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## NATIONAL REGISTRY

# Carotid Endarterectomy After Intracranial Endovascular Thrombectomy for Acute Ischaemic Stroke in Patients with Carotid Artery Stenosis

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## WHAT THIS PAPER ADDS

Intracranial endovascular thrombectomy (EVT) has revolutionised the care of patients with large vessel acute ischaemic stroke, reducing long term disability, but little is known about how to treat residual concomitant extracranial carotid stenosis. The present study is the first relatively large cohort study on patients treated with carotid endarterectomy (CEA) after successful EVT. Although the results are preliminary, and pending larger studies, and ideally a randomised controlled trial comparing CEA with stenting, it seems safe. Except in cases of large cerebral infarction, CEA can be performed early after EVT, without increased risk of post-operative stroke or death.

**Objective:** Recent randomised controlled trials demonstrated the benefit of intracranial endovascular thrombectomy (EVT) in acute ischaemic stroke. There is no consensus, however, on how to treat concomitant extracranial carotid artery stenosis after EVT. The aim of this study was to evaluate the outcome in patients treated with carotid endarterectomy (CEA) after EVT, comparing complication rates among patients undergoing CEA for stroke without previous EVT.

**Methods:** This was a registry study of all patients ( $n = 3\ 780$ ) treated with CEA after stroke in Sweden and the capital Helsinki region, Finland, from January 2011 to September 2020. Sixty three patients (1.7%; 0.5% 2011, 4.3% 2019) underwent EVT prior to CEA. The primary outcome was 30 day stroke and death rate.

**Results:** The EVT+CEA group had major stroke as the qualifying neurological event (QNE) in 79%, but just 5.9% had this in the CEA only group ( $p < .001$ ). Intravenous thrombolysis was administered before EVT in 54% of patients in the EVT+CEA group, but in just 12% in those receiving CEA only ( $p < .001$ ). The combined stroke and death rate at 30 days for EVT+CEA was 0.0% (95% confidence interval [CI] 0.0 – 5.7). One patient had a post-operative TIA, none had post-operative intracerebral or surgical site haemorrhage. CEA was performed within a median of seven days (interquartile range 4, 15) after QNE, and 75% had CEA  $\leq 14$  days from QNE. The main reason to postpone CEA was an infarct larger than one third of the middle cerebral artery territory. The stroke and death rate in patients treated with CEA only was 3.7% (95% CI 3.2 – 4.4), CEA was performed a median of eight days after QNE, and in 79.7% in  $\leq 14$  days. The three year survival after EVT+CEA was 93% (95% CI 85 – 100), compared with 87% (95% CI 86 – 88) after CEA only. Cox regression analysis adjusting for age showed no increased all cause mortality after EVT+CEA (HR 1.3, 95% CI 0.6 – 2.7,  $p = .52$ ).

**Conclusion:** These results indicate that CEA is safe to perform after previous successful EVT for acute ischaemic stroke. Results were comparable with those undergoing CEA only, despite the EVT+CEA patients having more severe stroke symptoms prior to surgery, and timing was similar.

**Keywords:** Carotid artery diseases, Carotid endarterectomy, Endovascular thrombectomy, Ischaemic stroke, Thrombectomy

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## INTRODUCTION

In recent years, several randomised controlled trials (RCTs) have proved the benefit of intracranial endovascular thrombectomy (EVT) of large vessel occlusion (LVO) of the anterior circulation on recovery after stroke.<sup>1</sup> In recent guidelines, EVT plus best medical treatment was recommended in patients with LVO related acute ischaemic stroke up to 24 hours after symptom onset.<sup>2,3</sup> Consequently, the number of EVT procedures has increased rapidly.

