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METHODOLOGICAL ASPECTS ON CAROTID ARTERY INTERVENTION

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Abstract

In Sweden, approximately 25000 patients suffer a cerebral infarction (stroke) annually. Stroke ranks as the third-leading cause of death, and is the leading cause of functional impairment. Carotid artery stenosis accounts for approximately 15% of all strokes and almost all of these are theoretically preventable.

There are two conceptually different invasive methods used to treat carotid stenosis: carotid artery stenting (CAS) and carotid endarterectomy (CEA). There are various aspects of these treatments that remain to be evaluated in order to minimize the risks of poor outcome, namely: any differences in short-term and long-term outcomes after CEA or CAS, the potential risks of CAS early after a previous transient ischaemic attack (TIA)/stroke, and the methods to indicate the need of shunting during CEA. Furthermore, since data from randomised controlled trials (RCTs) are often from specialized high volume centres with selected patients, it is important to evaluate population-based results after CAS and CEA.

The overall aim of this thesis was to investigate aspects of invasive treatment of carotid artery stenosis, in particular the outcome following endovascular treatment (CAS), and the efficacy of near-infrared spectroscopy in predicting selective shunt use during CEA.

The outcome after endovascular treatment was investigated in three cohort studies (study I, II, and III). In study I, we analysed Swedish national short-term results of CAS and CEA and compared a high-volume centre with national results for CAS. In study II we evaluated the procedural risk of CAS, in relation to time from previous TIA /stroke. Study III assessed the long-term population-based outcomes after CAS as compared to CEA. In study IV, a multi-centre diagnostic study, we evaluated the ability of near-infrared spectroscopy (NIRS) to predict cerebral ischaemia during CEA.

Study I was a retrospective single-centre review of all consecutive patients treated with CAS at Södersjukhuset between 2004-2011. These results were compared to data from the Swedish national registry for vascular surgery (Swedvasc), where data from all patients treated with CAS or CEA during the same period was extracted. We found that the Swedish national results for CAS were inferior to CEA, but also that it was possible to achieve acceptable results with CAS in a high volume centre. During the study period 464 CAS procedures were performed in Sweden, with 208 of them performed at Södersjukhuset. The stroke and death rate at 30 days among patients in Sweden (Södersjukhuset excluded) was 7.4%. In Södersjukhuset, the stroke and death rate was 2.9%. The results for CAS on a national basis improved over time, the stroke and death rate during the first half of the period was 6.4%, compared to 3.6% in the second part of the study period, which was probably due to the learning curve for the procedure.

In study II, all CAS performed for symptomatic carotid stenosis between 2005-2014, were included in a retrospective analysis. Study II revealed that it was safe to perform CAS early (within 1 week), following a TIA/stroke. The stroke and death rate for patient treated within 7 days from neurologic symptom was 4.1%, compared to 6.3% between day 8-14, 4.8% between day 15-28, and 3.6% between days 29-180.

The long-term results after CAS in Sweden were examined in study III. In this study, all primary CAS procedures registered in Swedvasc were included (all reoperations were excluded). We compared 409 CAS patients to a control group treated with CEA. The control group was matched with respect to known confounding factors. Postoperative stroke was identified by cross matching the cohort with the In-patient registry. Median follow-up time was 4.1 years, and follow-up data was almost complete. By using Cox regression, we found a substantial (59%) increased risk for late(>30 days) stroke or death for patients treated with CAS compared to CEA. This increased risk was mainly due to an increased risk of ipsilateral stroke during long-term follow-up.

In study IV, we have shown that near-infrared spectroscopy has a high sensitivity and acceptable specificity to predict cerebral ischemia during CEA. When a cut-off point of 9% relative decrease in regional SO2 during carotid clamping was chosen, the sensitivity for detecting cerebral ischemia was 95%, and the specificity 81%. This was clearly superior to the conventional and widespread technique of measuring, "stump pressure".

In conclusion, the national population-based results for CAS were inferior to CEA, both short- and long-term. The short-term results after CAS in Sweden have improved over time, and acceptable results can be achieved in high volume centres. If CAS is performed due to symptomatic stenosis it could be performed early after onset of neurologic symptoms.

Near-infrared spectroscopy is a reliable method for selective shunting during CEA and superior to stump pressure.

Keywords: carotid artery stenosis, carotid artery stenting, carotid endarterectomy, Near-infrared spectroscopy, shunting.

Summary in Swedish

(svensk sammanfattning)

Bakgrund

Slaganfall (stroke) är en av våra vanligaste folksjukdomar. Varje år drabbas cirka 25000 svenskar av stroke. I Sverige är stroke den tredje vanligaste dödsorsaken och en ledande orsak till allvarliga handikapp. Närmare 15% av alla stroke orsakas av en förträngning av halspulsådern (karotisstenos), detta gör denna grupp särskilt intressant eftersom denna typ av stroke kan förebyggas med kirurgiska ingrepp.

Karotisstenos är vanligen ett resultat av åderförkalkning och från denna förträngning kan ibland små fragment lossna och åka upp med blodet till hjärnan och därigenom orsaka en blodpropp och stroke. Stora randomiserade studier har visat att kirurgisk behandling av karotisstenos minskar risken för stroke jämfört med bästa medicinska behandling.

Det finns två principiellt olika kirurgiska metoder att behandla karotisstenos: endovaskulär stentbehandling, ofta kallat ”ballongvidgning” och öppen kirurgisk operation. Om någon av metoderna är överlägsen den andra är oklart.

Vid öppen kirurgisk behandling av karotisstenos stängs blodflödet till ena hjärnhalvan av under en del av ingreppet. Hos många patienter räcker blodtillförseln från andra hjärnhalvans blodkärl för att försörja hela hjärnan med blod. Hos andra räcker inte detta, utan blodet behöver ledas förbi operationsområdet i en tunn slang (shunt) upp till hjärnan under den period som blodflödet är avstängt. Att använda shunt gör att operationen blir tekniskt mer komplicerad varför många önskar använda shunt endast när det verkligen behövs. Det finns olika metoder för att avgöra vilka patienter som verkligen utvecklar syrebrist i hjärnan, men de hittills beprövade metoderna har alla sina tillkortakommanden. En ny och praktiskt enkel metod kan genom att två elektroder tejpas på pannan mäta syremättnaden i hjärnan, denna kallas near-infrared spectroscopy, NIRS.

