Eur J Vasc Endovasc Surg (2017) 54, 278—286

Editor's Choice — Very Urgent Carotid Endarterectomy is Associated with an Increased Procedural Risk: The Carotid Alarm Study

A. Nordanstig [a,b,*], L. Rosengren [a,b], S. Strömberg [c], K. Österberg [c], L. Karlsson [d], G. Bergström [d], Z. Fekete [e], K. Jood [a,b]

[a] Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[b] Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden
[c] Institute of Clinical Science, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[d] The Sahlgrenska Centre for Cardiovascular and Metabolic Research, Wallenberg Laboratory, Institute of Medicine, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[e] Department of Neurology and Rehabilitation, Södra Älvsborg Hospital, Borås, Sweden

WHAT THIS PAPER ADDS

There are diverse results in the literature regarding peri-operative risk in very urgent carotid endarterectomy (CEA). This prospective study adds further evidence in favour of a more careful approach with expedited CEA, in the first 2 days after an ischaemic event.

Objective/Background: The aim of the Carotid Alarm Study was to compare the procedural risk of carotid endarterectomy (CEA) performed within 48 hours with that after 48 hours to 14 days following an ipsilateral cerebrovascular ischaemic event.

Methods: Consecutive patients with symptomatic carotid stenosis undergoing CEA were prospectively recruited. Time to surgery was calculated as time from the most recent ischaemic event preceding surgery. A neurologist examined patients before and, after CEA. The primary endpoint was the composite endpoint of death and/or any stroke within 30 days of the surgical procedure. The study was designed to include 600 patients, with 150 operated on within 48 hours.

Results: From October 2010 to December 2015, 418 patients were included, of whom 75 were operated within 48 hours of an ischaemic event. The study was prematurely terminated owing to the slow recruitment rate in the group operated on within 48 hours. Patients undergoing CEA within 48 hours had a higher risk of reaching the primary endpoint than those operated on later (8.0% vs. 2.9%). Multivariate logistic regression analyses showed that CEA performed within 48 h (odds ratio [OR] 3.07; 95% confidence interval [CI] 1.04—9.09), CEA performed out of office hours (OR 3.65; 95% CI 1.14—11.67), and use of shunt (OR 4.02; 95% CI 1.36—11.93) were all independently associated with an increased risk of reaching the primary endpoint.

Conclusion: CEA performed within 48 hours was associated with a higher risk of complications compared with surgery performed 48 hours—14 days after the most recent ischaemic event.

Article history: Received 30 January 2017, Accepted 23 June 2017, Available online 26 July 2017

Keywords: Carotid endarterectomy, Internal carotid artery, Peri-operative outcome, Stroke, Symptomatic carotid stenosis

INTRODUCTION

Carotid endarterectomy (CEA), in combination with best medical therapy, is the recommended treatment for stroke prevention in patients with symptomatic stenosis of the internal carotid artery. A numbers of studies have reported a remarkably high risk of early stroke recurrence in patients with a transient ischaemic attack (TIA) or minor stroke due to a > 50% carotid stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria).[1—3] In a recent review, the stroke risk was estimated to be 6.4% within the first 2—3 days, 19.5% at 7 days, and 26.1% at 14 days.[4] In 2004, a meta-analysis of two large interventional studies of symptomatic carotid stenosis showed that surgery is more favourable when done within the first 2 weeks of the ischaemic event versus later surgical intervention.[5] However, these studies were not powered to determine whether surgery performed in the very early phase (i.e., within 48 hours following symptom onset) was even more beneficial. Given the early risk of a recurrent disabling event, there is reason to believe that CEA performed in the

* Corresponding author. Department of Neurology, Gröna stråket 5, våning 3, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden.
E-mail address: annika.nordanstig@vgregion.se (A. Nordanstig).

1078-5884/
http://dx.doi.org/10.1016/j.ejvs.2017.06.017

very early period following an ischaemic event could improve the benefit of CEA if the risk of per- and post-operative complications remains similar, or only slightly increased, compared with later surgery.

Several studies, with divergent results, have reported on the stroke and mortality risk associated with CEA in the very early period after carotid related ischaemic symptoms.[6–9] One prospective registry study noted that patients operated on within the first 2 days had increased peri-operative mortality and stroke risk (11.5% within two days versus 3.6% between 3 and 7 days).[6] In contrast, a number of large retrospective studies found no differences in the risk of stroke and mortality depending on whether surgery was done within the first 2 days, or 3–14 days after an ischaemic event.[7–9] A recent systematic review and meta-analysis on early carotid intervention concluded that the current evidence for very early CEA was limited, and that randomised controlled trials or prospective observational studies directly comparing acute CEA with subacute surgery were needed to determine the optimal timing of the intervention.[10]

Accordingly, the aim of this prospective study was to compare the per- and post-operative outcomes of CEA carried out within 48 hours with the outcome 48 hours–14 days after an ischaemic event. It was hypothesized that very early CEA would not increase, or only slightly increase, the risk of per- or post-operative complications versus CEA performed during the later period.