Carotid endarterectomy (CEA) is well established as secondary prevention for stroke in patients with a significant carotid artery stenosis and recent ipsilateral cerebrovascular symptoms. CEA is more beneficial if performed early after onset of symptoms. Guidelines recommend CEA as soon as possible after a neurological event to maximise the stroke prevention benefit of the operation.<sup>2,4</sup> There are conflicting data on CEA timing following thrombolysis — previous registry based studies showed that early CEA was safe, whereas a recently published meta-analysis showed increased risk of stroke/death when CEA followed early after thrombolysis.<sup>5–9</sup> Carotid artery stenting (CAS) was compared with CEA in several RCTs, and is associated with an increased risk of peri-operative stroke, especially when performed early after a neurological event.<sup>10</sup>

LVO related stroke often has serious adverse events, and despite best medical treatment and EVT, the mortality rate within 30 days is up to 20%.<sup>11</sup> LVO with concomitant stenosis of the internal carotid artery (ICA) is often refractory to intravenous thrombolysis and requires EVT. About 15% of patients with successful EVT have a residual significant ipsilateral ICA stenosis and may be candidates for CEA or CAS. As pointed out in the European Society of Vascular Surgery (ESVS) guidelines, there is no consensus on how to treat concomitant extracranial stenosis after successful EVT. The aim of this Scandinavian population based study was to evaluate the outcomes after CEA in patients with ischaemic stroke who had previously undergone EVT, comparing complication rates with patients undergoing CEA after stroke as a single procedure.

## MATERIAL AND METHODS

### *Study design*

This observational cohort study of prospectively collected data investigated all patients who underwent EVT (with or without previous intravenous thrombolysis) of the anterior cerebral circulation and were subsequently treated with CEA, during the period of January 2011 to September 2020. Also, all patients who underwent CEA after stroke as a single procedure during the same time period were included for comparison. Patients undergoing CEA for asymptomatic carotid stenosis, transient ischaemic attack (TIA), or amaurosis fugax were excluded, as well as patients treated with CAS or intra-arterial thrombolysis.

The first CEAs after EVT both in Helsinki and in Sweden were performed in 2011, explaining why 1 January 2011 was chosen as the starting point for this study. The primary outcome was 30 day combined stroke (ischaemic or

haemorrhagic) and death rate. Secondary outcomes were intracerebral haemorrhage, acute myocardial infarction, and re-operation for surgical site bleeding, all within 30 days, as well as long term mortality.

Stroke was defined as any new or worsened focal neurological deficit lasting for >24 hours. Primary subarachnoid and epidural haemorrhages were excluded.

The National Institutes of Health Stroke Scale (NIHSS) was used to quantify the neurological impairment before and after EVT, and at the time of CEA. The Thrombolysis In Cerebral Infarction (TICI) grading system was used to determine the response of the thrombectomy.<sup>12</sup>

A cohort of 3 780 CEAs performed for symptomatic carotid artery stenosis after minor or major stroke in all of Sweden (population approximately 10.1 million) and in the Hospital District of Helsinki and Uusimaa (HUS, population 2.2 million) in Finland was established. Data were collected from the national quality registry for vascular surgery in Sweden (Swedvasc), the Swedish Stroke Registry (Riksstroke), the vascular registry (HUSVASC), and Helsinki Stroke Quality Registry (HSQR) of the Hospital District of Helsinki and Uusimaa. The Swedvasc registry, covering all vascular centres performing carotid surgery, has had national coverage since 1994. The registry is continuously updated with the National Population Registry, thereby directly retrieving mortality data through cross matching. Thus, death is not registered by the physicians treating the patients, eliminating the risk of inaccuracy. Carotid procedures have previously been reported with high internal and external validity, at 97.4% and 100%, respectively.<sup>13</sup> Riksstroke covers all 72 hospitals in Sweden treating stroke patients, with an estimated coverage of 96%.<sup>14</sup>

The HUSVASC registry is a local vascular registry in Helsinki University Hospital where arterial procedures have been recorded since 1991. External validity of the registry is performed annually by comparing the registry data with the hospital anaesthesia records. Since 2015 procedures have been entered into the registry automatically, based on procedure codes. The HUSVASC registry receives patients' mortality data directly from the National Death Registry. Baseline risk factors and 30 day complications are registered by the treating physician and the vascular nurse 30 days after the procedure. HSQR includes detailed clinical information on EVT procedures.

### *Ethical approval*

All Swedish patients consented to be reported to the Swedvasc and Riksstroke registries. The study was approved by ethics committee in Sweden (2015/453 and 2020–02911). HSQR has the approval from HUS (HUS/125/2018) until October 2023. The study was approved by the IRB of Helsinki University Hospital Abdominal Centre (HUS/115/2020).

