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Editor's Choice – Sex Related Differences in Indication and Procedural Outcomes of Carotid interventions in VASCUNET

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WHAT THIS PAPER ADDS

This VASCUNET study included over 200 000 carotid procedures from 13 countries and confirmed that no significant sex related differences were found in peri-operative complication rates after interventions for carotid stenosis. The outcome was similar for both symptomatic and asymptomatic interventions, as well as for carotid endarterectomy and stenting. Practice patterns in participating countries were different; the biggest differences were seen in the provision of carotid artery stenting and the proportion of asymptomatic patients.

Objective: It has been suggested that peri-operative complications after carotid surgery may be higher in women than in men. This assumption may affect the treatment patterns, and it is thus possible that carotid endarterectomy (CEA) is provided to women less often. The aim of the current VASCUNET study was to determine sex related differences in operative risk in routine clinical practice among non-selected patients undergoing carotid revascularisation.

Methods: Data on CEA and carotid artery stenting (CAS) from 14 vascular registries were collected and amalgamated. Comprehensive data were available for 223 626 carotid artery procedures; these were analysed overall and by country. The primary outcome was any stroke and or death within 30 days of carotid revascularisation. Secondary outcomes were stroke, death, or any major cardiac event or haemorrhage leading to re-operation.

Results: Of the procedures, 34.8% were done in women. The proportion of CEA for asymptomatic stenosis compared with symptomatic stenosis was significantly higher among women than men (38.4% *vs.* 36.9%, $p < .001$). The proportion of octogenarians was higher among women than men who underwent CEA in both asymptomatic (21.2% *vs.* 19.9%) and symptomatic patients (24.3% *vs.* 21.4%). In the unadjusted analysis of symptomatic and asymptomatic patients, there were no significant differences between men and women in the rate of post-operative combined stroke and or death, any major cardiac event, or combined death, stroke, and any major cardiac event after CEA. Also, after stenting for asymptomatic or symptomatic carotid stenosis, there were no significant differences between men and women in the rate of post-operative complications. In adjusted analyses, sex was not significantly associated with any of the end points. Higher age and CAS *vs.* CEA were independently associated with all four end points.

Conclusion: This study confirmed that, in a large registry among non-selected patients, no significant sex related differences were found in peri-operative complication rates after interventions for carotid stenosis.

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INTRODUCTION

Carotid endarterectomy (CEA) has been shown to be effective in long term stroke prevention in patients with ≥ 50% carotid stenosis and recent symptoms, provided that the peri-operative morbidity and mortality are within accepted levels.[1–4] Carotid artery stenting (CAS) is a minimally invasive alternative to treat carotid stenosis. Compared with CEA, the risk of peri-operative minor stroke was significantly higher in randomised trials (RCTs), while the long term outcome was not inferior to CEA.[5] The subgroup analyses of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Asymptomatic Carotid Atherosclerosis Study (ACAS) have suggested that the net benefit of CEA may be lower in women than in men. Suggested reasons include a more stable plaque phenotype resulting in a lower natural risk, combined with a relatively higher peri-operative risk of stroke in women.[6,7] The Asymptomatic Carotid Stenosis Trial 1 (ACST-1) reported no benefit from CEA in women at five years, but at 10 years, a similar benefit to that observed in men was determined.[4,8] In a pooled analysis of Carotid Stenosis Trialists' Collaboration combining symptomatic patients from larger randomised trials, the CAS to CEA relative risk was lower in women than in men in EVA-3S and ICSS, but higher in women than in men in SPACE and CREST.[9] As a consequence, CEA is provided to women less often.[9,10] This observation has also been confirmed in larger CEA databases.[11,12]

All *post hoc* subgroup analyses reflect highly selected patients, and the results do not necessarily reflect the outcome of carotid surgery in daily practice. Furthermore, the recruitment of patients to randomised trials has been shown to be more selective for women than for men leading to sex distributions that are different from everyday clinical practice.[11,13]

International quality registry collaborations such as the European Society for Vascular Surgery subcommittee VASCUNET offers an opportunity to evaluate international practice and outcomes of vascular intervention.[14–17] The aim of the current VASCUNET study was to determine sex related differences in operative risk in routine clinical practice among non-selected patients undergoing carotid revascularisation.