Även om kirurgisk behandling av karotisstenos är ett välstuderat område så finns fortfarande kunskapsluckor som har avgörande klinisk betydelse för resultaten av den kirurgiska behandlingen.

Den övergripande målsättningen med avhandlingsarbetet var att belysa några av dessa kunskapsluckor och besvara frågorna:

1. Hur ser de svenska resultaten ut efter stentbehandling eller öppen operation av karotisstenos, på kort sikt och på lång sikt?

2. Hur nära inpå ett slaganfall eller TIA kan man behandla karotisstenos med endovaskulär stentbehandling?

3. Hur pålitligt är NIRS för att förutsäga vilka patienter som utvecklar syrebrist och därmed behöver shunt under öppen operation av karotisstenos?

Den första frågan studerades i två retrospektiva kohortstudier (arbete I och arbete III).

I arbete I analyserades resultaten av 464 stentbehandlingar utförda i Sverige mellan år 2004-2011, 208 av dessa var utförda på Södersjukhuset. Vi fann att de nationella resultaten vid stentbehandling var sämre än vid öppen kirurgisk behandling för karotisstenos på kort sikt, men att acceptabla resultat kunde uppnås på en enhet med stor volym. I Sverige (exklusive Södersjukhuset) drabbades 7.4% av patienterna av stroke eller död inom 30 dagar från operationen. I jämförelse drabbades 2.9% av patienterna behandlade på Södersjukhuset av stroke eller död. Vi fann att de nationella resultaten förbättrades under studietiden, sannolikt en effekt av en inlärningskurva.

I arbete III undersöktes resultaten efter samtliga karotisstentbehandlingar utförda i Sverige mellan 2005-2012 (reoperationer var exkluderade). Som jämförelse användes öppet opererade patienter som var matchade med avseende på kända riskfaktorer för stroke och död. Patienterna följdes i medeltal 4.1 år. Vi fann att patienter behandlade med stentning hade 59% ökad risk att drabbas av sen (mer än 30 dagar efter ingreppet) stroke eller död jämfört med öppet opererade. Den ökade risken berodde framförallt på en ökad risk för stroke på den behandlade sidan.

Den andra frågan studerades i en retrospektiv studie av stentbehandlade karotisstenoser och där resultaten av ingreppet delades upp i förhållande till hur lång tid som förflutit mellan operationen och den stroke eller TIA som var anledningen till ingreppet. Vi fann inte någon ökad risk med att behandla symptomgivande karotisstenos tidigt (inom en vecka) i anslutning till stroke eller TIA jämfört med att vänta längre tid till operation.

Den tredje frågan studerades i en prospektiv multicenterstudie med 185 patienter inkluderade. Studien visade att om NIRS-syremättnaden sjunker med 9% i samband med avstängning av halspulsådern så bör man använda shunt vid ingreppet. Med denna 9%-gräns för shuntning fann vi att NIRS har en sensitivitet på 95% och specificitet på 81% att detektera syrebrist i hjärnan. Detta var klart bättre än den konventionellt använda metoden ”stumptryck”.

Sammanfattningsvis har detta avhandlingsprojekt visat att i Sverige är resultaten efter öppen operation av karotisstenos mycket bra. Stentbehandling av karotisstenos på nationell nivå har något ökade risker jämfört med öppen operation på kort sikt och på lång sikt. Resultaten efter stentbehanding har dock förbättrats över tid och kan vara acceptabla på sjukhus med stor volym och erfarenhet. Vid de fall då stentbehandling är att föredra framför öppen kirurgi behöver behandlingen inte fördröjas utan kan ske skyndsamt (inom en vecka efter tidigare TIA eller stroke). NIRS är en säker metod som kan rekommenderas för att besluta om shuntning under öppen operation av karotisstenos.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Outcome after 7 years of Carotid Artery Stenting and Endarterectomy in Sweden – Single Centre and National Results.**
David Lindström, Magnus Jonsson, Johan Formgren, Martin Delle, Stefan Rosfors, Peter Gillgren
European journal of vascular and endovascular surgery: the official journal *of the European Society for Vascular Surgery. 2012;43(5):499-503.*

II. **Peri-procedural Risk with Urgent Carotid Artery Stenting: A Population based Swedvasc Study.**
Magnus Jonsson, Peter Gillgren, Anders Wanhainen, Stefan Acosta, David Lindström
European journal of vascular and endovascular surgery : the official journal *of the European Society for Vascular Surgery. 2015;49(5):506-12.*

III. **Long-Term Outcome After Carotid Artery Stenting - A Population-Based Matched Cohort Study.**
Magnus Jonsson, David Lindström, Peter Gillgren, Anders Wanhainen, Jonas Malmstedt
Stroke; a journal of cerebral circulation. 2016;47:2083-2089.

IV. **Near-infrared Spectroscopy (NIRS) as Predictor for Shunt Need During Carotid Endarterectomy.**
Magnus Jonsson, David Lindström, Anders Wanhainen, Khatereh Djavani-Gidlund, Peter Gillgren
Submitted

Contents

Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
AMI	Acute myocardial infarction
CAS	Carotid artery stenting
CEA	Carotid endarterectomy
CCA	Common carotid artery
CREST	Carotid Revascularization vs Stenting Trial
CI	Confidence interval
ECST	European Carotid Surgery Trial
EPD	Embolic protection device
EVA-3S	Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis
GA	General anaesthesia
ICA	Internal carotid artery
ICD	International Classification of Disease
ICSS	International Carotid Stenting Study
IPR	In patient registry
IQR	Inter quartile range
LA	Local anaesthesia
MRI	Magnetic resonance imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NNT	Numbers needed to treat
OR	Odds ratio
P-value	Probability value
RCT	Randomised controlled trial
ROC curve	Receiver operating characteristic curve
SD	Standard deviation
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for End arterectomy
SP	stump pressure
SPACE	Stent-Protected Angioplasty Versus Carotid Endarterectomy
SVS	The Society for vascular surgery
Swedvasc	Swedish national registry for vascular surgery
TCD	Transcranial doppler
TIA	Transient ischemic attack
WHO	World Health Organization

1 Aims of the thesis

The overall aim of the thesis was to investigate aspects of surgical treatment of carotid artery stenosis, in particular the outcome following endovascular treatment, and the efficacy of near-infrared spectroscopy in predicting the need for a shunt during carotid clamping.