### *Baseline data and definitions*

Patient characteristics for the entire cohort were retrieved from the vascular registries (Swedvasc and HUSVASC).

Diabetes was defined as treatment with insulin and/or oral hypoglycaemic medication. Current smoking included those who had stopped within the previous four weeks, and non-smoking included both never and former smokers. Other definitions included: hypertension if on antihypertensive medication, chronic renal insufficiency as chronic renal failure (need of renal replacement therapy) or creatinine  $>150 \mu\text{mol/L}$ , and chronic obstructive pulmonary disease (COPD) if diagnosed with COPD. The degree of stenosis was defined according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.

The qualifying neurological event (QNE) was the neurological event that made the patient seek medical advice in the healthcare system. In the vascular registries the QNE was categorised into TIA, amaurosis fugax, crescendo TIA, minor and major stroke. In the present study, only patients treated for minor or major stroke were included. Major stroke was defined as disabling neurological symptoms, minor stroke as mild and non-disabling symptoms lasting more than 24 hours.

For patients treated with EVT prior to CEA, charts and medical records were reviewed. Angiographic images of the thrombectomy were reviewed by senior neuro-interventionists.

### Organisation and indications for endovascular thrombectomy

Between 2014 and 2019 the number of EVTs/year increased rapidly. In Sweden the number more than tripled from 261 to 927 (91.8/million inhabitants).<sup>15</sup> In Helsinki University Hospital, the number of EVTs increased from 44 to 241 (109.5/million inhabitants).

In Sweden, 72 hospitals treated acute ischaemic stroke (IS), and performed intravenous thrombolysis. If EVT was indicated, the patient was sent to one of six centres performing EVT, covering different regions. After EVT, the patient was often sent back to their home stroke unit, and, if carotid surgery was indicated, referred to one of 20 vascular surgical units performing CEA. The increase in EVT is explained by an improved organisation for acute large vessel occlusion diagnosis and transportation to an EVT centre, as well as widened indications for performing EVT.

In Finland, the five university hospitals have centralised responsibility for EVT procedures in their hospital districts. Helsinki University Hospital has the largest catchment area with 2.2 million residents. Decisions regarding the treatment of extracranial stenosis in acute stroke patients are made by multidisciplinary consensus among stroke neurologist, interventionist, and vascular surgeon. Carotid surgery is performed in Helsinki University Hospital before transfer to a local hospital.

### Endovascular thrombectomy protocol

Eligibility criteria for EVT have changed during the study period after publication of important RCTs.<sup>1–3</sup> EVT is performed in patients with acute ischaemic stroke and occlusion of the intracranial segment of the ICA, the first, or proximal second segment, of the middle cerebral artery

(MCA). Intravenous thrombolysis is administered if not contraindicated. The EVT procedure is performed under conscious sedation, a stent retriever is most commonly used, with aspiration if needed. Completion angiography is performed to define TICI grade.