MATERIALS AND METHODS

VASCUNET is a quality improvement group of European and Australasian vascular registries. It started its activities in 1997 and was recognised in 2004 by the European Society for Vascular Surgery (ESVS) Council as an official ESVS committee. This article presents the data on carotid interventions originally submitted to the national registries during 2010 – 2017, and to VASCUNET in 2014 (interventions during 2010 – 2013) and 2018 (interventions during 2014 – 2017). Data from the contributing countries were submitted to VASCUNET data collection using an Excel data sheet including variables that were accepted by all participants prior to data collection. Principles were to keep the dataset to a minimum but to include useful comparative data fields collected by the majority of registries in the collaboration. It was accepted that because of the differences in national registries, not all countries would be able to contribute data in all fields and that the outcome data would include events during the hospital stay in some countries and 30 day data in other countries.

Data on CEAs and CASs from 14 national (Australia, Denmark, Hungary, Iceland, Italy, Malta, Netherlands, Norway, Sweden, Switzerland, UK) or regional population based vascular registries (Finland, France) were received during two data collection projects and amalgamated into one common data set. The UK, Switzerland, and Iceland provided data only in the first data collection and Italy and The Netherlands only in the second. All the other nine countries included data on both data collections.

The principles of the VASCUNET data collection have been described earlier.[15,17,18]

Data were analysed overall and by country. Amalgamated data included patient characteristics (age in years, dichotomised sex, indication for carotid intervention (symptomatic: stroke, transient ischaemic attack (TIA), or other); asymptomatic), pre-operative comorbidities (diabetes, cardiac history including ischaemic heart disease or congestive heart failure, hypertension history), type of procedure (CEA, CAS), post-operative outcome (30 day or in hospital stroke, death, major cardiac event, haemorrhage requiring re-intervention). Due to the differences in the registries, not all data were available from all of the countries; data missingness per registry is presented in Supplementary Table S1. Australia, Hungary, and New Zealand reported only in hospital mortality, which was used in the outcome analysis, and 30 day mortality was used in the remaining countries.

An analysis of the differences in indications, proportion of octogenarians and 30 day (in hospital) outcome between the sexes was carried out. The primary outcome was any stroke and or death within 30 days (in hospital) of carotid revascularisation. Secondary outcomes were 30 day (in hospital) combined stroke death and myocardial infarction (MI) rate, stroke rate, death, and any major cardiac event or

Table 1. Characteristics of patients having carotid artery stenosis treatment by endarterectomy (CEA) or carotid artery stenting (CAS) collected from 14 countries by VASCUNET for two time periods, 2010–2013 and 2014–2017

Characteristic	Men	Women	Total	*p*	Missing data
CEA					
Patients	86 497 (66.4)	43 732 (33.6)	130 229		
Age – y	72.1 ± 9.1	72.5 ± 9.4	72.2 ± 9.2	<.001	
Octogenarians	20.9	23.1	21.6	<.001	3 400 (2.6)
Diabetes	32.4	31.2	32.0	<.001	14 517 (6.5)*
Cardiac history	44.2	38.8	42.4	<.001	5 328 (2.4)*
Hypertension	81.5	81.8	81.6	.41	40 944 (31.4)*
Asymptomatic	36.9	38.4	37.4	<.001	0 (0)
Indication stroke	19.0	17.5	18.5	<.001	na
CAS					
Patients	59 395 (63.5)	34 002 (36.5)	93 397		
Age – y	74.3 ± 8.5	74.4 ± 8.8	74.3 ± 8.6	.063	123 (0.1)
Octogenarians	26.9	27.3	27.1	.20	123 (0.1)
Diabetes	29.8	30.1	29.9	.40	442 (0.5)
Cardiac history	30.8	30.5	30.7	.33	211 (0.2)
Hypertension	80.3	80.0	80.2	.22	491 (0.5)
Asymptomatic	67.0	67.2	67.1	.60	0 (0)
Indication stroke	6.2	6.0	6.1	.59	na