Specific aims:

- To analyse short-term results of carotid artery stenting compared with carotid endarterectomy and compare a high-volume single centre with national results of carotid artery stenting (paper I).
- To evaluate the procedural risk of carotid artery stenting for symptomatic carotid stenosis in relation to the time from the qualifying neurological event (paper II).
- To assess the long-term outcomes of carotid artery stenting as compared to carotid endarterectomy (paper III).
- To evaluate the efficacy of near-infrared spectroscopy in predicting the need for a shunt during carotid clamping in patients undergoing carotid endarterectomy (paper IV).

2 Background

2.1 Introduction

Stroke –a widespread disease

In Sweden, there are approximately 25000 patients who suffer a cerebral infarction (stroke) annually.[1] Stroke ranks as the third-leading cause of death in Sweden, after heart disease and cancer, and is a leading cause of functional impairment.[2 3] In the last decades, stroke incidence rates have fallen in high-income countries, like Sweden, but increased in low- and middle – income countries.[4] In 2010, an estimated 16.9 million people worldwide had their first stroke event.[5] Well known causal risk factors for stroke are; hypertension, hypercholesterolemia, carotid stenosis and atrial fibrillation; additional probable causes include cigarette smoking, diabetes mellitus and excessive alcohol use.[6] Other factors that might increase the risk of stroke include; environmental air pollution, childhood health circumstances and fitness, high-risk diet and poor nutrition, physical inactivity, obesity, blood pressure variability, sleep-disordered breathing, chronic inflammation, chronic kidney disease, hormonal contraception, hormone replacement therapy, psychosocial stress, depression, job strain and long working hours.[6]

The reason for the decreased stroke rate in high-income countries is believed to be driven by a decline in smoking, better blood pressure control, and decreased serum cholesterol levels. The serum cholesterol levels started to decrease long before the widespread use of statins in high-income countries, indicating a dietary effect.[4, 7] On top of the 25000 strokes per annum, approximately 10000 patients suffer a transient ischemic attack (TIA) yearly in Sweden.

Carotid artery stenosis accounts for approximately 15% of all strokes[8], and treatment of carotid stenosis can thereby reduce the number of strokes.

Early experience of carotid endarterectomy (CEA) and carotid artery stenting (CAS)

The impact of carotid artery occlusion on neurologic symptoms has been known since Hippocrates, but it was not until 1809 the British surgeon Sir Astley Cooper discussed the possibility of stroke after carotid ligation.[9] Miller Fisher described the association of occlusion of the carotid artery and embolism to the brain and ischemic stroke.[10] In 1953, Dr Michael DeBakey performed the first successful carotid endarterectomy[9], but the first reported carotid endarterectomy for symptomatic stenosis was published in 1954 by Eastcott, Pickering and Rob.[11] These events led to a general understanding of the stroke protective benefits of the operation. During the 1980s treatment by means of CEAs increased rapidly worldwide.

Angioplasty of the internal carotid artery was described in 1967 with open gradual dilation for fibromuscular dysplasia.[12] Mathias et al reported the first percutaneous angioplasty of the carotid artery in 1977[9, 13], and the first Carotid Artery Stenting (CAS), was performed by Kerber at al in 1980.[14] Ever since this first CAS, there has been a rapid development of different materials and devices to reduce the risk of distal embolization.

The first evidence from randomised controlled trials of benefit for treating carotid artery stenosis surgically

In the 1980s, reports about inappropriateness of indication and unacceptably high complications rates led to a decline in the number of carotid operations performed.[15, 16]And there was a need for evidence from randomized controlled trials to justify the operation. These events led to two large randomized controlled trials were set up: North American Symptomatic Carotid Endarterectomy Trial (*NASCET*)[17], and European Carotid Surgery Trial (*ECST*).[18] These trials showed that CEA could reduce the risk of stroke and death in patients with recent neurologic symptoms caused by carotid artery stenosis. Additionally, Asymptomatic Carotid Atherosclerosis Study *(ACAS)*[19] and Asymptomatic Carotid Surgery Trial *(ACST)*[20] showed that CEA could reduce the risk of stroke for patients with asymptomatic carotid stenosis compared to medical therapy alone. These trials led to a rebound of surgical treatment of carotid artery stenosis.

Ever since the publication of *NASCET* and *ECST*, carotid endarterectomy has been adopted as the standard treatment for symptomatic carotid artery stenosis.

In Sweden, over the last 10 years, approximately 1000 carotid procedures are performed annually, aiming to reduce the number of strokes in the population. It is therefore relevant to analyse the results from the carotid procedures with the aim to minimise the complication rate of the procedures.

2.2 Asymptomatic carotid artery stenosis

Carotid stenosis is a narrowing of the lumen of the carotid artery, usually caused by atherosclerosis. Most often this narrowing occurs at the division of the common carotid artery to the internal carotid artery (which supplies the brain with blood), and external carotid artery.

Definition

Asymptomatic carotid artery stenosis includes patients with no history of neurologic symptoms related to the ipsilateral carotid territory, or those with symptoms > 180 days ago. Consequently, patients with atypical or non-focal neurologic symptoms or vertebrobasilar symptoms are also considered “asymptomatic”.