METHODS

General study design

The Carotid Alarm Study, carried out in the Region Västra Götaland in Sweden, was a prospective study of consecutive patients with symptomatic carotid stenosis undergoing carotid surgery within 14 days of an ipsilateral ischaemic cerebrovascular event. Per- and post-operative complications were compared in patients operated on within 48 hours with those operated on between 48 hours and 14 days.

Patient selection

The two centres that perform CEA in the Region Västra Götaland in the south-west of Sweden are the Sahlgrenska University Hospital and the Södra Älvsborg Hospital. The aim was to recruit all patients undergoing CEA within 14 days of an ischaemic event within the Region. Recruitment started at the Sahlgrenska University Hospital in October 2010 and at Södra Älvsborg Hospital in June 2012. Recruitment continued until December 2015 at both centres.

Patients with retinal ischaemia (amaurosis fugax/retinal stroke), minor ischaemic stroke, TIA, and/or crescendo TIA (at least two episodes within 24 hours or at least three episodes within 7 days) with symptoms compatible with a thromboembolic event in the anterior circulation, an ipsilateral carotid stenosis of 50–99% (NASCET criteria), and carotid surgery within 14 days of an ischaemic event were eligible for the study. Patients with clinical findings indicating major stroke (National Institutes of Health Stroke Scale $>$ 5, or infarct size exceeding $>$ 3 cm in diameter on diffusion weighted magnetic resonance imaging [DW-MRI]) were excluded, as were patients with stroke in evolution, severe life limiting disease, and patients treated with intravenous thrombolysis due to the ischaemic event.

In hospital organisation

There are nine stroke units in this region and doctors from regional hospitals refer patients to the Carotid Alarm Study units at Sahlgrenska University Hospital or Södra Älvsborg Hospital by telephone or fax. A *fast track* for patients with recent symptoms of cerebrovascular ischaemia was introduced. The purpose of this fast track was to enable CEA within 48 hours for all patients seeking care within 24 hours of an ischaemic event, thus reducing selection bias in the group with very urgent CEA. Patients newly arrived at the hospitals' stroke units were screened twice daily. Eligible patients were investigated with a carotid Doppler ultrasound within 2 hours (daytime, 7 days a week). If a carotid stenosis ($>$ 50%) ipsilateral to the ischaemic event was found, the investigation was supplemented with acute neuro-imaging, which was deemed necessary in order to facilitate a fast treatment decision. Patients seeking medical care later than 24 hours following an ischaemic event were not processed according to the fast track. Doppler ultrasound, imaging, clinical assessment, and, when applicable, carotid surgery were performed as fast as possible, within 14 days.

Definition of qualifying event, time to surgery, referring event, and out of office hours

A qualifying event was defined as the most recent ischaemic event preceding CEA. The time to surgery was the time between the qualifying event and CEA. For multiple events, time to surgery was calculated using the most recent event preceding CEA, also when the event occurred after admission to hospital. In patients with a wake-up stroke, the time when the patient was last known to be free of symptoms was used. The referring event was the ischaemic event that brought the patient to medical care. Out of office hours were defined as hours when the vascular surgeon was on call (i.e., Monday–Thursday 4.00 pm–7.30 am, Friday 2.00 pm–7.30 am, weekends, and public holidays).

Diagnostic work-up and data collection

A neurologist examined the patients before, and 2 and 30 days after CEA. Data were prospectively documented in electronic case record forms and compiled in a predefined database. Duplex ultrasound scanning was used to assess the degree of carotid artery stenosis. Brain computed tomography was performed in all patients with cerebral hemisphere TIA or stroke (i.e., all patients except those with retinal stroke or amaurosis fugax) in order to rule out haemorrhage and other differential diagnoses. In addition, patients with stroke underwent DW-MRI to rule out large infarcts not suitable for early carotid surgery (Fig. 1).

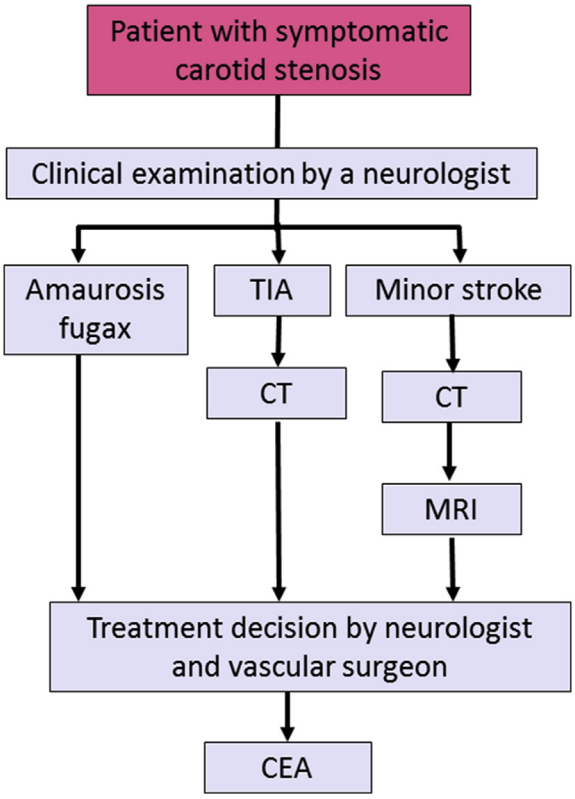

Figure 1. Pre-operative diagnostic work-up. *Note*. TIA = transient ischaemic attack; CT = computed tomography; MRI = magnetic resonance imaging; CEA = carotid endarterectomy.

