

NATIONAL REGISTRY

Low Incidence of Late Ipsilateral Ischaemic Stroke After Treatment for Symptomatic Carotid Stenosis in Sweden 2008–2017: Increased Risk in the Elderly and After Carotid Stenting

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WHAT THIS PAPER ADDS

This nationwide cohort study of Swedish patients treated surgically for symptomatic carotid stenosis 2008 – 2017 shows low rates of late ipsilateral ischaemic stroke, with a mean incidence of 0.73%/year. Age above 80 years was the only risk factor statistically significantly associated with ipsilateral ischaemic stroke using present day best medical treatment. Carotid artery stenting compared with carotid endarterectomy was associated with statistically significantly increased long term risk, supporting guidelines to limit its use in symptomatic patients.

Objective: Carotid stenosis is a major risk factor for stroke and surgical treatment is key in preventing recurrent ischaemic events. Previous randomised trials have demonstrated the net benefit of surgery for significant symptomatic carotid stenosis but, with present day medical treatment, there is limited evidence on the risk of late ipsilateral ischaemic stroke (IS) and its main risk factors.

Method: Ipsilateral IS after the peri-operative period (≤ 30 days) was investigated in a nationwide, registry based cohort study of patients treated for symptomatic carotid stenosis in Sweden between 2008 – 2017. The Swedish National Registry for Vascular Surgery (Swedvasc) was used to establish the cohort, and the Swedish stroke registry (Riksstroke), combined with hospital records, was used to determine outcome. Stroke of any type and all cause mortality after the peri-operative period were studied as secondary outcomes. Cox regression was used to analyse associations between clinical factors and outcomes.

Results: In total, 7 589 patients (mean age 72 ± 8 years, 68% men) were followed for 4.2 ± 2.6 years. Ipsilateral IS occurred in 232 patients corresponding to a yearly incidence of 0.73%. Age above 80 years compared with 65 – 79 years was associated with an increased risk of ipsilateral IS (adjusted HR 1.94, 95% CI 1.43 – 2.65). Carotid artery stenting (CAS) compared with carotid endarterectomy (CEA) was also associated with increased risk (adjusted HR 3.20, 95% CI 2.03 – 5.03). Stroke of any type occurred in 7.7% of patients, and 19.6% of patients died during the follow up period.

Conclusion: The incidence of ipsilateral IS after treatment for symptomatic carotid stenosis in Sweden 2008–2017 was low, demonstrating the effectiveness and durability of surgery in a real world setting. Only age above 80 years and CAS compared with CEA were associated with increased risk of ipsilateral IS.

Keywords: Carotid endarterectomy, Carotid stenosis, Risk factors, Stroke

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INTRODUCTION

Symptomatic carotid stenosis is a major risk factor for ischaemic stroke (IS) and treatment by carotid endarterectomy (CEA) substantially reduces the risk of ipsilateral IS for a patient with significant stenosis.¹ The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), both performed during the early 1990s, showed a net benefit of CEA added to medical treatment.^{2,3} In NASCET, incidence of late ipsilateral IS was 2%/year after CEA beyond the peri-operative period,^{2,4} while medical treatment alone gave a high incidence of ipsilateral IS in the first years after symptoms, which stabilised at 3%/year.² Since the studies were performed, there have been improvements in medical treatment and risk factor control, including reduced rates of smoking in high income countries.^{5,6}

While peri-operative and short term outcomes after carotid intervention have been studied extensively, evidence on medium to long term risk of ipsilateral IS with present treatment principles is more limited.^{7,8} Modern treatment may also have shifted associations between risk factors and ipsilateral IS after carotid surgery. In an updated review and subgroup analysis of NASCET and ECST, a higher net benefit was found in men compared with women and in patients aged >75 years compared with those aged <75 years. Surgery within two weeks of symptoms was associated with improved net benefit and is recommended in guidelines.^{1,9} The lower net benefit for women may have led to women being more closely scrutinised than men for carotid intervention.^{2,3} Concerning age, it was noted that studies could suffer from a selection effect, with recruitment of mainly comparatively healthy elderly patients. Other risk factors were not statistically significantly associated with the combined outcome late ipsilateral IS or any stroke or death within 30 days of surgery, but hypothetically could be associated with late ipsilateral IS with present day treatment. The aim of this study was 1) to determine the up to date incidence of late ipsilateral IS after carotid surgery for symptomatic carotid stenosis in a real world setting not limited by inclusion and exclusion criteria of randomised trials, and 2) to investigate associations between late ipsilateral IS and clinical factors. Swedish registry data were used to establish the cohort, and registry data combined with hospital records to determine outcomes. Late stroke of any type and all cause mortality were studied as secondary outcomes. The study period was chosen considering evolution of treatment guidelines and registry coverage/quality. In 2008 the Swedvasc registry was re-organised and European Stroke Guidelines for the first time recommended statin treatment for all non-cardio-embolic ischaemic strokes. The study period 2008 – 2017 was therefore selected.

METHOD

The study was performed according to the STROBE guidelines and was based on registry data combined with hospital records to determine outcomes.