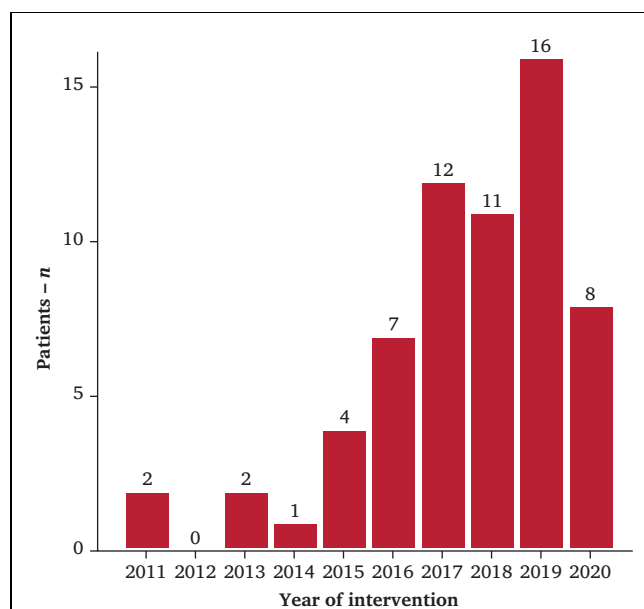
### Statistical analyses

Descriptive statistics were presented using mean and standard deviation (SD), median and interquartile range (IQR), counts, and percentages with 95% confidence intervals (CI) according to variable type. Group differences in categorical variables were examined with Fisher's exact test or chi square test as appropriate. For continuous normally distributed data the *t* test was used, and when data were skewed, the Mann–Whitney *U* test was used. All tests were two sided, and statistical significance was defined as  $p < .050$ . The cumulative incidence of all cause mortality was described using Kaplan–Meier curves, the survival distribution of the two groups was tested with the log rank test. The Cox regression hazard ratio (HR) with 95% confidence interval (CI) was calculated and adjusted for age. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp, Armonk, NY, USA) and R 3.4.3.

## RESULTS

### Demographic details

Among 3 780 CEAs with the indication of stroke during the study period, 63 patients (1.7%) underwent EVT prior to the endarterectomy: 39 patients in Sweden and 24 in Helsinki. As shown in Fig. 1, the proportion of patients treated with



**Figure 1.** Annual numbers of carotid endarterectomies (CEA) following intracranial endovascular thrombectomy during the study period 1 January 2011 to 30 September 2020 (2020 only nine months) in Sweden and Finland.

**Table 1.** Characteristics of 3 780 patients treated for stroke by carotid endarterectomy (CEA) only or by intracranial endovascular thrombectomy (EVT) and CEA in Sweden and Finland in January 2011 to September 2020

	CEA only (n = 3 717)	EVT + CEA (n = 63)	p value
Age – y	72.6 ± 8.4	67.0 ± 9.6	<.001
Male	2 483/3 693 (67.2)	16/63 (67.4)	.28
Ischaemic heart disease	1 041/3 618 (28.8)	16/63 (25.4)	.67
Pulmonary disease	322/2 647 (11.3)	5/62 (8.1)	.54
Diabetes mellitus	955/3 646 (26.2)	5/63 (7.9)	<.001
Hypertension	2 918/3 638 (80.2)	42/63 (66.7)	.011
Renal insufficiency	130/1 681 (7.7)	3/60 (4.8)	.63
Current smoker	886/3 084 (28.7)	17/51 (33.3)	.53
<i>Qualifying neurological event</i>			<.001
Minor stroke	3 395/3 607 (94.1)	13/62 (21.0)	
Major stroke	212/3 607 (5.9)	49/62 (79.0)	
<i>Ipsilateral stenosis/occlusion</i>			<.001
<50%	202/3 715 (5.4)	5/63 (7.9)	
50 – 69%	998/3 715 (26.9)	13/63 (20.6)	
70 – 99%	2 508/3 715 (67.5)	43/63 (68.3)	
Occlusion	7/3 715 (0.2)	2/63 (3.2)	
<i>Contralateral stenosis/occlusion</i>			.24
<50%	2 779/3 682 (75.5)	43/63 (68.3)	
50 – 69%	396/3 682 (10.8)	9/63 (14.3)	
70 – 99%	364 (9.9)	10/63 (15.9)	
Occlusion	143/3 682 (3.9)	1/63 (1.6)	
Thrombolysis before CEA/EVT	432/3 717 (11.6)	34/63 (54.0)	<.001

Data are presented as n (%) or mean ± standard deviation.

CEA after EVT increased over time from 0.5% of the CEAs in 2011 to 4.3% in 2019.

Table 1 lists the characteristics of the patients in the two groups. The EVT+CEA group was younger (67.0 vs. 72.6 years,  $p < .001$ ) and more often had diabetes (26.2% vs. 7.9%;  $p < .001$ ), than the CEA only group. Major stroke as the QNE was more common in the EVT+CEA group (79% vs. 5.9%,  $p < .001$ ), and thrombolysis prior to intervention was used more frequently in the EVT+CEA group (54% vs. 11.6%,  $p < .001$ ). The EVT+CEA group had more severe stenosis/occlusion on the ipsilateral side ( $p < .001$ ), but not on the contralateral side ( $p = .24$ ). With respect to other risk factors, the groups were similar.