Procedure

CEA was done according to routine clinical practice at each hospital, either as conventional endarterectomy with or without patch angioplasty, or (rarely) as an eversion endarterectomy, depending on the anatomical situation (Table 1). All procedures at Sahlgrenska University Hospital were carried out under general anaesthesia. Shunt insertion was used selectively, depending on arterial stump pressure level and/or regional oxygen saturation (assessed by near infrared spectroscopy). At Södra Älvsborg Hospital, CEA was routinely performed under local anaesthesia and shunt insertion was carried out selectively, depending on the neurological course during carotid cross-clamping. During the study period 23 vascular surgeons performed CEAs. The operating teams and operation room settings were the same during out of office hours and office hours. No surgery was performed after 10.00 pm.

Primary and secondary endpoints

The primary endpoint was the composite of death and/or any stroke within 30 days of the surgical procedure. Secondary outcomes were any stroke, ipsilateral stroke, and ischaemic ipsilateral stroke within 30 days of the surgical procedure.

Statistical analysis

During study planning, the number of patients eligible for CEA within 48 hours of an ischaemic event was estimated. The years before the study started, about 145 patients annually underwent CEA in the region (about 120 at the Sahlgrenska University Hospital and about 25 at Södra Älvsborg Hospital). Analysis of the referral pattern showed that the majority of patients were seeking medical care the same day as the symptoms arose. It was estimated that one quarter of patients, i.e., about 35 patients annually, would undergo CEA within 48 hours of the ischaemic event. With a power of 80%, a 6% increase of complications measured as primary outcome could be detected with a total of 600 patients, and 150 patients undergoing CEA within 48 hours ($p < .05$), rendering a study duration of 4—5 years.

Descriptive statistics are presented as frequencies or mean values and SDs. Differences in proportions were tested by Fisher's exact test. Odds ratios (OR) and 95% confidence intervals (CI) for the primary and secondary endpoints were calculated using logistic regression analysis. For the primary endpoint, variables with a p value $< .1$ in the univariate analyses were included in a multivariate model. Findings were considered significant at $p < .05$ (two-tailed test). SPSS for Windows (SPSS, Armonk, NY, USA) version 23.0 was used for the statistical analyses.

Ethics

Written informed consent was obtained from all participants. The Regional Ethical Review Board at the University of Gothenburg approved the study (no. 567-09).

RESULTS

Inclusion and baseline data

From October 2010 to December 2015, 418 patients were included, of whom 75 were operated on within 48 hours. The number of patients with the CEA within 48 hours was substantially lower than expected, and also decreased during the course of the study, with only three patients operated on within 48 hours during the last 6 months of the study. Given the slow and declining inclusion rates in the urgent CEA group, it was found to be unrealistic to include 150 patients with urgent CEA in the foreseeable future. The study was therefore prematurely terminated on 31 December 2015. In total, as many as 72% of the patients included in the study were admitted to the hospital within 24 hours of an ischaemic event. However, only 11% underwent CEA within 48 hours of the event that brought the patient to hospital (referring event). The main reason for postponed surgery was organisational/logistical.

Overall, 646 patients underwent CEA during the study period. When the predefined inclusion and exclusion criteria were applied, 466 patients were identified as eligible and 418 (90%) gave their informed consent to participate in the study. The majority of the patients were operated on at the Sahlgrenska University Hospital (see Fig. 2). Only two patients receiving CEA within 48 hours were excluded. Among the non-participants the 30 day stroke and mortality rate was 2.3%.

Table 1. Baseline demographics, risk factors, and technical data of the study population.