Study population

The Swedvasc registry was used to identify all patients having had surgery by CEA or CAS for symptomatic carotid stenosis from 1 July 2008 to 30 September 2017. Only primary procedures were included. Procedures with indication aneurysms, dissections, or trauma were excluded. Data on clinical factors, risk factors, and comorbidities were collected from the Swedvasc registry. The registry has had national coverage since 1994, with carotid procedures being reported with an internal validity of 97.4% and an external validity of 100%.¹⁰

Riksstroke was used to identify patients with stroke more than 30 days after surgery, using the unique Swedish 12 digit identification number given to all residents. Riksstroke covers all 72 hospitals in Sweden treating stroke patients, with an estimated coverage of 96%.¹¹ IS and haemorrhagic strokes are registered, but not subarachnoid haemorrhages.¹² By linking Swedvasc and Riksstroke based on identification number, patients with recurrent stroke during follow up could be identified.

Outcomes

The primary outcome was ipsilateral IS more than 30 days post-operatively and before the end of follow up (30 September 2017). Peri-operative stroke or death is reported for completeness. Secondary outcomes were 1) stroke of any type more than 30 days after surgery and 2) all cause mortality more than 30 days after surgery. Patients with non-fatal peri-operative stroke were analysed for late outcomes as mechanisms causing peri-operative and late outcomes probably differ.

Hospital records were requested from the treating hospital for patients with stroke during follow up. Type of stroke (ischaemic or haemorrhagic) and IS vascular territory (anterior/posterior circulation, laterality relative to the operated carotid) were evaluated by two experienced stroke physicians based on description of clinical symptoms and, where available, radiology. Differences were resolved by consensus. Data on all cause mortality were obtained from Swedvasc, which is linked to the Swedish National Population Registry (NPR) for date of death. Data on peri-operative stroke or death were also obtained from Swedvasc. Patients were censored after the first relevant outcome event.

All patients consented to being reported in the Swedvasc and Riksstroke registries. The study was approved by the Central Ethical Review Board in Stockholm (2017/1223–31/2).

Clinical factors

Clinical factors investigated were 1) cardiovascular risk factors: age, sex, smoking, diabetes, hypertension; 2) comorbidities: heart disease, pulmonary disease; 3) degree of ipsi- and contralateral carotid stenosis; 4) type of qualifying neurological event; and 5) surgical factors: time to surgery, size of operating centre, and CEA or CAS as surgical method. These are documented in Swedvasc and were defined and categorised according to [Supplementary Table S1](#).

Statistical analysis

Numerical variables were presented as mean with standard deviation (SD) if normally distributed, otherwise as median with interquartile range (IQR). Categorical variables were presented as numbers with proportions. Differences between independent groups were analysed by Student *t* test or Mann–Whitney *U* test as appropriate for numerical variables, and by χ^2 test or Fisher exact test as appropriate for categorical variables. The associations between clinical factors and outcomes were analysed by Kaplan–Meier analysis and Cox regression. Cox regression hazard ratios (HR) with 95% confidence interval (CI) were calculated crudely (univariable analysis) and adjusted for all investigated clinical factors (multivariable analysis). HR reported in text are fully adjusted unless otherwise stated. All tests were two sided, and statistical significance was defined as $p < .050$.

Peri-operative complications stroke or death within 30 days were determined for completeness. Logistic regression was used to determine associations between peri-operative stroke or death and clinical factors (Supplementary Table S2).

The list of clinical factors includes many expected confounders. Considering the number of clinical factors investigated, confounding effects were evaluated by comparing crude and adjusted HR. Interactions between individual clinical factors were not analysed separately. Death as competing risk was analysed according to the model of Fine and Gray for clinical factors with statistically significantly increased HR for the primary outcome.

Considering the number of clinical factors investigated, the aim was to have as large a cohort as possible respecting the above limitations; exact power was not calculated. A yearly surgery rate of 800 patients and an ipsilateral IS event rate of 1%/year over a mean follow up time of four to five years would result in about 300 events of the primary outcome, which in theory would allow for analyses of up to

30 categorical variables. A post hoc power calculation showed that with the observed cohort size and event rate, a HR of ≥ 1.35 would become statistically significant for a clinical factor with a prevalence of 20% with 80% power and statistical significance $p < .050$.

Data were analysed in Statistical Package for the Social Sciences (SPSS) version 25.0.0 (SPSS, Chicago, IL, USA), STATA, with figures created by R 3.4.3.

RESULTS

Baseline characteristics and early complications

A total of 7 653 patients undergoing primary CEA or CAS for symptomatic carotid stenosis were identified in Swedvasc during the study period (Fig. 1). Baseline characteristics are listed in Table 1. Mean age was 72 years (SD \pm 8) and 67% of patients were men. Transient ischaemic attack (TIA) and minor ischaemic stroke were the most common qualifying neurological events, 40% and 35.5%, respectively. Median time from qualifying neurological event to surgery was 8 days (IQR 5, 14) and 75% had surgery within 14 days. The vast majority were operated by CEA; only 252 patients (3.3%) were treated by CAS.