Data are presented as %, *n* (%), or mean ± standard deviation. na = not available.
* Diabetes and hypertension history are not collected in The Netherlands. In the UK hypertension data are missing.

haemorrhage leading to re-operation. Furthermore, the proportion of fatal strokes of all post-operative strokes in both men and women is reported.

Statistical analysis

Continuous variables were reported as mean values and standard deviation. Proportions were presented as percentages with 95% confidential interval (95% CI). The chi squared test was used to compare dichotomous variables and the Student *t* test to compare continuous variables. Post-operative outcome analysis was run for CEA and CAS procedures separately. As there were three countries reporting only in hospital outcome and 11 countries reporting 30 day outcome, to assure difference in outcome reporting did not bias the central analysis, sensitivity analysis was performed. To evaluate the risk factors for combined 30 day stroke and or death and for combined 30 day stroke, any major cardiac event, and death after CEA, a univariable analysis was performed including pre- and perioperative variables with less than 30% of missing data. These were age, sex, procedure (CEA or CAS), diabetes, cardiac history. Pearson's chi squared test was used for univariable analysis and for comparing proportions. A binary logistic regression model was used as a multivariable analysis to find independent risk factors for poor outcome after the carotid procedure. Predictors of each end point were identified in a univariable screen using $p < .20$ as a threshold for inclusion in the binary logistic regression model. Statistical evaluation was carried out using SPSS 22.0 software (SPSS Inc.; Chicago, IL, USA). Values with a $p < .010$ were considered significant. Missing data were handled by complete case exclusion. No correction for multiple hypothesis testing was applied.

RESULTS

Overall study patients

The data included 223 626 carotid procedures (58.2% CEA, 41.8% CAS) (Table 1). There were significant differences between countries in terms of proportion of patients treated for asymptomatic disease, as well as in terms of use of CAS (Supplementary Table S1); this is in line with previous observations in VASCUNET studies comparing carotid practice between countries.[19] Of the procedures, 34.8% were done in women. In 49.9% of the total population, the indication for the procedure was asymptomatic stenosis, the proportion being 51.5% among women and 49.2% among men ($p< .001$).

Symptomatic patients undergoing carotid endarterectomy

In total, 130 229 of the procedures were CEAs and 62.6% ($n = 81\ 492$) had been done for a symptomatic carotid stenosis. In 33.1%, procedures were for women. The most common indication for CEA among symptomatic patients was TIA (63.5%), followed by stroke (29.4%) and symptomatic stenosis, other than TIA or stroke (5.3%). The variable symptomatic was used without more detailed symptom information in 1.8%. In men, TIA and stroke were the indications in 63.0% and 30.0% of the symptomatic cases, respectively, and in women 64.6% and 28.3%, respectively (between men and women $p < .001$).

In the unadjusted analysis of the CEAs for symptomatic stenosis, there were no significant differences between men and women in the rate of post-operative combined stroke and or death (2.5% *vs* 2.7%, $p = .18$), stroke rate, death, any major cardiac event (1.1% *vs* 1.2%; $p = .12$), or combined death, stroke, and any major cardiac event (3.0% *vs* 3.2%;

Table 2. Thirty day or in hospital complication incidences after carotid endarterectomy (CEA) and carotid artery stenting (CAS) in asymptomatic and symptomatic patients