Delay to CEA from onset of most recent ischaemic event	< 48 h (n = 75)	48 h–14 d (n = 343)
Mean ± SD age (y)	73.05 ± 8.52	73.70 ± 8.51
Female	20 (27)	106 (31)
Functional outcome before surgery (mRS ≤ 2)	70 (93)	324 (94)
Degree of stenosis (NASCET)		
50–69%	16 (21)	101 (29)
70–99%	59 (79)	242 (71)
Degree of contralateral stenosis (NASCET)		
< 50%	66 (88)	251 (73)
50–69%	4 (5)	33 (10)
70–99%	5 (7)	42 (12)
Occlusion	0 (0)	17 (5)
Qualifying event		
Amaurosis fugax/retinal stroke	18 (24)	82 (24)
TIA	28 (37)	106 (31)
Crescendo TIA	14 (19)	17 (5)
Minor stroke	15 (20)	137 (40)
Major stroke	0 (0)	1 (0)
New ischaemic event after the event that brought the patient to hospital	37 (49)	37 (11)
New stroke after the event that brought the patient to hospital	7 (9)	6 (2)
Risk factors		
Diabetes mellitus	15 (20)	76 (22)
Hypertension	58 (77)	264 (77)
Current smoking	16 (21)	80 (23)
Coronary artery disease, heart failure	27 (36)	117 (34)
Pulmonary disease	5 (7)	31 (9)
Procedure		
Without patch	46 (61)	191 (56)
Eversion endarterectomy	3 (4)	16 (5)
Shunt	8 (11)	56 (16)
Doppler before surgery	72 (96)	334 (97)
Cerebral imaging before surgery		
CT	66 (88)	315 (92)
CTA	14 (19)	96 (28)
MRI	40 (53)	192 (56)
MRA	30 (40)	148 (43)
Surgery out of office hours	37 (49)	152 (44)
Mean ± SD days between the qualifying event and CEA	1.3 (0.69)	6.7 (2.9)

Note. Data are *n* (%) unless otherwise specified. CEA = carotid endarterectomy; mRS = modified Rankin Scale; NASCET = North American Symptomatic Carotid Endarterectomy Trial; TIA = transient ischaemic attack; CT = computed tomography; CTA = computed tomography angiography; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography.

Table 1 summarizes demographic risk factors, surgical characteristics, and qualifying events in the two groups (CEA < 48 hours vs. 48 hours–14 days). Pre- and post-operative pharmacotherapy is shown in Table S1 (see Supplementary Material). All patients received antithrombotic treatment before CEA. The proportion of patients with pre-operative statin therapy was somewhat lower in the group with CEA < 48 hours than in those with CEA within 48 hours–14 days.

Primary and secondary endpoints

The overall 30 day rate for mortality and any stroke was 3.8%. The primary outcome was similar at both recruiting centres (3.6% at Sahlgrenska University Hospital vs. 5.4% at Södra Älvsborg Hospital). The characteristics of the 16 patients who suffered a complication are shown in Table 2. All events in the group undergoing CEA within 48 hours were ipsilateral ischaemic strokes. In the group undergoing CEA 48 hours–14 days the complications were more diverse. As shown in Table 3, patients undergoing CEA within 48 hours had a significantly higher risk of the combined endpoint of mortality and/or any stroke compared with the group treated 48 hours–14 days after the qualifying event; 8.0% versus 2.9% (OR 2.90, 95%CI 1.02–8.23; p = .049). The risk of any stroke, ipsilateral strokes, and ipsilateral ischaemic strokes were also increased in patients who underwent CEA within 48 hours (Table 3).

