error [SE] 0.08) and 77.6% in males (SE 0.03), with no statistically significant difference (Log rank 1.3, $P = 0.2$; Fig. 1).

Seven new ipsilateral neurological events were recorded during the follow-up period, with four in female patients (one minor stroke and three major strokes) and three in males (one TIA and two major strokes). Additionally, nine contralateral neurological events were recorded, all among males (four TIAs, one minor stroke, and four major strokes). The estimated 10-y stroke-free survival rate was 61% in females (SE 0.08) and 70% in males (SE 0.05), showing no statistically significant difference (log rank 1.9, $P = 0.1$; Fig. 2).

The estimated 10-y rate of any neurological symptom, both ipsilateral and contralateral, was 8.5% in the female group and 10% in the male group, with no statistically significant difference (log rank 0.08, $P = 0.5$).

Regarding the patency of the operated carotid artery, the estimated 10-y absence of significant restenosis was 87.7% (SE 0.04) in females and 82.2% (SE 0.06) in males, showing no statistically significant difference (Log rank 0.4, $P = 0.5$; Fig. 3).

Discussion

Our study provides an insight into the outcomes of CEA in asymptomatic patients, with a specific focus on sex-based differences. The findings challenge the conventional notion that female patients inherently have worse outcomes following CEA compared to male patients.

In fact, data from our large retrospective series showed that not only female sex does not represent a risk factor for increased perioperative events following CEA in asymptomatic patients, but rather we found a slightly lower incidence of minor stroke, major stroke, and death in the female population, both individually and overall. Furthermore, female subjects exhibited a lower overall rate of stroke, death, acute myocardial infarction, local complications, and systemic

Table 2 – Type of carotid reconstruction.

Technique	Females ($n = 758$)	Males ($n = 1436$)	P	OR
Primary closure, *n* (%)	18 (2)	29 (2)	0.8	0.9
Patch, *n* (%)	707 (93)	1382 (96)	0.7	0.8
Eversion, *n* (%)	29 (4.5)	17 (1.5)	<0.001	1.4
Bypass/graft, *n* (%)	4 (0.5)	8 (0.5)	0.9	1

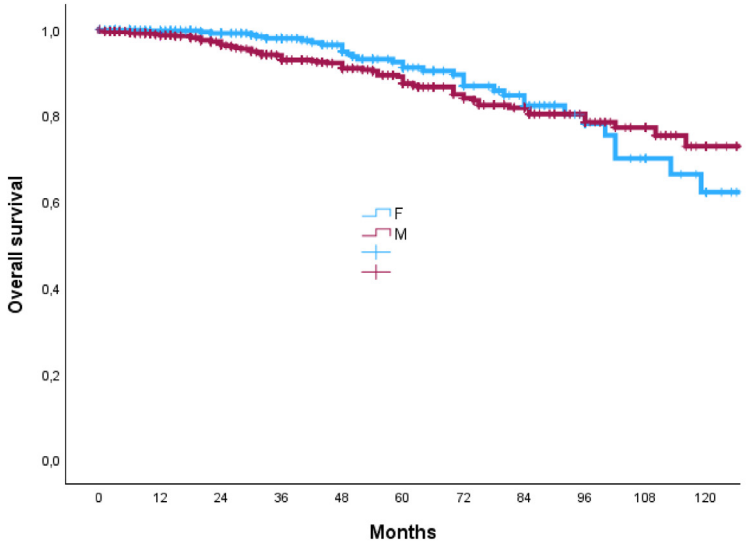
Table 3 – Univariate and multivariate analysis for 30-d stroke risk.

Examined factor	Univariate		Multivariate		
	30-d stroke and death rate (*n*. And %)	*P*	95% CI	HR	*P*
Female sex			0.04-0.9	0.2	05
Yes	3 (0.4)	09			
No	15 (1)				
Octogenarians					
Yes	3 (0.7)	6			
No	15 (1)				
Hypertension					
Yes	2 (0.9)	0.8			
No	16 (0.8)				
Hypercholesterolemia			0.1-1.9	0.5	0.3
Yes	15 (1)	0.2			
No	1 (0.5)				
Diabetes			0.1-1.1	0.4	0.08
Yes	7 (1.4)	0.07			
No	11 (0.6)				
Ischemic heart disease			0.2-2.2	0.7	0.6
Yes	7 (1.2)	0.3			
No	11 (0.7)				
Peripheral arterial occlusive disease		0.6			
Yes	4 (1)				
No	14 (0.7)				
Chronic renal failure					
Yes	4 (0.9)	0.8			
No	14 (0.8)				
Silent brain lesions ac CT Scan		0.9			
Yes	10 (1)				
No	8 (0.9)				
Contralateral Carotid occlusion		0.3	0.3-2.6	0.6	0.5
Yes	0				
No	18 (0.9)				
Synchronous Cardiac intervention		<0.001	2.6-18.9	6.6	0.02
Yes	2 (13.3)				
No	16 (0.8)				
Shunt insertion			0.9-10.3	3.1	0.06
Yes	6 (1.6)	0.05			
No	12 (0.6)				
Neurological monitoring			0.4-4.8	1.2	0.6
Clinical	14 (0.8)	0.2			
Instrumental	4 (1.5)				