### Intracranial endovascular thrombectomy

The median NIHSS was 12 (IQR 8, 15) prior to this intervention. Median time from onset of neurological symptoms to puncture of the groin was 177 minutes (range 55 – 603 minutes). The occlusive thrombus was in the proximal part of the middle cerebral artery (MCA) in 58% ( $n = 36$ ) of patients, in the intracranial part of ICA in 26% ( $n = 16$ ), and in distal MCA in 16% ( $n = 10$ ).

After EVT, 85% of patients had complete recanalisation of the vessels (see Table 2 for TICl grade). Five patients had a loading dose of clopidogrel; none was stented in the carotid artery or intracranially.

At the time of stroke, 30% of EVT+CEA patients were on antiplatelet therapy, and 32% on statins (see Table 2 for further details).

### Carotid endarterectomy after endovascular thrombectomy

At the time of CEA, most patients had good recovery from their strokes. The median NIHSS had improved from 12 (IQR 8, 15) prior to thrombectomy, to 2 (IQR 1, 4) at the time of CEA ( $p < .001$ ) (Table 2).

The median interval between QNE and CEA was seven days (IQR 4, 15), and 75% underwent CEA within 14 days from QNE (Fig. 2). This did not differ from the CEA only group; median time to surgery was eight days (IQR 5, 13) ( $p = .40$ ) and 79.7% were operated on within 14 days (Table 3).

At the time of CEA, 94% of EVT+CEA patients were on statins and 97% were on antiplatelet or anticoagulant therapy (Table 3).

Shunt and patch use, as well as types of CEA performed, did not differ between treatment groups (Tables 2 and 3).

### Complications and follow up

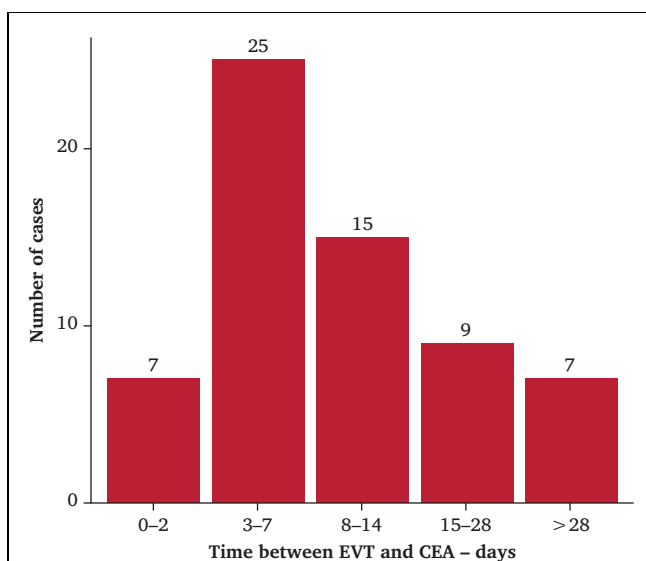
The stroke rate within 30 days in the CEA only group was 3.0% (95% CI 2.5 – 3.6), death 1.0% (95% CI 0.7 – 1.3), and the combined stroke or death rate 3.7% (95% CI 3.2 – 4.4).

In the EVT+CEA group, none of the patients had an ischaemic stroke or intracerebral haemorrhage nor did anyone die within 30 days; combined stroke or death rate

**Table 2.** Specific characteristics of 63 patients treated with intracranial endovascular thrombectomy (EVT) and subsequent carotid endarterectomy (CEA) for stroke

Variable	Patients (n = 63)
Atrial fibrillation	6 (9.5)
NIHSS before EVT	12 (8, 15)
NIHSS at the time of CEA	2 (1, 4)
NIHSS at 30 d after CEA	2 (1, 4)
<i>Sites of thrombotic occlusion</i>	
ICA intracranial	16 (25.8)
Proximal MCA	36 (58.1)
Distal MCA	10 (16.1)
Median time from QNE to puncture of the groin (IQR) (range) – min	177 (131, 267) (55–603)
<i>TICI grade</i>	
0 No perfusion	2 (3.4)
1 Minimal filling	1 (2.7)
2a Partial filling	6 (10.2)
2b Complete filling but slow	20 (33.9)
3 Complete filling	30 (50.8)
<i>Medication at the time of QNE</i>	
Antiplatelets	19 (30.2)
Statins	20 (31.7)
Anticoagulants	4 (6.3)
<i>Medication at the time of CEA</i>	
Antiplatelets	57 (91.9)
Statins	59 (93.7)
Anticoagulants	3 (4.8)
<i>Medication 30 d after CEA</i>	
Antiplatelets	52 (82.5)
Statins	55 (94.8)
Anticoagulants	6 (9.5)

Data are presented as *n* (%) or median (interquartile range, IQR), unless stated otherwise. NIHSS = National Institutes of Health Stroke Scale; ICA = internal carotid artery; MCA = middle cerebral artery; TICI = Thrombolysis In Cerebral Infarction; QNE = qualifying neurological event.