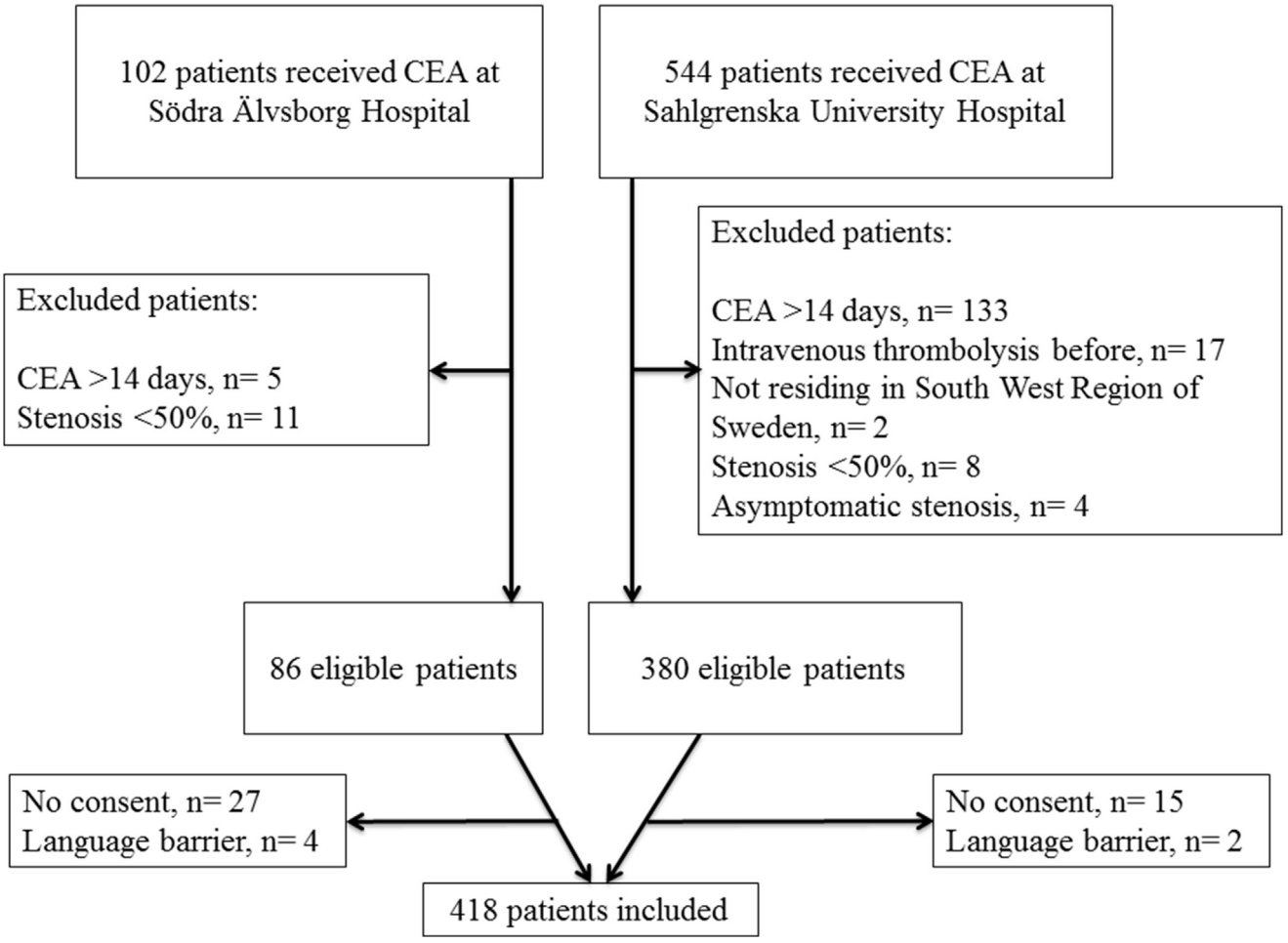

Figure 2. A flow diagram of all patients treated by carotid endarterectomy (CEA) at the two participating centres.

Results from logistic regression analyses are given in Table 4. CEA performed within 48 hours, CEA performed out of office hours, and use of shunt were all independently and significantly associated with an increased risk of the primary endpoint (OR 3.07 [95% CI 1.04—9.09], OR 3.65 [95% CI 1.14—11.67], and OR 4.02 [95% CI 1.36—11.93], respectively).

Post-hoc analysis

The frequency of stroke and/or death is presented separately for patients with stroke, TIA, crescendo TIA, and retinal ischaemia as the qualifying event in Table 5. For all types of qualifying events, the proportion of stroke and/or death within 30 days was higher in those operated on within 48 hours.

Of the 75 patients operated on within 48 hours of the qualifying event, 46 patients were operated on within 48 hours from the referring event. The combined mortality and stroke rate for patients in this latter group was 10.9% (5/46) versus 3.0% (11/372) for the group treated 48 hours to 14 days after the referring event (OR 4.00, 95% CI 1.33—12.09). In contrast, only one out of the 29 patients (3.4%) operated on within 48 hours of the most recent ischaemic event, but more than 48 hours from the referring event, had a primary endpoint.

Two hundred and twenty nine (55%) procedures were carried out during office hours. For patients who underwent CEA within 48 hours of the qualifying event, the combined mortality and stroke rate for surgery done during office hours was 0% (0/38) versus 16.2% (6/37) for the patients treated during out of office hours ($p = .012$). However, there was no significant increased risk of stroke and/or death in patients operated on out of office hours in the group operated on 48 hours—14 days after the qualifying event (office hours 4/191 [2.1%] vs. out of office hours 6/152 [3.9%]; $p = .348$).

Six patients suffered from a myocardial infarction. Two of these had been operated on within 48 h.

DISCUSSION

Refuting the hypothesis, this prospective controlled study showed that CEA performed within 48 hours of an ischaemic event was associated with a threefold increased risk of stroke and/or mortality within 30 days of surgery versus CEA performed 48 hours—14 days following an ischaemic event. This risk remained after adjustment in a multivariate regression model.

This finding corresponds well with the results reported from the Swedish Quality Registry for Vascular Surgery

Table 2. Detailed analysis of primary and secondary endpoints.