Prevalence

The prevalence of carotid stenosis increases with age. Before 70 years of age, the prevalence of moderate stenosis (≥50%) is 4.8% in men, and 2.2% in women as compared to 12.5% in men and 6.9% in women over 70 years.[21, 22]

Treatment for asymptomatic carotid artery stenosis

Two large-scale randomized trials, *ACST-1* (Asymptomatic Carotid Surgery Trial-1) and *ACAS* (Asymptomatic Carotid Atherosclerosis Study) have demonstrated that CEA reduces the risk

of having a stroke as compared to medical treatment alone.[19, 20] Even later data, has proven a long-lasting stroke protective effect of CEA at 10 years.[23] However, only 50-60 strokes per 1000 CEAs will be prevented, thus approximately 95% of the patients will undergo an unnecessary intervention.[24]

The best treatment for asymptomatic carotid stenosis is controversial, and different strategies are proposed in different countries. Current SVS (society for vascular surgery) guidelines propose that asymptomatic patients with ≥60% stenosis should be considered for CEA provided that the patient has a 3 to 5 year life expectancy and perioperative stroke/death rates of less than 3%.[25] A systematic review of guidelines in different countries and regions identified several different strategies for asymptomatic carotid stenosis in different countries: best medical treatment, CEA and/or CAS. [26]

The patients in *ACST-1* and *ACAS* were included in these trials in 1993-2003 and 1987-1993 respectively. In more recent studies, the reported annual risk for ipsilateral stroke among non-surgically treated patients with asymptomatic carotid stenosis has decreased significantly, and an annual stroke rate of less than 1-1.5% may be achieved with modern medical therapy. [27-30] The main reason is that current best medical treatment is more effective than during the ACST-1 and ACAS, including higher statin doses, better blood pressure control and more effective antithrombotic medication.

Identifying patients at high risk for stroke

There may be a subgroup of patients with asymptomatic stenosis who have a higher annual stroke risk than the average asymptomatic patient and therefore would benefit more from intervention. In the *ACSRS* (Asymptomatic Carotid Stenosis and Risk of Stroke study), patients with previous TIA or stroke on the contralateral side had an increased risk, as well as patients with stenosis progression.[30, 31] Large plaque area, microulcers, microembolization on TCD and silent infarctions have all been reported to increase the risk of stroke.[24, 32-34, 195] Echolucent, "soft" plaques on duplex has been associated to increased stroke risk.[35, 194, 195] Also, intra-plaque haemorrhages on MRI have been reported to be associated with ischemic stroke [36, 37] There is, unfortunately, no established "risk score" for asymptomatic carotid stenosis.

Discrepancies between regions

Due to these uncertainties regarding asymptomatic carotid stenosis, other factors, such as economical incentives can play a role in the choice of treatment. In the United States, more than 90% of the carotid procedures (both CEA and CAS) were performed for asymptomatic stenosis, compared to 0% in Denmark in 2015.[38-40] In Sweden, the proportion of carotid procedures for asymptomatic stenosis has decreased significantly the last 10 years; 28% in 2006 compared to 8.9% in 2015.[38]

2.3 Symptomatic carotid artery stenosis

The World Health Organization's definition of **stroke** is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin."[41] Since this definition was introduced, new techniques of diagnoses and treatment such as MRI (magnetic resonance imag-

ing) and thrombolysis, have become widespread. The American Heart Association/American Stroke Association have proposed a new definition, in which the term stroke should be more broadly used and "include pathological, imaging, and/or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and with other aetiologies excluded".[42] To be able to compare outcome in different studies, it is important to use the same definitions of outcome. In reporting standards for carotid surgery, stroke is defined as a cerebral infarction that manifests as a sudden onset of focal neurological deficits that persist for more than 24 hours. In instances where a new cerebral infarction is demonstrated on MRI or DT, the occurrence of stroke should be documented even if the symptoms lasted < 24 hours.[43]

Transient ischemic attack (TIA) has several different definitions in use. Often, the definition of TIA is a sudden onset of focal neurological symptoms with duration of up to 24 hours, with total resolution or return to baseline, and with no image evidence of infarction. [44] [2, 6, 43]

Amaurosis fugax used to be defined after pathoetiology: embolic (type I), hypoperfusion (type II), angiospasm (type III) and unknown (type IV).[45] It has been redefined as to transient monocular visual loss attributed to ischemia or vascular insufficiency. Typically, the patients describe rapid progression of visual impairment that progress over seconds or a few minutes. The loss of vision usually begins in the upper visual field as a "curtain phenomenon".[46]

Symptomatic patients

Patients with carotid stenosis should be considered symptomatic if: they have a history of contralateral symptoms of TIA/stroke, or amaurosis fugax involving the ipsilateral carotid territory. For practical reasons, and due to the fact that the risk of new neurological symptoms decreases with time after the initial symptoms, only patients with symptoms within 180 days are considered symptomatic.[43]

Stroke can be classified into different subgroups depending on severity of the functional impairment. Modified Rankin scale (mRS) is a simple method often used for this purpose. Often, the term major stroke or disabling stroke is considered for patients with mRS≥2.