Complications	Patients <80 years			Patients >80 years		
	Men	Women	Total	Men	Women	Total
CEA, asymptomatic patients[*]						
Combined stroke and or death	2.4	2.5	2.4	2.6	2.8	2.6
Combined stroke death and MI	3.3	3.5	3.4	3.8	4.2	4.0
Stroke	1.7	1.9	1.8	1.6	1.9	1.7
Death	0.8	0.6	0.7	1.0	0.9	1.0
Any major cardiac event	1.1	1.1	1.1	1.5	1.6	1.5
Haemorrhage	1.6	1.7	1.6	1.6	1.4	1.6
CEA, symptomatic patients[†]						
Combined stroke and death	2.3	2.4	2.4	2.9[‖]	3.5[‖]	3.1
Combined stroke death and MI	2.8	2.8	2.8	3.6[‖]	4.3[‖]	3.8
Stroke	1.8	1.7	1.8	2.0[‖]	2.1	2.0
Death	0.9	1.0	1.0	1.5[‖]	2.3[‖]	1.8[¶]
Any major cardiac event	1.0	1.0	1.0	1.6[‖]	2.0	1.7
Haemorrhage	2.6	2.6	2.6	3.4[‖]	3.4[‖]	3.4
CAS, asymptomatic patients[‡]						
Combined stroke and death	2.9	2.9	2.9	2.6	2.6	2.6
Combined stroke death and MI	3.9	4.0	4.0	3.6	3.7	3.6
Stroke	2.0	2.2	2.0	1.6	1.8	1.7
Death	0.9	0.8	0.9	1.1	0.8	1.0
Any major cardiac event	1.1	1.1	1.1	1.0	1.2	1.1
Haemorrhage	1.4	1.5	1.4	1.3	1.3	1.3
CAS, symptomatic patients[§]						
Combined stroke and death	2.6	2.8	2.7	3.2	3.3	3.1
Combined stroke death and MI	3.8	3.9	3.8	4.6	4.2	4.4
Stroke	1.8	2.0	1.9	2.0	1.9	1.9
Death	0.8	0.9	0.8	1.3	1.2	1.2
Any major cardiac event	1.2	1.1	1.2	1.4	1.3	1.3
Haemorrhage	1.3	0.9	1.1	1.6	1.1	1.4

Data are presented as %. MI = myocardial infarction.
[*] < 80 years $n = 38\,432$; > 80 years ($n = 9\,859$).
[†] < 80 years ($n = 60\,326$); > 80 years ($n = 17\,489$).
[‡] < 80 years $n = 45\,614$; > 80 years $n = 17\,008$.
[§] < 80 years $n = 22\,301$; > 80 years $n = 8251$.
[‖] Significant difference between patients < 80 years compared with patients > 80 years.
[¶] Significant difference between the sexes.

$p = .044$) or wound haemorrhage requiring re-operation (2.8% *vs* 2.8%; $p = .52$).

When the indication was stroke, the rates of combined stroke and or death in men and women were 3.1% and 2.8%, respectively ($p = .18$), and when the indication was TIA, 2.2% and 2.5%, respectively ($p = .011$).

Among symptomatic patients, 22.5% were octogenarians, the proportion being 21.4% among men and 24.3% among women ($p < .001$). The post-operative complication rates were higher in octogenarians than in patients less than 80 years of age in both men and women (Table 2).

Asymptomatic patients undergoing carotid endarterectomy

In total, 48 737 CEAs were done for asymptomatic stenosis, 34.4% were women. In the unadjusted analysis, no significant differences existed between men and women in the rates of combined stroke and or death (2.5% *vs* 2.6%, $p = .47$), stroke rate, death, any major cardiac event (1.2% *vs* 1.2%; $p = .72$), or combined death, stroke, and any major cardiac event (3.4% *vs* 3.6%; $p = .28$), or post-operative haemorrhage (1.6% *vs* 1.6%; $p = .71$).