Peri-operative stroke or death occurred in 275 patients (64 deaths, 211 strokes), corresponding to 3.6% of the cohort. The subgroup analysis of peri-operative stroke or death vs. clinical factors is given in Supplementary Table S2. In summary, the main risk factors for peri-operative stroke or death were intervention within two days of index neurological event (odds ratio, OR 2.24, 95% CI 1.54 – 3.26), diabetes (OR 1.72, 95% CI 1.31 – 2.24), age >80 years (OR 1.38, 95% CI 1.04 – 1.85) and non-ocular qualifying neurological symptom (see Supplementary Table S2 for details). In total, 6% of patients had intervention because of stenosis $<50\%$, the majority of which had repeated symptoms. Ipsilateral stenosis $<50\%$ and contralateral stenosis 70% – 99% were associated with increased peri-operative risk, (OR 1.93, 95% CI 1.21 – 3.08 and OR 1.78, 95% CI 1.22 – 2.58).

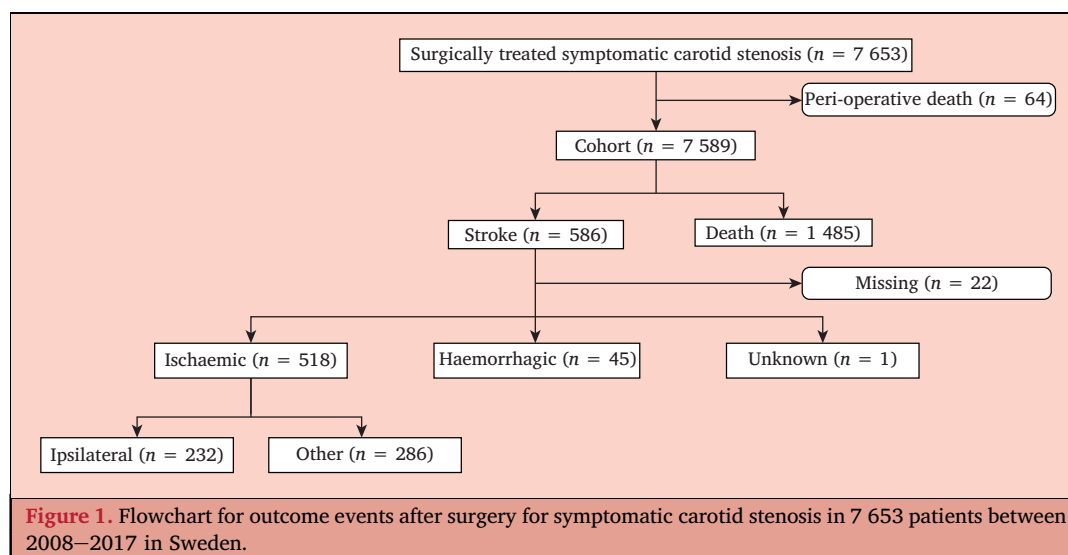


Table 1. Baseline characteristics of 7 653 patients treated surgically for symptomatic carotid stenosis between 2008–2017 in Sweden

Variable	Patients – n	Cohort (n = 7 653)	Ipsilateral ischaemic stroke during follow up		p value
			Yes (n = 232)	No (n = 7 357)	
Age – y	7 653	72 ± 8.2	73 ± 8.5	72 ± 8.2	.002
<65		1 343 (17.5)	39 (16.8)	1 300 (17.7)	
65 – 79		4 816 (62.9)	127 (54.7)	4 653 (63.2)	
≥80		1 494 (19.5)	66 (28.4)	1 404 (19.1)	
Male sex		5 152 (67.3)	142 (61.2)	4 973 (67.6)	.041
Hypertension	7 250	5 822 (76.1)	176 (75.9)	5 589 (76.0)	.75
Diabetes	7 270	1 520 (19.9)	53 (22.8)	1 447 (19.7)	.19
Heart disease	7 166	2 222 (29.0)	64 (27.6)	2 134 (29.0)	.046
Pulmonary disease	7 019	748 (9.8)	20 (8.6)	711 (9.7)	.41
Current smoking	6 181	1 589 (20.8)	51 (22.0)	1 528 (20.8)	.91
Thrombolysis	1 998	261 (3.4)	7 (3.0)	248 (3.4)	.78
Qualifying event	7 567				.002
Amaurosis fugax		1 499 (19.6)	21 (9.1)	1 476 (20.1)	
TIA		3 065 (40.0)	104 (44.8)	2 933 (39.9)	
Crescendo TIA		148 (1.9)	5 (2.2)	149 (1.9)	
Minor stroke		2 726 (35.5)	96 (41.4)	2 601 (35.4)	
Major stroke		193 (2.5)	6 (2.6)	184 (2.5)	
Ipsilateral stenosis	7 577				.022
<50%		460 (6.0)	21 (9.1)	438 (6.0)	
50–69%		2 235 (29.2)	79 (34.1)	2 141 (29.1)	
70–99%		4 946 (64.6)	132 (56.9)	4 766 (64.8)	
Contralateral stenosis	7 577				.21
<50%		5 710 (74.6)	168 (72.4)	5 510 (74.9)	
50–69%		899 (11.7)	35 (15.1)	851 (11.6)	
70–99%		661 (8.6)	15 (6.5)	634 (8.6)	
Occlusion		371 (4.8)	14 (6.0)	350 (4.8)	
Type of operation	7 538				<.001
CEA		7 349 (96.0)	207 (89.2)	7 083 (96.3)	
CAS		252 (3.3)	25 (10.8)	223 (3.0)	
High volume centre	7 589	3 779 (49.4)	134 (57.8)	3 618 (49.2)	.010
Time to intervention – d	7 568	8 (5–14)	8 (5–15)	8 (5–14)	.68