Qualifying event[a]	Pre-operative mRS	Pre-operative NIHSS	Time to surgery[b]	Endpoint, timing	Type of endpoint	Probable aetiology to stroke	Patency of the treated artery after primary endpoint	Outcome at 30 d mRS	Outcome at 30 d NIHSS
Stroke	1	0	9 d	Day 3	Ipsilateral haemorrhagic stroke and death	No hyperperfusion[e]	Not investigated	6	
Amaurosis fugax	1	0	2 d	Day 0–2[c]	Ipsilateral ischaemic stroke	Undetermined	Not investigated	2	1
TIA	0	0	4 d	Day 0[d]	Ipsilateral ischaemic stroke	Thrombosis or occlusion of the carotid artery[f]	CTA showed thrombosis in ICA	1	0
Stroke	1	0	3 d	Day 0[d]	Ipsilateral ischaemic stroke	Thrombosis or occlusion of the carotid artery[f]	CTA showed thrombosis in ICA	3	3
Stroke	1	0	3 d	Day 0–2[c]	Ipsilateral ischaemic stroke	Undetermined	Not investigated	0	0
TIA	1	0	5 d	Day 1	Contralateral ischaemic stroke	Symptomatic carotid stenosis on contralateral side	Not investigated	0	0
Stroke	2	1	6 d	Day 28	Contralateral ischaemic stroke	Small artery occlusion	Not investigated	1	1
TIA	0	0	9 d	Day 2	Ipsilateral haemorrhagic stroke	No hyperperfusion[e]	Not investigated	5	18
Stroke	1	0	6 d	Day 28	Death (in sepsis)	—	Not investigated	6	
Retinal stroke	1	0	6 d	Day 0[d]	Ipsilateral ischaemic stroke	Thrombosis or occlusion of the carotid artery[f]	ICA thrombosis at re-operation, CTA not performed	0	2
TIA	0	0	< 48 h	Intra-operative	Ipsilateral ischaemic stroke	Undetermined	Not investigated	1	0
Stroke	3	5	< 48 h	Intra-operative	Ipsilateral ischaemic stroke	Thrombosis or occlusion of the carotid artery[f]	CTA confirmed occluded ICA	3	5
Amaurosis fugax	0	0	< 48 h	Day 1	Ipsilateral ischaemic stroke	Thrombosis or occlusion of the carotid artery[f]	Re-operation showed suture-rupture, thrombosis of ICA, and massive bleeding	5	16
Crescendo TIA	2	0	< 48 h	Day 0–2[c]	Ipsilateral ischaemic stroke	Undetermined	Not investigated	2	1
TIA	0	0	< 48 h	Intra-operative	Ipsilateral ischaemic stroke	Thrombosis or occlusion of the carotid artery[f]	CTA confirmed occluded ICA	4	7
Stroke	1	0	< 48 h	Intra-operative	Ipsilateral ischaemic stroke	Undetermined	CTA showed normal anatomy in extra- and intracranial arteries	4	8

Note. mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischaemic attack; CTA = computed tomography angiography; ICA = internal carotid artery.

[a] Most recent ischaemic event preceding surgery.

[b] Time to surgery was calculated as time from the most recent ischaemic event preceding surgery.

[c] Observed by neurologist at day 2.

[d] Symptom onset a few hours post-operatively.

[e] No evidence for hyperperfusion syndrome (no hypertension and no headache).

[f] Stroke mechanism was considered to be "thrombosis or occlusion of the carotid artery" when the carotid artery was non-patent (defined as a ≥ 50% residual stenosis or occlusion of the carotid) on imaging after procedural stroke or at re-exploration, irrespective of whether there was evidence for embolic or haemodynamic mechanism.

Table 3. Primary and secondary outcomes.

Primary and secondary outcomes	< 48 h (*n* = 75)	48 h–14 d (*n* = 343)	*p*[a]	OR (95% CI) very urgent CEA[b]
Stroke and/or death	6 (8)	10 (3)	.049	2.90 (1.02–8.23)
Stroke	6 (8)	9 (3)	.035	3.23 (1.11–9.36)
Ipsilateral stroke	6 (8)	7 (2)	.016	4.17 (1.36–12.80)
Ipsilateral ischaemic stroke	6 (8)	5 (2)	.006	5.88 (1.75–19.81)

Data are *n* (%). OR = odds ratio; CI = confidence interval; CEA = carotid endarterectomy.
[a] Statistical analysis by Fisher's exact test.
[b] Bivariate OR and 95% CIs were calculated using logistic regression analysis.

Table 4. Univariate and multivariate logistic regression analysis.

Factor	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.01 (1.00–1.1)	.661	–	–
Female sex	1.06 (0.36–3.10)	.922	–	–
Hypertension	0.77 (0.21–2.75)	.683	–	–
Cardiac disease	0.43 (0.12–1.52)	.190	–	–
Diabetes	2.24 (0.79–6.33)	.129	–	–
Current smoking	0.77 (0.21–2.75)	.683	–	–
Contralateral occlusion	1.61 (0.20–12.94)	.655	–	–
Pre-operative statin use	0.45 (0.12–1.61)	.215	–	–
CEA < 48 h from most recent event	2.90 (1.02–8.23)	.046	3.07 (1.04–9.09)	.042
CEA out of office hours	3.81 (1.21–12.03)	.022	3.65 (1.14–11.67)	.029
Shunt	3.58 (1.25–10.23)	.017	4.02 (1.36–11.93)	.012

Note. Variables included in the multivariate models were selected by univariate analysis at $p < .10$. OR = odds ratio; CI = confidence interval; CEA = carotid endarterectomy.

Table 5. Outcome in relation to type of qualifying event.