Modified Rankin Scale
0-No symptoms
1-No significant disability, despite symptoms; able to perform all usual duties and activties.
2-Slight disability; unable to perform all previous activities but able to look after own affairs.
3-Moderate disability; requires some help, but able to walk independently.
4-Moderate severely disability; unable to walk without assistance and unable to attend to own body needs without assistance.
5-Severe disability; bedridden, incontinent and requires constant nursing care and atttion.
6-Death

The National Institutes of Health Stroke Scale, or NIHSS

The NIHSS is another widely used tool to evaluate and quantify the severity of stroke. NIHSS early after stroke onset can be used to predict final outcome after a stroke.[47] A baseline NIHSS ≤ 3 at admission is associated with good long-term outcome, and has been proposed to be used for "minor stroke".[48]

NIHSS[49]

Instruction	Scale definition	Score
1a. Level of consciousness (LOC)	0 = Alert, 1 = Not alert; but arousable by minor stimulation, 2 = Not alert; requires repeated stimulation to attend, 3 = Responds only with reflex motor or autonomic effects or totally unresponsive	
1b. LOC questions - The patient is asked the month and his/her age	0 = Both questions correctly, 1 = One question correctly, 2 = Neither question correctly.	
1c. LOC commands - The patient is asked to open and close the eyes and grip and release	0 = Performs both tasks correctly, 1 = Performs one task correctly, 2 = Performs neither task correctly.	
2. Best gaze - Only horizontal eye movements will be tested	0 = Normal, 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic manoeuvre.	
3. Visual - upper and lower quadrants are tested	0 = No visual loss, 1 = Partial hemianopia, 2 = Complete hemianopia, 3 = Bilateral hemianopia	
4. Facial palsy - show teeth or raise eyebrows and close eyes	0 = Normal symmetrical movements, 1 = Minor paralysis, 2 = Partial paralysis (total or near-total paralysis of lowerface), 3 = Complete paralysis of one or both sides	
5. Motor arm - The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting)	0 = No drift; limb holds for full 10 seconds, 1 = Drift; limb holds 90 degrees, but drifts down before full 10 seconds, 2 = Some effort against gravity, 3 = No effort against gravity, 4 = No movement, UN = Amputation or joint fusion, explain:	
6. Motor leg - hold the leg at 30 degrees	0 = No drift; leg holds position for full 5 seconds, 1 = Drift; leg falls by the end of the 5-second period, 2 = Some effort against gravity, 3 = No effort against gravity, 4 = No movement. UN = Amputation or joint fusion, explain:	
7. Limb ataxia - The finger-nose-finger and heel-shin tests are performed on both sides	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain	
8. Sensory - Sensation or grimace to pinprick when tested,	0 = Normal; no sensory loss, 1 = Mild-to-moderate sensory loss, 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best language - the patient is asked to describe what is happening in the attached picture	0 = No aphasia; normal, 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression, 2 = Severe aphasia; all communication is through fragmentary expression, 3 = Mute, global aphasia	
10. Dysarthria - asking patient to read or repeat words from the attached list.	0 = Normal. 1 = Mild-to-moderate dysarthria, 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible, or is mute. UN = Intubated or other physical barrier.	
11. Extinction and inattention (formerly neglect)	0 = No abnormality, 1 = Visual, tactile, auditory, spatial, or personal inattention, 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	

Treatment for symptomatic carotid artery stenosis

In 1991, randomization within *NASCET* was halted for patients with severe stenosis (70-99%) due to a substantial benefit in major outcome (stroke and death) at 2 years for the surgical group.[50] Absolute risk reduction of ipsilateral stroke was 16.5%, with a relative risk reduction of 65%. Similar results were reported in the interim results of *ECST*.[51]

In 1998, the final results of *ECST* and *NASCET* were published. They concluded that there was a moderate effect of carotid endarterectomy in symptomatic patients with moderate stenosis, and a substantial effect in patients with symptomatic severe stenosis.[17, 18]

2.4 Carotid endarterectomy and carotid artery stenting

Imaging before intervention

The degree of ICA stenosis can be measured by different modalities. The gold standard has been selective digital subtraction angiography (DSA), which was the modality used in the randomized trials, *NASCET* and *ECST*. These two trials measured the degree of stenosis on different locations on the arteries and there are clinically important disparities between them. Thus, it is important to explicit describe what method is used for a certain degree of stenosis, "% stenosis according to *NASCET*" and "% stenosis according to *ECST*". It is possible to convert measurements made by one method to the other using a simple equation.[52]

Today, DSA is rarely used for stenosis grading, and has largely been replaced by other modalities: duplex ultrasound, CT angiography, or MR angiography which all have high sensitivity and specificity for detection of severe carotid artery disease.[53, 54, 55]

Jogestrand et al showed that peak systolic velocity is the most reliable parameter to describe degree of stenosis for duplex ultrasound.[56] They also demonstrated the relevance of using correct doppler angle and that different peak velocity criteria should be used at different doppler angles.[54]

Many patients undergo duplex ultrasound for screening, and CT/MR angiography, which can give additional information about the intracerebral circulation, and characterization of the plaque as discussed earlier. CT/MR angiography also gives information about the aortic arch and in-flow stenosis.

Surgical technique of CEA

The operation begins with a skin incision parallel to the sternocleidomastoid muscle, centred over the carotid bifurcation, through the platysma and the sternocleidomastoid muscle is retracted laterally. The facial vein is ligated. The jugular vein is exposed and the carotid sheath is opened on the anterior border of the vein, which is retracted laterally. The common carotid artery is then dissected free and behind the artery, the vagus nerve is usually exposed. The dissection is continued upward to isolate the external carotid artery. The distal internal carotid artery is mobilized where the vessel is normal. The digastric muscle can be divided if necessary. Mobilization of the carotid bifurcation should be minimized to avoid embolization. The

ansa cervicalis, a branch of the hypoglossal nerve, may be divided. Attention must be paid to the hypoglossal nerve and traction of the cranial nerve should be gentle to avoid injuries on the marginal mandibular branch of the facial nerve.

Anaesthetic- and shunt perspectives are discussed in section 2.6, shunting during carotid endarterectomy.

Type of endarterectomy

In *eversion CEA* the internal carotid artery is transected through the bifurcation. The adventitia is rolled back and the plaque can be removed and the internal carotid artery reimplanted.

In *conventional CEA* a longitudinal arteriotomy is performed and the plaque is then removed. The arteriotomy should be closed with a patch, synthetic patches are superior to vein patches.[57, 58]

Eversion CEA has some potential advantages over conventional CEA, namely: fewer restenoses, shorter operation time and no synthetic material, but the perioperative results between eversion CEA and conventional CEA are equal.[59, 60]

Present technique of CAS

After access via a femoral puncture, a long catheter is introduced in the common carotid artery. An arteriogram is obtained in an anterior oblique angulation. A stiff guidewire is placed in the external carotid artery and a sheath is placed in the common carotid artery. The next step is to advance a protection device: either positioning a filter distally to the lesion in the internal carotid artery, or to reverse the flow, by occluding the external carotid artery and common carotid artery with balloons. A self-expandable stent with or without predilation is placed across the lesion and deployed. After balloon dilatation, a completion angiogram is performed.