Data are presented as n (%) or mean ± standard deviation or median (interquartile range). Percentages refer to proportions with a risk factor of the total cohort. TIA = transient ischaemic attack; CEA = carotid endarterectomy; CAS = carotid artery stenting.

Intervention at a high volume centre was associated with a slightly reduced peri-operative risk.

Late outcome events and crude incidence rates after carotid surgery

The mean follow up time with respect to the primary outcome was 4.21 (± 2.55) years, corresponding to a total follow up of 31 949 patient years. Of 7 589 patients followed up after the peri-operative period, 586 patients had stroke. Hospital records were obtained for 564 patients (96.2%). Of these, 232 were categorised as ipsilateral IS (207 after CEA, 25 after CAS). The mean ipsilateral IS incidence rate was 0.73%/year.

Forty five strokes were haemorrhagic, and for one patient the type of stroke could not be determined (no radiology performed). The incidence rate of any stroke was 1.9%/year after the peri-operative period. In total, 1 485 patients died (19.6%), corresponding to a mortality rate of 4.6%/year.

The five year cumulative incidence for late (>30 days after the operation) ipsilateral IS was 3.5%, 9.1% for any stroke, and 18.8% for death.

Cox regression analysis of late outcome events after carotid surgery

Crude and adjusted HRs for ipsilateral IS depending on clinical factors are presented in Table 2. (Cox regression proportional hazards condition was met for statistically significant HRs, data not shown.) Patients aged >80 years had an increased risk of ipsilateral IS compared with patients aged 65 – 79 years (HR 1.94, 95% CI 1.43 – 2.65). The HR for patients aged <65 years did not differ from those aged 65 – 79 years (Fig. 2).

There was a similar ipsilateral IS risk in women compared with men (HR 1.25, 95% CI 0.65 – 1.25, $p = .12$).

Amaurosis fugax as a qualifying neurological symptom was associated with a substantially lower late ipsilateral IS risk than other types of neurological events. Neither degree of ipsilateral nor contralateral stenosis was statistically significantly associated with ipsilateral IS.

Patients treated by CAS had an increased risk of ipsilateral IS compared with those operated by CEA (HR 3.20, 95% CI 2.03 – 5.03). Kaplan–Meier analysis shows maintained separation of event curves over time (Fig. 3).

Table 2. Cox regression analysis of ipsilateral ischaemic stroke >30 d after surgical treatment for symptomatic carotid stenosis in 7 589 patients

	Univariable analysis (n = 7 589)		Multivariable analysis (n = 7 527)	
	HR (95% CI)	p value	HR (95% CI)	p value
<i>Age – y</i>				
65–80	1.00			
<65	0.96 (0.67–1.38)	.83	0.87 (0.60–1.26)	.46
>80	1.88 (1.40–2.54)	<.001	1.94 (1.43–2.65)	<.001
<i>Sex</i>				
Male	1.00			
Female	1.30 (1.00–1.70)	.050	1.25 (0.65–1.25)	.11
<i>Hypertension</i>				
No	1.00			
Yes	1.07 (0.77–1.49)	.70	0.98 (0.69–1.38)	.88
<i>Diabetes</i>				
No	1.00			
Yes	1.33 (0.97–1.81)	.074	1.31 (0.95–1.80)	.10
<i>Heart disease</i>				
No	1.00			
Yes	1.06 (0.79–1.43)	.68	1.00 (0.74–1.36)	1.0
<i>Pulmonary disease</i>				
No	1.00			
Yes	1.02 (0.64–1.61)	.94	0.96 (0.60–1.54)	.87
<i>Current smoking</i>				
Never smoked	1.00			
Quit smoking	0.92 (0.65–1.29)	.62	1.05 (0.74–1.49)	.80
Smoker	1.02 (0.70–1.49)	.93	1.27 (0.84–1.91)	.26
<i>Qualifying event</i>				
Amaurosis fugax	1.00			
TIA	2.52 (1.58–4.02)	<.001	2.29 (1.42–3.69)	.001
Crescendo TIA	2.35 (0.89–6.24)	.086	2.20 (0.82–5.90)	.12
Minor stroke	2.73 (1.70–4.37)	<.001	2.53 (1.57–4.08)	<.001
Major stroke	2.25 (0.91–5.58)	.079	2.09 (0.84–5.19)	.11
<i>Ipsilateral stenosis</i>				
50–69%	1.00			
70–99%	0.90 (0.68–1.19)	.47	0.90 (0.68–1.19)	.46
<50%	1.38 (0.85–2.23)	.19	1.46 (0.90–2.39)	.13
<i>Contralateral stenosis</i>				
<50%	1.00			
50–69%	1.34 (0.93–1.92)	.12	1.35 (0.93–1.95)	.11
70–99%	0.88 (0.52–1.48)	.62	0.91 (0.53–1.56)	.73
Occlusion	1.29 (0.75–2.22)	.37	1.23 (0.71–2.14)	.46
<i>Type of operation</i>				
CEA	1.00			
CAS	3.25 (2.15–4.93)	<.001	3.20 (2.03–5.03)	<.001
<i>Time to intervention – d</i>				
3–14	1.00			
0–2	1.20 (0.76–1.92)	.44	1.36 (0.85–2.18)	.20
>14	0.88 (0.65–1.19)	.40	1.01 (0.74–1.37)	.97
<i>High volume centre</i>				
No	1.00			
Yes	1.37 (1.05–1.77)	.019	1.28 (0.97–1.68)	.080