Among asymptomatic patients, 20.4% were octogenarians, 21.4% among men and 24.3% among women ($p < .001$). There was a trend towards a higher post-operative mortality and any major cardiac event rate in octogenarians than in patients less than 80 years of age in both sexes (Table 2).

Symptomatic patients undergoing carotid artery stenting

Of the total of 93 397 CASs, 32.9% were for symptomatic stenosis. The symptom was TIA in 72.8 % and stroke in 18.7% of the procedures. Symptomatic or other was the indication in 8.5%. In men, TIA was indication for the procedure in 72.6% and stroke in 18.8 % of the cases; in women the respective proportions were 73.1% and 18.4% ($p = .41$). There were no significant differences between men and women in the rate of post-operative combined

Table 3. Binary logistic regression model on the risk factors for 30 day or in hospital combined stroke and or death, combined stroke, death and or myocardial infarction (MI), stroke, and death after treatment of carotid stenosis. Study data collected from 14 countries by VASCUNET for two time periods, 2010–2013 and 2014–2017

Complication	OR	95% CI
Combined stroke and or death		
Age/year	1.008*	1.005–1.005
Women *vs.* men	1.047	0.91–1.105
Procedures CAS *vs.* CEA	1.114*	1.054–1.178
Indication stroke *vs.* asymptomatic	1.168*	1.078–1.266
Indication TIA *vs.* asymptomatic	0.932	0.876–0.991
Indication symptomatic unspecified *vs.* asymptomatic	1.575*	1.197–2.071
Combined stroke, death, and/or MI		
Age/year	1.009*	1.006–1.012
Women *vs.* men	1.051	1.002–1.102
Procedures CAS *vs.* CEA	1.191*	1.135–1.250
Indication stroke *vs.* asymptomatic	1.033*	0.961–1.110
Indication TIA *vs.* asymptomatic	0.887	0.841–0.936
Indication symptomatic unspecified *vs.* asymptomatic	1.656*	1.309–2.095
Death		
Age/year	1.006*	1.003–1.009
Women *vs.* men	1.034	0.984–1.087
Procedures CAS *vs.* CEA	1.139*	1.083–1.197
Indication stroke *vs.* asymptomatic	1.025	0.943–1.114
Indication TIA *vs.* asymptomatic	0.953	0.900–1.009
Indication symptomatic unspecified *vs.* asymptomatic	1.107	0.842–1.455
Diabetes	1.074*	1.019–1.131
Cardiac history	0.991	0.941–1.043
Stroke		
Age/year	1.007*	1.004–1.011
Women *vs.* men	1.035	0.977–1.096
Procedures CAS *vs.* CEA	1.188*	1.122–1.258
Indication stroke *vs.* asymptomatic	1.139*	1.042–1.246
Indication TIA *vs.* asymptomatic	0.941	0.882–1.003
Indication symptomatic unspecified *vs.* asymptomatic	1.394	1.041–1.867
Cardiac history	0.948	0.894–1.004

OR = odds ratio; CI = confidence interval; CAS = carotid artery stenting; CEA = carotid endarterectomy; TIA = transient ischaemic attack.
* $p < .010$.

stroke and or death (2.8% *vs.* 2.8%), stroke rate, death, any major cardiac event (1.1% *vs.* 1.1%), or haemorrhage (1.4% *vs.* 1.4%). When the indication for CAS was stroke, the combined stroke and or death rates in men and women were 3.1% and 2.6%, respectively ($p = .33$), and when the indication was TIA, the respective rates were 1.7% and 2.0% ($p = .022$).

Among symptomatic patients, 26.9% were octogenarians, the proportion being 26.3% among men and 27.8% among women ($p \leq .001$). In both men and women, the post-procedural complication rates were similar in patients under and over 80 years of age. Complication rates after CAS in both sexes according to age group are presented in the Table 2.