Qualifying event[a]	Stroke and/or death/total numbers in the group (%)		
	Total	CEA < 48 h	CEA 48 h–2 wk
Amaurosis fugax/retinal stroke	3/100 (3)	1/18 (6)	2/82 (2)
TIA	5/134 (4)	2/28 (7)	3/106 (3)
Crescendo TIA	1/31 (3)	1/14 (7)	0/17 (0)
Stroke	7/153 (5)	2/15 (13)	5/138 (4)
Total	16/418 (4)	6/75 (8)	10/343 (3)

Note. Data are *n* (%). CEA = carotid endarterectomy; TIA = transient ischaemic attack.
[a] Most recent ischaemic event preceding surgery.

(Swedvasc),[6] which showed an increased risk of complications for CEA performed within the first 2 days of an ischaemic event. Although both studies were performed in Sweden, the overlap of patients in the two studies was small (95 patients) as they were mainly accomplished during different time periods. Interestingly, both these studies are prospective, whereas studies showing low risk of complications are all retrospective,[7–9] possibly indicating that the risk of complications may be underestimated in retrospective studies.

In the Carotid Alarm Study, a fast track system was used for patients seeking treatment within 24 hours of an ischaemic event. Besides speeding up the process, the purpose of the fast track was to reduce the risk of aggregation of patients with unstable symptoms in the group undergoing surgery within 48 hours, which is a potential source of bias in registry studies. However, the use of a fast track in a prospective study may facilitate urgent surgery in stable patients, whereas unstable patients at a higher risk of complications may be delayed owing to additional time consuming evaluations. Therefore, it is believed that a possible selection bias in this study would, if anything, rather lead to an underestimation of the risk of complications associated with urgent surgery.

When comparing results from different studies, it is important to be aware of the precise definition of the qualifying event.[11] In the Swedvasc study the qualifying event was defined as the referring event.[6] In the present study the qualifying event was defined as the most recent event before surgery, as it was hypothesized that the most recent event more accurately reflects the biological risk of complications. However, the post-hoc analysis may indicate that patients with CEA within 48 hours of the most recent event, but later than 48 hours from the referring event may have a lower risk of complications (1/29; 4.4%) when compared with patients who underwent CEA within

48 hours of a referring event (5/46; 10.9%). Hypothetically, the patients with new symptoms after seeking medical care may have had properly instituted medical therapy for a longer time period, which may stabilise the atherosclerotic plaque and hence decrease the risk of complications. Thus, the differences in definitions of qualifying event may partly explain why the risk of stroke and/or mortality associated with very early CEA was even higher (almost fourfold) in the Swedvasc study compared with the present study. Moreover, when comparing different studies with regard to the proportion of patients undergoing very urgent CEA, it is also important to consider the definition of qualifying event. For example, Rantner *et al.* reported that 27% underwent CEA within 48 hours of the onset of the most recent ischaemic event, but it is unclear how many who underwent CEA within 48 hours of the event that brought the patient to medical attendance (referral event).[8] By contrast, only 5.7% of Swedvasc patients underwent CEA in the first 2 days of the referral event, and the proportion of patients that underwent surgery within 48 hours of the most recent event was not reported.[6] In 2015, a meta-analysis of case series and registries concluded that very early CEA within the first 2 days of TIA is relatively safe, with a peri-procedural stroke/death risk of 2.8%, whereas early CEA after stroke may be associated with a higher peri-procedural stroke/death risk (8.4%).[10] Thus, divergent findings between studies with respect to peri-procedural risk could also be influenced by the type of qualifying event. Owing to the relatively small sample size of the present study, differences between TIA, stroke, and retinal ischaemia could not be analysed. However, the observed rates of stroke and/or death within 30 days were higher in those operated on within 48 hours for all types of qualifying events.

Multivariate logistic regression analysis also showed an increased risk of complications in those who had surgery out of office hours. This risk seemed to be confined to patients who underwent CEA within 48 hours. As the aim of the study was not to study the risk of CEA during office hours versus out of office hours, this result should be interpreted with some caution and the finding needs confirmation in further studies.

The strengths of the present study include the prospective design, the fast track for all patients seeking care within 24 hours, that all patients were systematically followed up by a neurologist, and that data were prospectively documented in a predefined protocol. However, the study is limited by its relatively small size, making the CIs large. The rather low proportion of CEA performed within 48 hours may have influenced the overall study results. However, as the main observed reason for postponed surgery was not medical, but rather organisational/logistical, there is reason to believe that an increased proportion of CEA performed very early would impose only minor changes with regard to the main study endpoints. Compared with other studies,[12] thrombosis was a more frequent cause of procedural ipsilateral ischaemic stroke. Given the relatively low proportion of patients with dual antiplatelet treatment in the present study, it may be speculated that some of the ipsilateral strokes could have been avoided with a more aggressive pre-operative medical therapy.[13]