NS = non-statistically significant; TIA = transient ischaemic attack; CEA = carotid endarterectomy; CAS = carotid artery stenting; HR = hazard ratio; CI = confidence interval.

Summaries of adjusted HR for the outcomes stroke of any type and all cause mortality are presented in [Tables 3 and 4](#), respectively. Clinical factors associated with the primary outcome also resulted in statistically significant HRs for both secondary outcomes (see [Supplementary Table S1](#), supplementary material). Heart disease and smoking were associated with both secondary outcomes. In addition, diabetes, pulmonary disease and contralateral stenosis were associated with all cause mortality.

Competing risk analysis

As the all cause mortality incidence was substantially higher than late ipsilateral IS, death as competing risk was analysed according to the Fine-Gray model for clinical factors with statistically significantly increased HR: age (analysed as an ordinal variable) and CAS vs. CEA. The calculated subdistribution HR (sHR) did not increase compared with the crude HR and associations remained statistically significant.

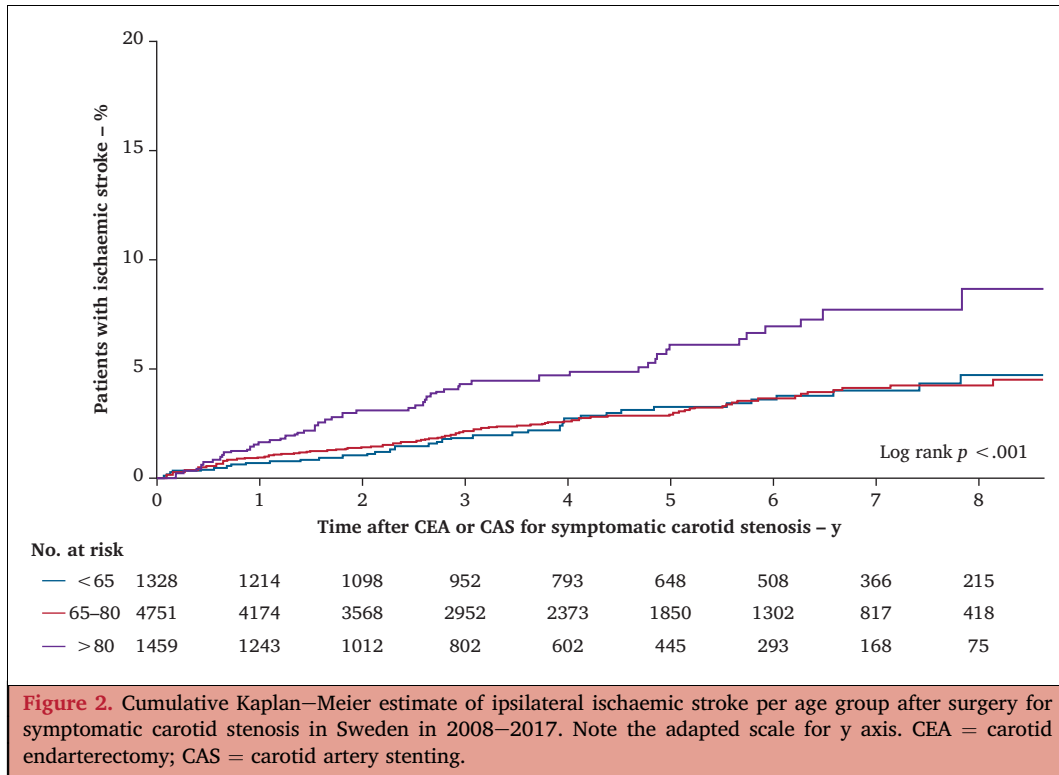


Figure 2. Cumulative Kaplan–Meier estimate of ipsilateral ischaemic stroke per age group after surgery for symptomatic carotid stenosis in Sweden in 2008–2017. Note the adapted scale for y axis. CEA = carotid endarterectomy; CAS = carotid artery stenting.