Asymptomatic patients undergoing carotid artery stenting

In total, 62 681 procedures CASs were performed for asymptomatic stenosis. There were no significant differences between men and women in the rates of combined stroke and or death (2.8% *vs.* 2.8%), or combined death, stroke, and any major cardiac event (3.8% *vs* 3.9%), post-operative haemorrhage (1.4% *vs* 1.5%), and any major cardiac event (1.1% *vs.* 1.1%).

Of the asymptomatic patients, 27.1% were octogenarians, the proportion being 27.2% among men and 27.0% among women. After CAS, complication rates were not significantly higher in octogenarians compared with younger patients (Table 2).

Sensitivity analysis

No significant difference between men and women were found in the combined stroke and or death rate after CEA and CAS for asymptomatic and symptomatic carotid stenosis, when outcome analyses were performed separately for countries providing 30 day outcome data and for countries providing only in hospital outcome data (Supplementary Table S2).

Furthermore, no sex differences were found when study countries were analysed separately (Supplementary Tables S3 and S4).

Multivariable analysis

In adjusted analyses, sex was not significantly associated with any of the end points. For a combined endpoint of stroke, any major cardiac event and death, women had a trend towards an increased complication rate compared with men (odds ratio [OR] 1.051, 95% CI 1.002 — 1.102; $p = .041$). Higher age and CAS *vs.* CEA were independently associated with all four end points. Furthermore, stroke *vs.* asymptomatic stenosis as an indication for the intervention was independently associated with post-operative stroke and the combined stroke and or death rate. Independent risk factors for post-operative death were CAS as opposed to CEA, as well as higher age and diabetes (Table 3).

DISCUSSION

A higher risk related to surgery has been suggested to be one of the reasons why women benefit less from surgery than men.[6,19] In the current study including over 200 000 procedures, no statistically significant differences in post-operative stroke or death rates or in their combinations were found, nor in the combined stroke, any major cardiac event, and death rate, between men and women after an intervention for carotid artery stenosis. In line with several previous studies on peripheral arterial disease, the female patients were older than their male counterparts, they were more often asymptomatic, and in symptomatic women, the

indication was less often stroke than in men. While sex was not associated with complications, it was clear that higher age, in turn, was associated with higher complication rates after CEA. Age was an independent risk factor for all main outcome measures. The difference between the two age groups was significantly less pronounced after CAS than after CEA. The fact that CAS is clearly less invasive than open surgery may explain the finding. However, it has been shown in earlier studies that the stroke rate during CAS is high, especially among octogenarians. Thus, the finding is different. In the data, CEA patients were submitted from all participating countries, CAS only from few countries, the vast majority being from Italy. Thus, the overall comparison of CEA and CAS outcome is not reliable.

Strengths and limitations

The data have been collected in 14 countries into national registries, which may have used slightly different definitions of risk factors or post-operative complications. Validity of participating registries is the first concern. Four of the 14 registries have recently been validated regarding carotid interventions, and their validity has been good.[20–23] In the current study, in order to achieve reliable results, the most important variables are sex, age, type of procedure, and post-operative complications. Of these, age, sex, and procedure type (CEA or CAS) are robust, and errors in these are less likely than, for example, in pre-operative risk factor variables where the data may not be known or available at the time when the information is recorded in the database. Diabetes and cardiac risk factors were used in multivariable analysis. Some 32% of the patients had diabetes and, 42% a cardiac risk factor, proportions being in line with RCTs on carotid stenosis,[1,3,5] hence suggesting that there are no major errors in these variables that would significantly affect the reliability of the main results. Post-operative complications are also vulnerable to errors, as they require a follow up of at least 30 days after the intervention and the updating of the registry. It has been proven that stoke incidence is higher in series in which patients have been examined by a neurologist at the follow up visit. Several hospitals collected data first from their national registry and thereafter from the common VASCUNET database. Not all hospitals had independent physician scrutiny for post-operative complications. According to estimation by VASCUNET collaborators, the proportion varied from 0% to 80% in different registries. It is usually minor strokes that are missed, while major strokes, which are clearly significant and related to the patient's independence, are recognised, and recorded. Due to this, the results and conclusions are justified despite this possible under recording. One limitation is that three countries only registered in hospital outcome instead of 30 day outcome. As patients stay at hospital on average two to three days after intervention, complications between discharge and 30 days may not be registered at all. In the sensitivity analysis, complications rates were lower in the in hospital than in 30 day group, but no sex differences were seen in groups, nor when study countries were analysed separately. Thus, despite this limitation, the main conclusion of the study remains valid. There is however a risk of selection bias. Patients represent all patients operated and the original VASCUNET database was not designed to distinguish sex related differences. Finally, due to the nature of registry data, neither could the mechanism behind the peri-operative events be scrutinised nor whether there are any sex related differences affecting long term outcome. Despite these limitations, the reports on clinical patterns in unselected patients are highly valuable and the role of VASCUNET is important to distinguish discrepancies between treatment standards and clinical reality.[24]