CI = confidence interval; HR = hazard ratio; CT = computed tomography.

complications. This contrasts with historical studies suggesting poorer outcomes for females.[4-6] However, recent research has started to challenge this perspective, showing comparable outcomes between sexes in asymptomatic patients.[23] Our findings align with this more recent trend, suggesting that with contemporary surgical techniques and postoperative care, sex may not be a critical determinant of perioperative outcomes.

Data from the literature showed that women are more likely to have more stable atherosclerotic plaques, particularly in asymptomatic cases. This could be attributed to the effects of estrogen, which inhibit monocyte migration, thereby reducing plaque inflammation levels. Additionally, estrogen lowers endothelin levels, which may deter coagulation and vascular proliferation.[24-26]

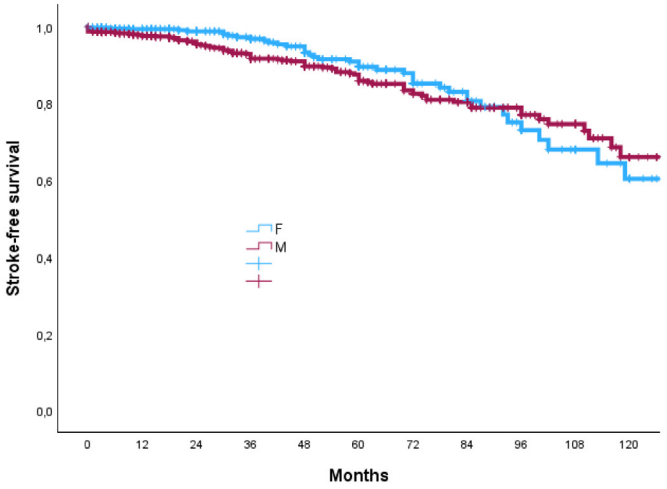


Months	0	48	84	120
Females				
• n. at risk	672	172	83	10
• S.E.	0.001	0.01	0.03	0.08
• Survival (%)	99	94.8	82.3	62.2
• 95% CI	98.8-99.2	92.7-96.6	75.7-87.4	46.1-76
Males				
• n. at risk	1265	361	116	21
• S.E.	0.002	0.01	0.02	0.04
• Survival (%)	99.6	92.2	81.8	72.8
• 95% CI	99-99.8	90-93.9	77.6-85.4	64.4-79.9

Fig. 1 – Estimated 10-y overall survival in both groups with number of patients at risk, SE, estimates and 95% confidence intervals at each time interval.

In our study, we observed that female sex provided protection against perioperative risks of stroke and death when compared to males. This finding was surprising and somewhat unexpected when considering the above-cited existing literature. Male patients in our study exhibited a higher prevalence of cardiovascular comorbidities and more severe carotid artery stenosis compared to females. Additionally, males more frequently experienced occlusion of the contralateral internal carotid artery. These factors may have contributed to the observed sex difference. However, the advantage for females persisted even after adjusting for other confounding factors. When considering the composite outcome of death, stroke, and local and systemic complications, there was a noticeable trend toward better results among females. Although this trend was not statistically significant, we believe it holds clinical relevance, particularly when analyzing CEA results among asymptomatic patients, where the benefit of the intervention is reflected in small percentages, often close to 1%.

Regarding the 10-y outcomes in terms of survival and stroke-free survival, we did not identify any significant differences between the two groups, although there was a