Protection device

No large scale randomized controlled trial has investigated the efficacy of embolic protection devices, but cohort studies support the use of a protection device.[61, 62] There are two principally different protection devices on the market: proximal occlusion, and distal filter. Theoretically, proximal occlusion has some advantages over distal filters, since it reverses the flow over the stenosis and redirects embolic particles; also, the stenosis is never crossed without protection. There is some support that filters create more micro emboli than proximal occlusion, but no study has showed any difference in stroke frequency.[63-65] A combination of distal filter and proximal occlusion might be even more effective in reducing distal embolization than each method used separately.[66, 67]

Transcervical approach

Almost 10 % of all perioperative strokes with CAS are on the contralateral side, indicating that avoiding manipulation of the aortic arch could reduce the stroke rate. One way to avoid the problem with the arch is the direct cervical approach, which has reported excellent results for stenting. [68, 69] In 2015, the *ROADSTER* trial (Reverse flow used during carotid artery stenting procedure) presented the lowest perioperative stroke rate ever reported after CAS in a prospective multicentre trial, 1.4%.[70] In the *ROADSTER* trial, the common carotid artery was exposed

through a small incision and the intervention was performed directly through the common carotid artery, and a reversed flow system was used as an embolic protection device.

New stents and materials

Microembolisation and trapped/prolapse debris and plaque through and within the struts of the stents are believed to be the major causes of postoperative stroke. To manage this, a closed cell design has been used.[71] In closed cell design there are bridges between every cell in the stent so that the struts cannot penetrate the intima, but this has the disadvantage that it makes the stent more rigid than open designed stents. In a small RCT with embolization detected by TCD as the endpoint, the authors could not find any difference between open- and closed cell design.[72] A new generation of stents has been developed with a double layer of mesh to reduce the interstices in the cells, and thereby deal with the protruding plaque, the so called mesh-stents.[73, 74] These stents have showed promising results in the CLEAR-ROAD study, with a stroke/death/AMI rate of 2.1% at 30 days.[75]

Intervention for symptomatic carotid stenosis

After the introduction of CAS in the 1980s, several RCTs have compared the efficacy of CAS and CEA.

As demonstrated in table 1, the rate of stroke and death at 30 days was lower with carotid endarterectomy than carotid artery stenting. This was also the conclusion of a systematic review.[76] However this excessive risk seems to be most pronounced in elderly patients. An analysis of pooled data from *EVA-3S*, *SPACE* and *ICSS* showed that the risk of perioperative stroke or death from stenting were similar to that from CEA in patients younger than 70 years.[77]

Paraskevas et al., analysed and compared the results for CEA and CAS reported from registries, and found that stroke and death rates were significantly higher after CAS than after CEA, and that the results have not really improved over time, which would have otherwise been expected from improved experience and the development of a new technique.[78]

Table 1. Major randomized controlled trials comparing short-term outcome after CEA and CAS.

Study	No Patients	Symptomatic Patients	30 d stroke / death CAS (%)	30 d stroke / death CEA (%)	OR stroke/death CAS vs CEA (95% CI)
SAPPHIRE 2004[79]	334	96	5.5	8.4	Non-inferiority
EVA-3S 2006[80]	527	527	9.6	3.9	2.5 (1.2-5.1)
SPACE 2006[81]	1214	1214	7.68	6.51	1.19 (0.75-1.92)
ICSS 2010†[82]	1713	1713	8.5	4.7	1.86 (1.26-2.74)*
CREST 2010#[83]	2502	1321	4.4	2.3	1.90 (1.21-2.98)*

* Hazard Ratio

† 120 day follow up

Includes postprocedural ipsilateral stroke

Intervention for asymptomatic stenosis

The *ACT I* trial had a 3:1 allocation ratio with 1089 CAS patients and 364 patients undergoing endarterectomy for asymptomatic stenosis. At 30-day follow-up, there was a non-significant difference for stroke or death: 2.9% in the CAS group, and 1.7% in the CEA group.[84]

Although the *CREST* trial was not powered to identify differences among patients with asymptomatic stenosis, CEA and CAS, both had low perioperative stroke or death rates with no significant difference between the methods, CAS 2.5% versus CEA 1.4%, ($p = 0.15$).[83]

The on-going *ACST-2* trial, aiming to randomize 5000 patients, is comparing CAS and CEA for asymptomatic carotid stenosis. An interim report from 691 randomized patients within this trial showed a 30-day stroke rate of 2.9% for all patients.[85]

Thus, among asymptomatic patients, it seems to be more important to identify who should be intervened rather than which method should be chosen.

Long-term outcome after CAS and CEA

Stenting of the arteries in the lower limb have been associated with more occlusions and restenoses than after endarterectomy, and one concern has been that CAS might be associated with more restenoses and subsequent strokes, than CEA. The *CAVATAS* study (Carotid and Vertebral Artery Transluminal Angioplasty), reported a 31% risk of restenosis at 5 years after CAS compared with 10% after CEA.[86] Also *EVA-3S* and *SPACE* studies reported higher incidence of restenosis in the stented group than in the CEA group (12% vs 5% at 3 years and 11% vs 5% at 2 years respectively).[87, 88] In contrast, in *CREST* and *ICSS* there was no difference in rate of restenosis between CAS and CEA at long-term follow up.[89-91]

The *CREST*, *ICSS* and *EVA-3S* trials have reported long term outcomes: in the *CREST* trial there was no difference in stroke rate in the postprocedural period.[89] In the *ICSS*, there were more strokes after 30 days in the stented group as compared to the endarterectomy group (HR 1.53, 95% CI 1.02-2.31), but no difference between the groups with respect to postprocedural ipsilateral stroke.[91] In *EVA-3S* there were similar rates of ipsilateral stroke after the periprocedural period.[92]

The *ACT-1* trial with patients treated for asymptomatic carotid artery stenosis found no differences between CAS and CEA in target lesion revascularisation, non-procedure ipsilateral or any stroke, and survival up to five years after intervention.[84]

The randomised controlled trials show little or no difference between CEA and CAS after the periprocedural period. Nevertheless, participating units are often specialized high volume units, and patients within these trials are highly selected, and there is a need for good quality data cohort studies to compare CEA and CAS in a real world setting.