**Figure 2.** Time period between qualifying neurological event and intracranial endovascular thrombectomy (EVT) and carotid endarterectomy (CEA) in 63 patients treated for stroke.**Table 3.** Surgical details of 3 780 patients treated for stroke by carotid endarterectomy (CEA) only or by intracranial endovascular thrombectomy (EVT) and CEA

	CEA only (n = 3 717)	EVT + CEA (n = 63)	<i>p</i> value
Time between QNE and operation – d	8 (5–13)	7 (4–15)	.48
<i>Type of CEA</i>			.11
Eversion	765/3 700 (20.7)	18/61 (29.5)	
Conventional	2 935/3 700 (79.3)	43/61 (70.5)	
Shunt use	1 051/3 706 (28.4)	20/62 (32.3)	.48
Patch use	2 357/3 711 (63.5)	42/62 (67.7)	.60

Data are presented as *n* (%) or median (interquartile range). QNE = qualifying neurological event.

\* Mann–Whitney *U* test.

was therefore 0.0% (95% CI 0.0 – 5.7). One patient had a TIA on the day of CEA. This patient had TICI grade 2b and was operated on Day 3 after thrombectomy. The 30 day EVT outcomes are shown in Table 4. At 30 day follow up, 95% in the EVT+CEA group were on statins, and 92% were treated with antiplatelets or anticoagulation.

The unadjusted survival for the EVT+CEA group at three years was 93% (95% CI 85 – 100), compared with 87% (95% CI 86 – 88) for CEA only. The survival curves were similar up to five years after CEA (log rank test *p* = .82) (Fig. 3). Cox regression analysis adjusted for age (the EVT+CEA group was younger) demonstrated that there was no difference in all cause mortality in the EVT+CEA group (HR 1.3, 95% CI 0.6 – 2.7, *p* = .52).

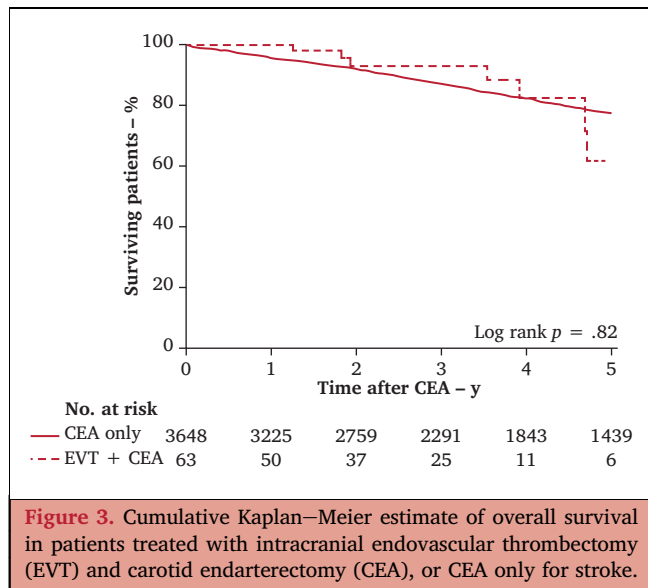
## DISCUSSION

This Scandinavian cohort study, including all patients undergoing CEA for minor or major stroke in Sweden and the Helsinki region, showed that EVT prior to CEA did not carry any increased risk of peri-operative stroke or death. During an almost 10 year period, 1.7% (63/3 780) of patients underwent carotid surgery following EVT. The proportion of

**Table 4.** Thirty day outcomes of 3 780 patients treated for stroke by carotid endarterectomy (CEA) only or by intracranial endovascular thrombectomy (EVT) and CEA