Confounding

Differences between crude and fully adjusted HR values were limited and exceeded 20% for only two clinical factors. Smoking was associated with an increase in adjusted HR for all late outcomes. This was probably because of the smokers being younger than non-smokers (mean age 67 vs. 73 years). In addition, the HR for all cause mortality, depending on presence of hypertension, decreased after adjustment

and became non-statistically significant, possibly because of interaction with age and/or heart disease.

DISCUSSION

In this nationwide cohort study of patients operated on for symptomatic carotid stenosis in Sweden 2008 – 2017, there was a low incidence of late (>30 days after surgery) ipsilateral ischaemic stroke, with levels similar to the lowest

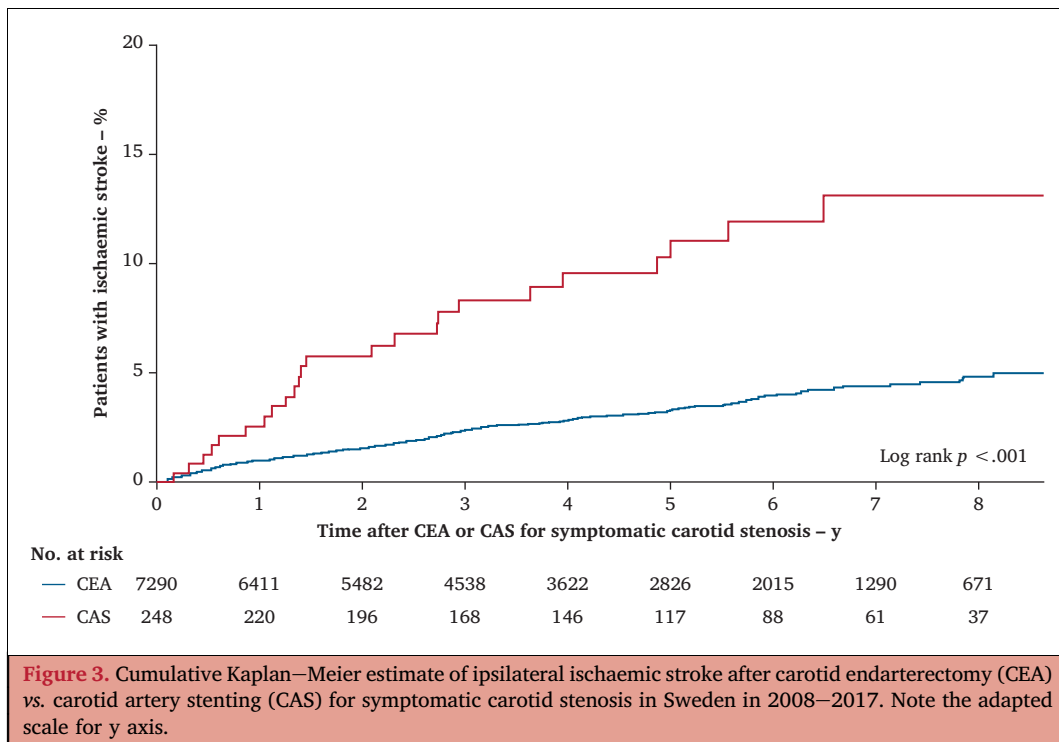


Figure 3. Cumulative Kaplan–Meier estimate of ipsilateral ischaemic stroke after carotid endarterectomy (CEA) vs. carotid artery stenting (CAS) for symptomatic carotid stenosis in Sweden in 2008–2017. Note the adapted scale for y axis.

Table 3. Cox regression analysis of stroke of any type >30 d after surgery for symptomatic carotid stenosis in 7 589 patients

	Patients – n	Multivariable analysis	
		HR (95% CI)	p value
<i>Age – y</i>	7 589		
65–79		1.00	
<65		0.63 (0.49–0.82)	<.001
≥80		1.65 (1.36–2.00)	<.001
<i>Current smoking</i>	6 181		
Never smoked		1.00	
Smoker		1.34 (1.03–1.73)	.027
<i>Qualifying event</i>	7 567		
Amaurosis fugax		1.00	
TIA		1.83 (1.39–2.40)	<.001
Crescendo TIA		2.46 (1.43–4.20)	.001
Minor stroke		1.95 (1.48–2.57)	<.001
<i>Ipsilateral stenosis</i>	7 577		
50–69%		1.00	
70–99%		0.82 (0.69–0.98)	.033
<i>Type of operation</i>	7 538		
CEA		1.00	
CAS		1.94 (1.38–2.75)	<.001

TIA = transient ischaemic attack; CEA = carotid endarterectomy; CAS = carotid artery stenting; HR = hazard ratio; CI = confidence interval.

incidences reported in previous studies of both symptomatic and asymptomatic carotid stenosis.^{7,13} Multivariable Cox regression analysis showed a statistically significant risk increase only for age >80 years and intervention by CAS compared with CEA. The study demonstrates the clear and durable effects of CEA in a real world setting independent of most clinical risk factors.