Complication rates in asymptomatic patients

In several meta-analyses comparing the peri-operative results between CEA and CAS in asymptomatic patients, CEA has had significantly lower 30 day stroke and also stroke or death rates compared with CAS, but higher major cardiac event rates.[25] In the recently published ACST-2 trial, there was a small excess of non-disabling strokes after CAS and a small excess of MI after CEA, but the overall risk of death or disabling stroke was similar: the incidence of stroke and or death was 3.7% after CAS compared with 2.7% after CEA when also minor strokes were included.[26] In the unselected real life asymptomatic patients, the combined stroke and death rates were 2.5% after CEA and 2.8% after CAS ($p = .001$). As the stroke data also include minor strokes, the results regarding combined stroke and death rates are in line with ACAS-2 results. Considering that 13% of the data only have in hospital outcome and that some minor strokes have probably not been recorded, true 30 day complication rate is probably higher. However, higher major cardiac event rates in CEA compared with CAS were not seen in asymptomatic patients. One reason may be selection bias in the registry study, that patients who underwent CAS may have had a higher risk profile than CEA patients and thus also patients in RCTs. A recent pooled analysis of the four major randomised controlled trials comparing CEA and CAS showed that if these procedures were performed safely, most patients who were revascularised could anticipate freedom from stroke for up to 10 years after either CEA or CAS.[5]

Complication rates in symptomatic patients

Study of Carotid Stenosis Trialists' Collaboration included outcomes of symptomatic patients in EVA-3S, SPACE, ICSS and CREST to study the sex differences between CAS and CEA for any stroke or death three months after the carotid procedure.[9] Interestingly, the CAS to CEA relative risk of the primary outcome was significantly lower for women than men in one trial, nominally lower in another, and nominally higher in the other two. In the data there were no significant differences in CAS to CEA ratio between the sexes, being the lowest among asymptomatic men (0.8), and the highest among women >80 years of age (1.1).

Symptomatic patients have a higher complication risk than asymptomatic patients, as the plaque is more

vulnerable at the time of the intervention. The incidence of peri-operative complications has declined during the last decades, and the decrease has been clearer after CEA than after CAS. In a pooled analysis of four RCTs in symptomatic patients, the crude risk of combined stroke or death after CAS decreased from 8.2% in 2000 − 2002, to 5.8% in 2007 − 2008. After CEA, the decrease was from 7.1% in 2000 − 2002 to 2.0% in 2007 − 2008.[27] The combined stroke and death rate in symptomatic patients was 2.5% after CEA and 2.8% after CAS ($p = .005$), and the combined stroke, death, and MI rates were 3.0% and 4.0% after CEA and CAS, respectively. Due to the reasons discussed in the previous paragraphs, minor strokes are probably missing to some extent from the data and the true incidences of complications may be somewhat higher. Furthermore, in the data, direct comparison of CEA and CAS may be biased because the vast majority of the CAS patients were from one country and there were several countries performing high numbers of CEAs but no CASs.