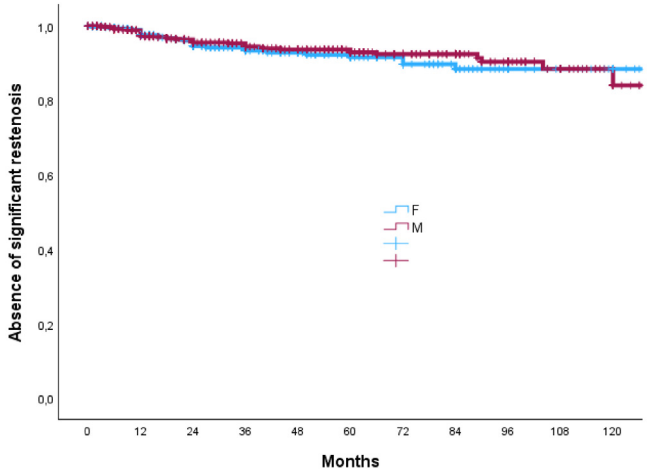


Months	0	48	84	120
Females				
• n. at risk	671	170	61	9
• S.E.	0.002	0.01	0.03	0.08
• Stroke-free survival (%)	99.7	94.9	83	61
• 95% CI	99-99.9	92.6-96.5	76.3-88.1	45-74.9
Males				
• n. at risk	1253	348	115	20
• S.E.	0.003	0.01	0.02	0.05
• Stroke-free survival (%)	98.8	90.9	80.4	69.8
• 95% CI	98.1-99.3	88.7-92.7	76.2-84	59.3-78.6

Fig. 2 – Estimated 10-y stroke-free survival in both groups with number of patients at risk, SE, estimates and 95% confidence intervals at each time interval.

trend toward worse results in female subjects, which, even if not statistically significant, probably due to a limited power of the study, can be considered clinically relevant. Also the risk of restenosis during follow-up in the female population was comparable to that in males, and this finding differs from recent results reported in the literature[27,28] which have suggested a higher long-term risk of significant restenosis in females. This study's results confirm the findings of our previous research, which examined a different historical period.[29] Additionally, the study suggests that sex alone should not determine the indication for CEA in asymptomatic patients, particularly when the surgical indication is controversial. This is particularly important given the evolving guidelines and the historical hesitancy to perform CEA in women due to perceived higher risks.

To support such a hypothesis, we have to remember that, recently, Yogendakrumar *et al.*[30] performed a scoping review on sex-differences in carotid surgery, and found that even if only half of the previously published RCTs and systematic reviews report sex-specific outcomes, a lower absolute risk for 5-y stroke and periprocedural death with CEA in women compared with men does exist. Nevertheless, conflicting evidence still exists, and future research should focus on prospective multicenter studies with randomized designs to validate these findings further. Particularly, there is a need to investigate the biological mechanisms underlying any sex-based differences in vascular disease and surgical outcomes. Studies should also consider the impact of lifestyle, genetic factors, and advancements in medical therapy that could differentially affect men and women undergoing CEA.



Months	0	48	84	120
Females				
• n. at risk	669	166	59	9
• S.E.	0.001	0.01	0.03	0.05
• Absence of restenosis (%)	99.9	92.9	88.4	87.7
• 95% CI	99.4-100	90.7-94.6	81.2-93.1	74.7-94.5
Males				
• n. at risk	1247	315	103	15
• S.E.	0.002	0.01	0.01	0.06
• Absence of restenosis (%)	99.9	94.7	92.3	82.2
• 95% CI	98.3-100	92.4-96.3	90.1-94	67.8-91

Fig. 3 – Absence of significant restenosis estimated at 10 y in both groups with number of patients at risk, SE, estimates and 95% confidence intervals at each time interval.

Limitations

The large series presented in this study has several limitations. Firstly, the retrospective nature of the study poses inherent limitations. Secondly, there was a higher number of males than females in the cohort, despite the prevalence of the disease being almost equal between sexes. It is also important to consider that access to health care and medical therapy may have varied in previously published studies, potentially explaining differences in their results compared to ours. Women may have had less access to health care and suboptimal medical therapy, which could have masked better outcomes.[31,32] Moreover, potential differences in medical management over the study period may have impacted outcomes. Another important limitation is that, due to the low event rate, the study might have limited power to detect differences between groups. Finally, for a limited number of patients, we had to rely on indirect methods to assess postoperative events.

Conclusions

The findings of this study suggest that female sex is not associated with an increased risk of adverse outcomes following carotid surgery. In fact, there may be a protective effect associated with being female in the early postoperative period. However, due to conflicting results from previous studies and the limited literature on postoperative risk in

asymptomatic female patients, further research with larger sample sizes and prospective designs is needed to provide more conclusive evidence.

Study Type

Single-center, retrospective, comparative cohort study.

Disclosure

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

The authors received no financial support for this paper.

CRediT authorship contribution statement

Elena Giacomelli: Writing – original draft, Methodology, Conceptualization. **Walter Dorigo:** Writing – original draft, Formal analysis, Conceptualization. **Francesca Sibaldi:** Investigation, Data curation. **Rossella Di Domenico:** Writing – review & editing, Data curation. **Mascia Nesi:** Investigation. **Aaron Thomas Fargion:** Formal analysis, Data curation. **Sara Speziali:** Writing – review & editing, Formal analysis. **Raffaele Pulli:** Writing – review & editing, Formal analysis, Conceptualization.

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