The mean incidence of confirmed ipsilateral IS was 0.73%/year. Loss to follow up consisted of 22 stroke patients for whom hospital records were not obtained and one patient without radiological diagnosis. Assuming half of these (12 patients) had ipsilateral IS, gives a projected mean incidence of 0.76%/year. In NASCET, the mean incidence of late ipsilateral IS was 1.44%/year for 70% – 99% stenosis and 2%/year for 50% – 69% stenosis after five years follow up, with a lower mean age than in the present study (66 years vs. 72 years).^{2,4} A post hoc analysis of ECST reported the incidence of late ipsilateral IS to be 0.88%/year over five years, but included only 19 events with symptom duration more than one week, underestimating the incidence of any late ipsilateral IS.¹⁴ A recent meta-analysis of randomised studies comparing CEA and CAS for symptomatic carotid stenosis reported yearly incidence of late ipsilateral IS of 0.60%/year and 0.64%/year, respectively, beyond the first 120 days post-intervention.⁷ Rates of stroke or death within 120 days were 5.5% for CEA and 8.7% for CAS compared with 3.6% in the first 30 days in the present study. It is concluded that a low incidence of late ipsilateral IS is achievable in real world settings, outside the strict inclusion and exclusion criteria of randomised trials.

As the present study was observational, conclusions cannot be drawn on the net benefit of carotid surgery, in particular for the different subgroups. Both rates of peri-operative

Table 4. Cox regression analysis of all cause mortality > 30 d after surgery for symptomatic carotid stenosis in 7 589 patients

	Patients – n	Multivariable analysis	
		HR (95% CI)	p value
<i>Age – y</i>	7 589		
<65–79		1.00	
<65		0.37 (0.30–0.45)	<.001
≥80		2.47 (2.20–2.77)	<.001
<i>Diabetes</i>	7 270		
No		1.00	
Yes		1.54 (1.36–1.74)	<.001
<i>Heart disease</i>	7 166		
No		1.00	
Yes		1.51 (1.35–1.68)	<.001
<i>Pulmonary disease</i>	7 019		
No		1.00	
Yes		1.97 (1.70–2.29)	<.001
<i>Current smoking</i>	6 181		
Never smoked		1.00	
Smoker		1.49 (1.25–1.76)	<.001
<i>Qualifying event</i>	7 567		
Amaurosis fugax		1.00	
Minor stroke		1.35 (1.16–1.58)	<.001
Major stroke		1.86 (1.37–2.54)	<.001
<i>Contralateral stenosis</i>	7 577		
<50%		1.00	
50–69%		1.29 (1.11–1.49)	.001
<i>Type of operation</i>	7 538		
CEA		1.00	
CAS		1.63 (1.30–2.06)	<.001
<i>High volume centre</i>	7 589		
No		1.00	
Yes		0.88 (0.79–0.98)	.024
<i>Time to intervention – d</i>	7 568		
3–14		1.00	
0–2		0.76 (0.60–0.97)	.028

HR = hazard ratio; CI = confidence interval; TIA = transient ischaemic attack; CEA = carotid endarterectomy; CAS = carotid artery stenting.

complications and late ipsilateral IS were lower than in the original randomised trials, which should have a positive effect on benefit.^{2,3} A recent study of ipsilateral IS in patients with symptomatic carotid stenosis for whom surgery was delayed found an accumulated incidence of 18.8% over the first three months despite best medical treatment.¹⁵ This is similar to or higher than the incidence found in the medical group of NASCET, suggesting that the risk of ipsilateral IS with best medical treatment alone has not decreased substantially over time. Despite the limitations of an observational study, certain subgroup results warrant comment. A lower net benefit for women compared with men was found in the randomised trials, and was attributed to higher peri-operative risk and lower late ipsilateral IS risk.^{2,3} However, a recent study showed similar risks of peri-operative complications in women compared with men.¹⁶ The present study found no statistically significant sex difference in the risk of peri-operative complications or late ipsilateral IS, indicating that sex should not be a factor in evaluating eligibility for carotid intervention in symptomatic patients. Age >80 years compared with 65 – 79 years resulted in an adjusted HR 1.94 for late ipsilateral IS.

Considering that the risk of ipsilateral IS with medical treatment alone also increases with age and that the overall incidence was low, patients aged >80 years with reasonable life expectancy are likely to benefit from surgery.¹

Six per cent of patients were treated for carotid stenosis < 50%. The majority had repeated symptoms and may have had high risk plaques; for these groups, guidelines support surgery. These patients had a higher risk of peri-operative complications and a non-statistically significant but numerically higher risk of late ipsilateral IS. The results may be caused by unstable plaques, but this group warrants further study.

CAS was associated with a higher late ipsilateral IS rate than CEA, in contrast with findings from randomised trials.⁷ In Sweden intervention with CAS is rare and often chosen because of comorbidities or complicating factors, making selection effects likely. However, the risk increase was substantial, and was not affected by multivariable adjustment or adjustment for death as competing risk and Kaplan–Meier curves continued to separate over time. Confounders not included in the multivariable model could have contributed to the result, for instance malignancy, previous radiation in the neck area, chronic kidney disease, obesity, and substance abuse. However, it cannot be excluded that patients presently selected for CAS in Sweden are not the ones most likely to benefit from this procedure.⁷ Underlying factors warrant further investigation.