The prevalence of cardiac risk factors was higher in men than women (44.4% *vs.* 38.8%). It was highest in patients who underwent CEA for symptomatic carotid stenosis and it was more prominent in the patients less than 80 years of age, being 48% in men and 40% in women compared with 55% in men and 52% in women in octogenarians. It is assumed that the reason for the decrease in the prevalence gap between men and women is that in the younger age group prevalence remains significantly lower due to the protective effect of oestrogen on arterial disease. Despite lower prevalence of cardiac risk factors, the incidence of cardiac complication after CEA for symptomatic octogenarians was higher in women. This finding is interesting and has not been addressed in the literature previously. It raises the question whether among women there is more undiagnosed or under treated coronary artery disease, as it is known that women are less engaged to statin and antithrombotic medication, for example.[28,29]

Other registry studies have also analysed sex related differences after carotid interventions: The Statutory German Assurance Database of all carotid endarterectomies performed in 2009 − 2014 did not show any sex related differences in complications after CEA (in hospital stroke or death rate after CEA 1.8% in women and 1.9% in men, ns),[12] nor did a study on 70 000 patients from New York state operated on in 2000 − 2009 (the combined stroke and death rate after CEA 1.89% in men and 1.94% in women; and after CAS 2.54% in men and 2.57% in women).[30] In a systematic review of all available publications released by 2015, including 58 articles, an unselected meta-analysis of RCTs revealed that women undergoing CEA had a higher combined risk of death and stroke after the intervention than men, but in database analyses, the authors did not find any difference in overall peri-operative stroke rates and combined death and stroke rates for CEA between the sexes.[31] Although there were no significant differences between the sexes in the primary outcome measures in the current study, a few trends ($p = .050 - .010$) in crude complication incidences were found: in symptomatic patients $>$ 80 years of age, women had a higher mortality rate (1.5% *vs.* 2.3%, $p = .010$) and a higher combined stroke, death, and any major cardiac event rate (3.6% *vs.* 4.3%, $p = .011$) than men. In this older age group, such a trend was seen after CAS. In contrast, the crude complication rates were higher in men, but the significance remained low.

Due to the general assumption that women have higher complication rates and benefit less from the intervention, clinical practice may have been more selective in including women to receive the intervention, especially for asymptomatic patients. As the benefit is gained slowly after the intervention for asymptomatic stenosis, an over five year life expectancy has been recommended in order to receive a net benefit in the form of a reduction in the risk of stroke and death. The age threshold for women has been even lower than for men. However, in general, women live longer than men, the mean difference in life expectancy in Western countries being five years. The ESVS 2023 Clinical Practice Guidelines on the management of atherosclerotic carotid and vertebral artery disease recommendations on the indications for invasive treatment for men and women are similar.[32] Unfortunately, the current study, which focuses on patients undergoing surgical treatment, cannot comment on the natural history of carotid stenosis based on sex, and the potential difference in risk of stroke without surgery. Further natural history studies with modern medical treatment for men and women would be of value in this context. Furthermore, the underlying pathophysiology of the strokes is unknown. It would be interesting to analyse the pathophysiological differences between the sexes and modalities. An analysis of ICSS patients showed that the mechanism of procedural stroke in both CAS and CEA is diverse; after CAS the most common mechanism was haemodynamic while it was hyperperfusion after CEA.[33]

Conclusions

The study confirmed that, in a large registry of non-selected patients, no significant sex related differences in peri-operative complication rates were found after interventions for carotid stenosis. Octogenarians are more fragile, and their complication frequency is higher compared with younger patients, particularly after CEA, with an intervention for symptomatic carotid stenosis. This study supports earlier studies about the higher short term risk of death or stroke after CAS compared with endarterectomy for both sexes.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.04.022

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