Primary CAS in Sweden

In 2004, the results from the *SAPPHIRE* (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) were published. This trial compared patients with elevated

surgical risk, based on cardio-pulmonary comorbidity, stenosis following previous endarterectomy or irradiation, or contralateral carotid occlusion. The results of this trial showed non-inferiority for treatment with CAS with respect to stroke or death at 30 days or ipsilateral stroke in the first year of treatment.[79] After the publication of *SAPPHIRE*, there was growing enthusiasm for stenting, and in Sweden the number of CAS performed increased rapidly. A few years later, after the publication of *EVA-3 S*, *CREST* and *ICSS*, which showed an increased risk with CAS for symptomatic patients, combined with a more restrictive approach to treatment of asymptomatic stenosis, the number of CAS in Sweden has declined dramatically. In 2015, stenting accounted for only 3 % of all primary carotid procedures.[38] Figure 1 illustrates the rise and fall of CAS in Sweden and the adoption to the results of the RCTs.

Nevertheless, CAS still has an important role in selected cases, and is often used for treating restenosis, after radiotherapy, and is the treatment of choice for patients with a contralateral recurrent laryngeal nerve paresis.

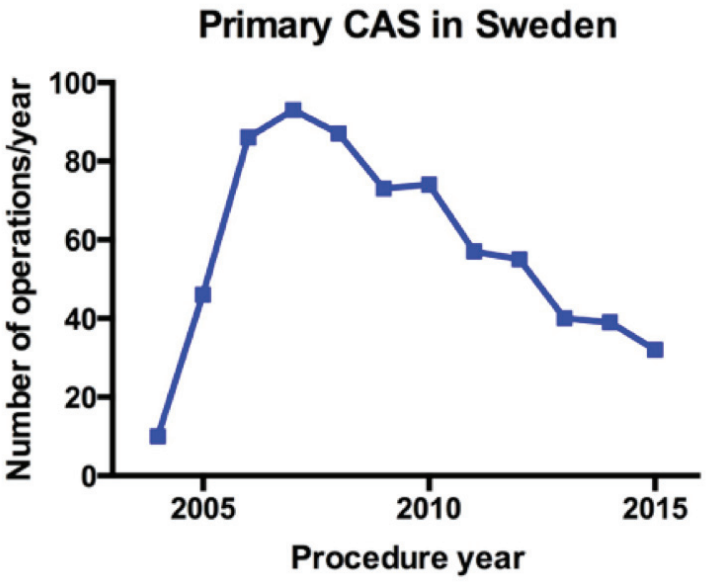

Figure 1. *The rise and fall of primary CAS in Sweden.*

2.5 Timing of carotid intervention

– The time relation between symptoms and intervention.

Patients with carotid stenosis who have suffered a TIA or minor stroke are at high risk of having a recurrent stroke, up to 15% the first week,[93-97] although recent Swedish literature have reported a lower risk of recurrent stroke (2-8% within 1 week).[98, 99] A declined recurrent stroke rate has also been reported for all TIA patients.[100] The declined recurrent stroke rate might be attributable to better medical treatment.[101, 102] Nevertheless, in symptomatic patients, a large

proportion of the recurrent strokes that occur after TIA, occur within the first 48 hours, and the majority of the recurrent strokes occur within a week.[96, 98, 103-105] Patients with a stroke due to large artery atherosclerosis (thus including ICA) are at higher risk of having recurrent symptoms, as compared to stroke due to small vessel atherosclerosis or cardio-embolic strokes.[8, 106] In Sweden, in 2015, 19.2% of all patients treated for symptomatic carotid stenosis had new neurologic symptoms after the alarm symptom, and half of them were within 3 days.[38] In the light of this, carotid intervention should be performed as soon as possible after a neurologic event.

Is there a risk of early CEA?

The early experience of CEA described conversion of ischemic infarcts to haemorrhagic strokes if CEA was performed shortly after a neurologic event, and most surgeons waited at least 4-6 weeks between presentation of symptoms and surgery.[107-109]

In 2004, Rothwell et al. published pooled data from the large randomized trials, and showed that the numbers needed to treat (i.e. how many patients needs to be treated to prevent one stroke) was five for those randomized within 2 weeks after their last ischemic event, compared to 125 for patients randomized after more than 12 weeks.[110] In the current recommendations from the European Society of Vascular Surgery guidelines symptomatic patients should undergo treatment, preferably within 14 days of onset of symptoms.[111]

Rockman et al. reported in 2006, that early (< 4 weeks) endarterectomy was associated with poorer outcome.[112] These findings were supported by the Swedish study from Strömberg et al. who found an 11.5% stroke or death risk in patients operated on within 48 hours from onset of alarm symptom.[113] In contrast, two recent studies could not support that the time interval after index event influenced the perioperative stroke or death rate.[114, 115]

Cerebral infarcts larger than 4000 mm^3, and stroke in evolution have been reported with poorer outcome in the acute setting.[116-118] In conclusion, a possible higher perioperative stroke risk with early CEA is counterbalanced by a much higher stroke preventive effect, supporting early intervention in most cases.

Early CAS

There is a concern of performing CAS early after the onset of neurologic symptoms, since one could suspect that passing a fresh thrombus with a guide wire would increase the risk of distal embolization and perioperative stroke. Furthermore, the potential advantage of proximal occlusion device compared to distal filter is theoretically more pronounced for unstable plaques as compared to more calcified lesions.