The finding that CEA carried out within 48 hours confers an increased 30 day risk of stroke and/or mortality emphasizes the need for a randomised trial, to determine whether the increased risk of recurrent events will outweigh the increased risk of complications observed during very early surgical intervention. If the same risk of complication as in the Carotid Alarm Study is assumed, a randomised study will have to incorporate $>$ 700 patients in each arm to reach a power of 80% (Appendix S1; see Supplementary Material). There are reasons to believe that even if a large, multinational, multicentre randomised trial managed to include a sufficient number of patients in total, the study would still face a substantial risk of excessive crossovers from very early to later surgical intervention. Therefore, a RCT may not be feasible. With a lack of RCTs, prospective data on large contemporary cohorts of patients undergoing standardised intervention may be the best alternative. To include a sufficient number of patients in such a study, a multicentre design is needed. However, to optimise the timing of CEA, it is important to study not only the peri-operative risk, but also the risk for patients with very urgent medical treatment alone in the very early phase after the referring event, as recent data suggest that the early risk of recurrent stroke may not be as high as some earlier studies have shown.[14,15]

CONCLUSION

This prospective controlled study showed that CEA performed within 48 hours of an ischaemic event was associated with a higher risk of complications than surgery performed 48 hours—14 days after the event. This result further emphasizes the need for a randomised trial to determine whether the increased risk of recurrent events will outweigh the increased risk of complications. However, such a study would require a large sample, which may be very difficult to recruit to, and therefore may not be feasible. With a lack of randomised trials, prospective data on large contemporary multicentre cohorts of patients undergoing standardised intervention may be the best alternative.

ACKNOWLEDGEMENTS

We thank the research nurses, Monica Argus (Sahlgrenska University Hospital) and Sara Ahlvin (Södra Älvsborg Hospital).

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2017.06.017.

CONFLICT OF INTEREST

None.

FUNDING

This study was supported by grants from the Sahlgrenska University Hospital (HTA-centre and ALFGBG-446721), Region Västra Götaland, and the Swedish Stroke Association.

REFERENCES

1 Bonifati DM, Lorenzi A, Ermani M, Refatti F, Gremes E, Boninsegna C, et al. Carotid stenosis as predictor of stroke after transient ischemic attacks. *J Neurol Sci* 2011;**303**:85—9.
2 Ois A, Cuadrado-Godia E, Rodriguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. *Stroke* 2009;**40**:2727—31.
3 Johansson EP, Arnerlöv C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. *Int J Stroke* 2013;**8**:220—7.
4 Tsantalis P, Kuhnl A, Kallmayer M, Knappich C, Schmid S, Kuetchou A, et al. Stroke risk in the early period after carotid related symptoms: a systematic review. *J Cardiovasc Surg* 2015;**56**:845—52.
5 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;**363**:915—24.
6 Strömberg S, Gelin J, Osterberg T, Bergstrom G, Karlstrom L, Osterberg K. Very urgent carotid endarterectomy confers increased procedural risk. *Stroke* 2012;**43**:1331—5.
7 Sharpe R, Sayers RD, London NJ, Bown MJ, McCarthy MJ, Nasim A, et al. Procedural risk following carotid endarterectomy in the hyperacute period after onset of symptoms. *Eur J Vasc Endovasc Surg* 2013;**46**:519—24.
8 Rantner B, Schmidauer C, Knoflach M, Fraedrich G. Very urgent carotid endarterectomy does not increase the procedural risk. *Eur J Vasc Endovasc Surg* 2015;**49**:129—36.
9 Tsantilas P, Kuehnl A, König T, Breitkreuz T, Kallmayer M, Knappich C, et al. Short time interval between neurological event and carotid surgery is not associated with an increased procedural risk. *Stroke* 2016;**47**:2783—90.
10 De Rango P, Brown M, Chaturvedi S, Howard V, Jovin T, Mazya M, et al. Summary of evidence on early carotid intervention for recently symptomatic stenosis based on. meta-analysis of current risks. *Stroke* 2015;**46**:3423—36.
11 den Hartog AG, Moll FL, van der Worp HB, Hoff RG, Kappelle LJ, de Borst GJ. Delay to carotid endarterectomy in patients with symptomatic carotid artery stenosis. *Eur J Vasc Endovasc Surg* 2014;**3**:233—9.
12 Huibers A, Calvet D, Kennedy F, Czuriga-Kovács KR, Featherstone RL, Moll FL, et al. Mechanism of procedural stroke following carotid endarterectomy or carotid artery stenting within the International Carotid Stenting Study (ICSS) randomised trial. *Eur J Vasc Endovasc Surg* 2015;**50**:281—8.
13 Jones DW, Goodney PP, Conrad MF, Nolan BW, Rzucidlo EM, Powell RJ, et al. Dual antiplatelet therapy reduces stroke but increases bleeding at the time of carotid endarterectomy. *J Vasc Surg* 2016;**63**:1262—70.
14 Strömberg S, Nordanstig A, Bentzel T, Österberg K, Bergström GM. Risk of early recurrent stroke in symptomatic carotid stenosis. *Eur J Vasc Endovasc Surg* 2015;**49**:137—44.
15 Shahidi S, Owen-Falkenberg A, Gottschalksen B, Ellenmann K. Risk of early recurrent stroke in symptomatic carotid stenosis after best medical therapy and before endarterectomy. *Int J Stroke* 2016;**11**:41—51.