	CEA only (n = 3 717)	EVT + CEA (n = 63)	<i>p</i> value
Stroke or death	3.7 (3.2–4.4)	0.0 (0.0–5.7)	.17
Stroke	3.0 (2.5–3.6)	0.0 (0.0–5.7)	.26
Death	1.0 (0.7–1.3)	0.0 (0.0–5.7)	1.0
Intracerebral haemorrhage	0.6 (0.4–0.9)	0.0 (0.0–5.7)	1.0
TIA	0.6 (0.4–0.9)	1.6 (0.3–8.5)	.31
Re-operation for surgical site bleeding	3.8 (3.3–4.5)	1.6 (0.3–8.5)	.73
AMI	0.6 (0.4–0.9)	0.0 (0.0–5.7)	1.0

Data are presented as % (95% confidence interval). TIA = transient ischaemic attack; AMI = acute myocardial infarction.



patients treated with CEA after EVT increased over time from 0.5% of the CEAs in 2011 to 4.3% in 2019. Post-operative complications consisted of one neurological event (TIA) and no stroke or death and no intracerebral haemorrhage were seen within 30 days. Patients had severe neurological symptoms with a median NIHSS of 12 at the time of EVT and about half of the patients were treated with systemic, intravenous, thrombolysis before EVT.

Carotid endarterectomy was performed a median of seven days after QNE (and EVT), and 75% had a CEA within the recommended 14 days. In comparison, the CEA only group was operated on within a median of eight days from QNE, and 79.7% were operated on within 14 days. Carotid surgery has often been delayed after stroke because of a greater risk of post-operative complications.<sup>16</sup> Even though the greatest stroke prevention benefit from CEA is achieved when the CEA is performed within 14 days of the QNE,<sup>17</sup> patients with large cerebral infarcts might have a higher incidence of post-operative complications when CEA is performed early.<sup>18–20</sup> At the same time, however, the risk of recurrent stroke is highest immediately after the QNE, meaning that revascularisation performed earlier gives fewer recurrent ischaemic events, and offers a more effective stroke prevention. The ESVS carotid guidelines recommend that CEA should be performed as soon as possible after a neurological event, but should be deferred in large structural brain infarcts because of the increased risk of intracerebral haemorrhage.<sup>4</sup> In the present study, the majority of the patients undergoing EVT had severe symptoms with a median NIHSS of 12 before EVT but recovered after successful EVT and recanalisation and had mild strokes with a median NIHSS of 2 (IQR 1, 4) at the time of CEA and at 30 day follow up. It is concluded that the EVT was successful, both in terms of symptoms, and in terms of preventing large cerebral infarction, as the proportions of patients deferred were similar in the EVT+CEA and the CEA only groups.

Intravenous thrombolysis is a risk factor for intracerebral haemorrhage and might increase the risk of poor outcome after CEA and CAS.<sup>21,22</sup> A recently published systematic review and meta-analysis of outcome after CEA following thrombolysis, found an increased risk of stroke/death if CEA was performed early after thrombolysis.<sup>9</sup>

In total, 54% of the EVT patients in the present study had intravenous thrombolysis before thrombectomy, but the rate of thrombolysis decreased during the study period; from 61% in 2011–2017, to 49% in 2018–2020, as a consequence of changed indications for EVT.

No randomised clinical trial (RCT) exists on how to treat concomitant lesions in the extracranial part of the ICA, which are identified during EVT. As endovascular access is already in place, it is tempting to treat a possible tight ICA stenosis with CAS, but there may be long term advantages with CEA. CAS requires dual antiplatelet therapy (DAPT), which may increase the risk of intracerebral and gastrointestinal haemorrhage. The ESVS Carotid Guidelines<sup>4</sup> advise against using DAPT long term after CEA, and the European Society of Cardiology (ESC) and ESVS joint Guidelines<sup>23</sup> recommend DAPT after CAS, but not after CEA. Furthermore, the risk of re-stenosis is greater after CAS than after CEA, and although such a re-stenosis is associated with a stroke risk of only 3.7%, more intense surveillance may be necessary.<sup>24</sup> Even though there was a relatively long delay between EVT and CEA, the present results support that CEA can be performed within normal time frames. A larger study is needed to analyse the optimal timing of CEA. To reduce the delay between EVT and CEA, the CEA should probably be performed in the same centre as the EVT. Referring the patients back to the centres that referred the patients for EVT is probably not the best solution.