The incidences of all stroke and all cause mortality were similar to those found in the randomised trials, despite a higher mean age.^{2,3} Cox regression for these outcomes showed stronger associations for general markers of increased risk (e.g., age, smoking, premorbid heart disease) than was seen for late ipsilateral IS. Further, Kaplan–Meier curves for secondary outcomes were linear (data not shown). Both secondary outcomes may thus reflect the overall risk profile rather than events related to carotid surgery. For future studies, outcomes such as “stroke free survival” may be less suitable to study the efficacy of carotid surgery.

Strengths and limitations

The main strength of the study is its size, with near complete coverage of Swedish patients operated on for symptomatic carotid surgery between 2008 – 2017 and total follow up in patient years almost twice that of NASCET and ECST combined. The cohort is based on Swedish criteria for surgery, which may involve selection effects. On the other hand, it includes patients who may have been excluded from the randomised trials, with a substantial proportion of patients aged > 80 years. The external validity is considered high for Swedish conditions. As Sweden follows European guidelines, high external validity would be expected for European and other countries with similar healthcare systems. However, mean age at surgery, low rates of smoking, and a low number of CAS procedures may not be representative of other countries, which may influence external validity, in particular with respect to the subgroup analysis. The multivariable model does not include possible confounders for which data are unavailable or incomplete in

Swedvasc, including hyperlipidaemia, alcohol use, malignancy, chronic kidney disease, heart failure, BMI, atrial fibrillation, and medical treatment. The number of variables lacking input values in Swedvasc was low, with only 62 patients missing in the multivariable model.

Conclusion

This study shows that low incidence of late ipsilateral ischaemic stroke is obtainable after CEA for symptomatic carotid stenosis.

Age >80 years, and CAS compared with CEA were the only independent risk factors for late ipsilateral IS in a multivariable Cox regression model including 13 clinical factors.

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CONFLICT OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2021.09.019>.

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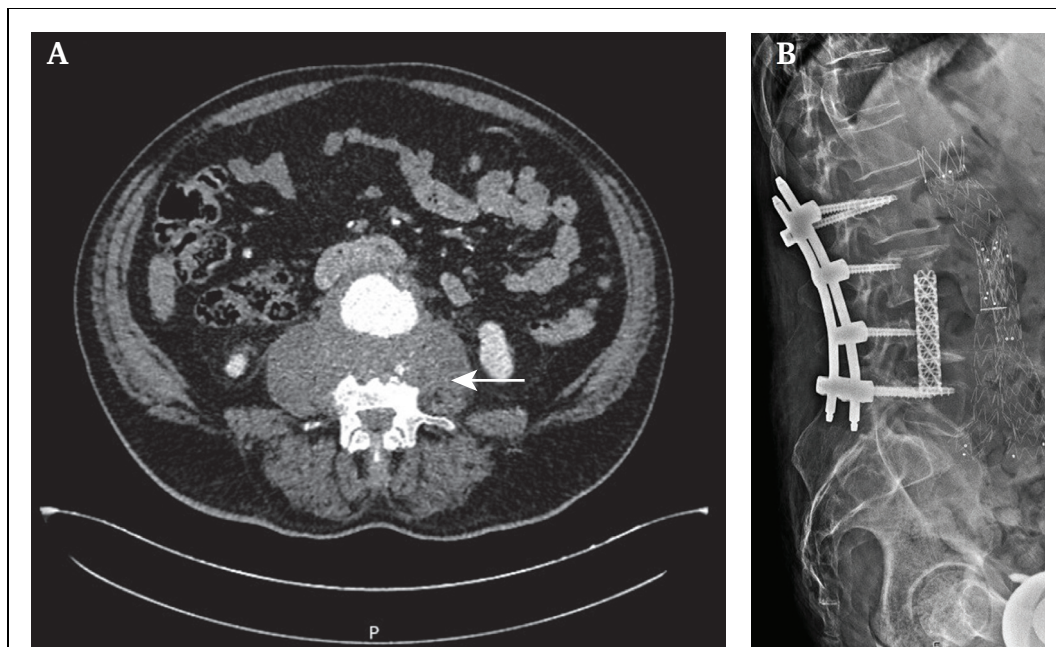
Pott's Disease

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A 64 year old man with a recent diagnosis of spinal tuberculosis was admitted to the emergency department after routine computed tomography angiography (CTA) for a mycotic infrarenal aneurysm. He had been on oral tuberculostatic therapy for two days. (A) The CTA revealed a large 75 mm aneurysm with psoas muscle infiltration (arrow). The aneurysm was urgently excluded with a bifurcated stent graft (Endurant II; Medtronic, Santa Rosa, CA, USA) under local anaesthesia. (B) Three weeks later his lumbar spine was reconstructed in a two step operation shown in the abdominal Xray.

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