In a systematic review and meta-analysis of 16 cohort studies of tandem lesion patients treated with EVT and CAS or PTA for concomitant extracranial carotid lesions, the incidence of severe intracranial haemorrhage was 8%.<sup>25</sup> Immediate CAS may not be technically feasible in all patients and CEA may offer an advantage compared with CAS in patients with increased risk of bleeding from DAPT, such as those with a history of gastrointestinal bleeding. In a small series, Singh *et al.* found that emergency CEA had less intracranial haemorrhage than emergency CAS.<sup>26</sup> In a small study from Slawski *et al.* on patients with tandem occlusions of the intra- and extracranial ICA, three patients in the EVT+CAS group and none of the patients in the EVT+CEA group had symptomatic intracerebral haemorrhage.<sup>27</sup> In the TITAN registry, 24 of 170 of patients (16%) with severe ICA stenosis had an intracerebral haemorrhage after a combination of EVT and emergency CAS.<sup>28</sup> No patient in this study had a post-operative intracerebral haemorrhage.

Overall, the complication rate within 30 days was extremely low in the present study, with no post-operative stroke, death, or intracerebral haemorrhage in the EVT + CEA group, compared with a stroke or death rate of 3.7%, and 0.6% intracerebral haemorrhage in the CEA only group. The probability of survival was similar in both groups, with more than 85% survival at three years. Also, after adjusting

for age differences between the groups, the mortality rates were similar. These results were achieved despite the EVT+CEA group having more severe stenosis on the ipsilateral side and much more often having major stroke as the QNE. The reasons for this promising result can only be speculated. One possible explanation is that after EVT the patients are carefully monitored and treated in the stroke unit for neurological symptoms, until stable for CEA. Also, the majority of the patients were operated on in high volume centres, and nearly all patients had a patent MCA on angiogram. These factors may decrease the overall rate of peri-operative complications.

The strength of this study was its relatively large size and high quality multicentre data. Including patients treated with EVT+CAS was considered, which would have added important information, but the decision was taken not to include such patients for two reasons. First, CAS is performed as an emergency during EVT, whereas CEA is performed subacutely days later. Comparing results of such interventions would not have been appropriate. Secondly, such a study would have required many more collaborators, and would have been far more complicated to perform. Denmark and Norway were also invited to participate in this Scandinavian study but unfortunately did not have enough robust data for this analysis. Even though the number of EVTs is increasing over time, the total number remains quite small and thus a type 2 statistical error cannot be ruled out. It was believed important to get an idea of the magnitude of complications in the studied EVT+CEA group, and therefore the study included the control group, CEA only in full awareness of the risk of selection bias. There are also inherent limitations to large registry data, although in this study they were supplemented with complete case records. Furthermore, information about medication in the control group was lacking. However, the external and internal validities of the used registries have been shown to be excellent in multiple validations.<sup>13,29,30</sup>

Another limitation is that patients with high grade ICA stenosis may have occluded while waiting for CEA and thus may not have been included in the present study, reporting only on patients treated with CEA for their extracranial lesions. Furthermore, all EVT+CEA patients had mild strokes with a median NIHSS 2 (IQR 1, 4) at the time of CEA, and thus results are not generalisable to all patients with more severe strokes and larger cerebral infarcts, as patients with severe remaining disability after EVT will not be treated with CEA.

More data are needed on patient selection, timing, and optimised adjuvant medical therapy, which should be the focus of future studies. Ideally, a RCT comparing CEA and emergency CAS in patients with concomitant lesions in the extracranial part of the ICA after EVT should be performed. If that is not feasible, a larger observational study, with one to three year of follow up, that enables propensity score matching is another alternative.<sup>31</sup>

In conclusion, this population based cohort study indicates that CEA appears to be safe to perform after previous EVT and could be recommended in patients with concomitant significant ipsilateral carotid stenosis. The

operation should not be deferred and can be performed within a recommended time frame, depending on the volume of the cerebral infarction, without increased risk of stroke or death.

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## CONFLICT OF INTEREST

None.

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