The available data regarding risk with CAS, stratified for timing after onset of symptoms, is limited. The CAPTURE registry reported an increased rate of stroke or death when CAS was performed within 2 weeks of symptoms compared to after 2 weeks. Table 2 summarizes the published data so far.

Clearly, there is a knowledge gap whether it is safe to perform CAS urgently, and what protection device should be used in this acute setting.

Table 2. Thirty-day stroke or death rate after CAS stratified for delay from index symptom.

	Time to CAS			
	0 to 2 days	3 to 7 days	8 to 14 days	15 to 180 days
Wach, MM et al 2013[119]	5/70 (7.1%)	4/88 (4.5%)	1/36(2.8%)	0/27 (0%)
Rantner, B et al 2013[120]		13/138 (9.4%)*	19/234 (8.1%)	78/1062 (7.3%)
Topakian, R et al 2007[121]			6/23 (26%)†	1/54 (1.9%)
Gröschel, K et al 2008[122]			10/142 (7.0%)‡	17/178 (10.0%)#
Setacci, C et al 2010**[123]	1/26 (3.8%)			

*0-7 days
†0-14 days
‡0-13 days
#14-180 days
**Only patients with TIA included

Trends in Sweden

There is a clear trend in Sweden, whereby patients are being operated closer to alarm symptom. This is illustrated in figure 2 and figure 3 for the period 2008 to 2015, respectively (data from Swedvasc).[38]

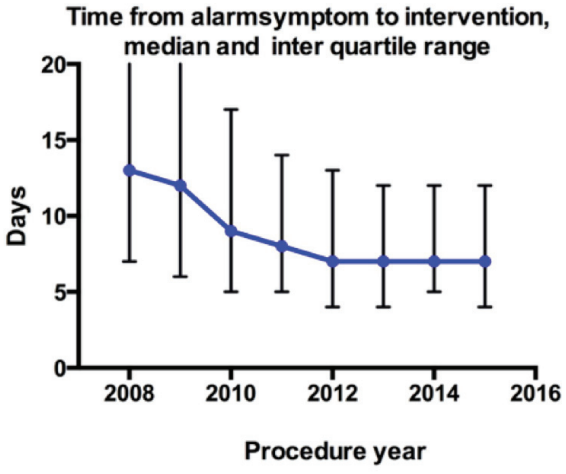

Figure 2. *Decreasing time from alarm symptom to intervention over the past 8 years. Data from Swedvasc.*

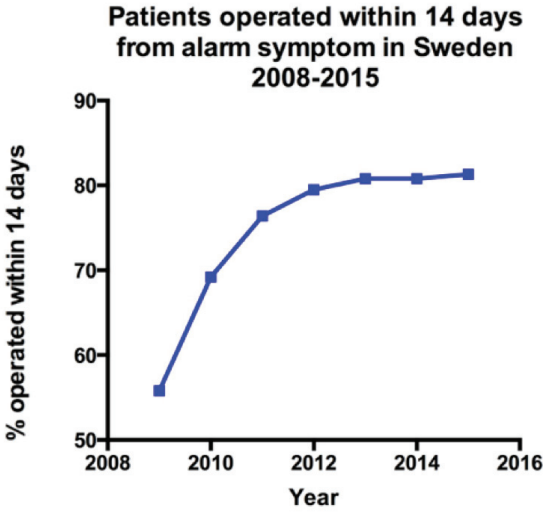

Figure 3. *The proportion of patients operated within the recommended 14 days from alarm symptom has increased the last 8 years. Data from Swedvasc.*

Intervention after thrombolysis

An increasing proportion of stroke patients are receiving thrombolytic therapy as acute treatment for stroke. Some of them will be considered for carotid intervention and the proportion of patients undergoing carotid intervention after thrombolytic therapy in Sweden has increased, see figure 4. Several small cohort studies have reported that CAS and CEA could be performed early (< 14 days) after thrombolytic therapy without increased risk of perioperative stroke or death.[124-126 127] It is unclear whether there is an increased risk of intracranial haemorrhage with intervention within the first 72 hours, but a recently published study indicates that it might be safe to treat the carotid stenosis even urgently (< 12 hours) after thrombolysis.[126, 128]

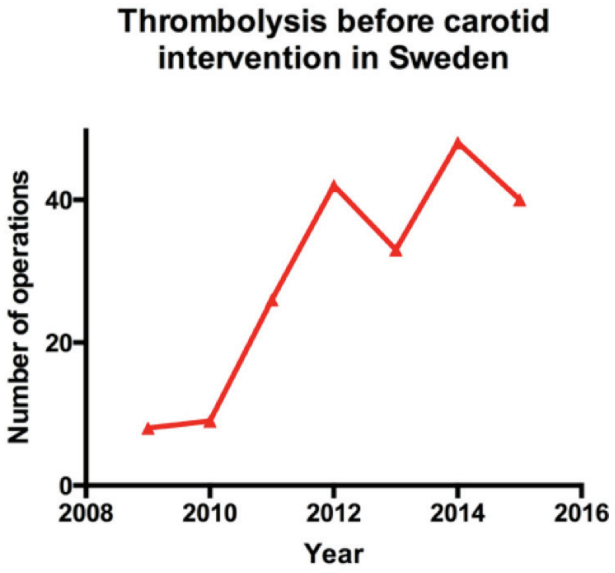

Figure 4. *Carotid intervention after thrombolytic therapy has increased in recent years. Data from Swedvasc.*

2.6 Shunting during carotid endarterectomy

Why use shunt during CEA?

A shunt is a thin tube that can lead blood from the common carotid artery and back into healthy internal carotid artery distal to the plaque during the endarterectomy. Most of the strokes that occur during/after CEA are ischaemic and some may be caused by the temporary interruption of blood flow during the procedure when the common carotid artery is clamped. To restore the circulation to the brain an intraluminal shunt can be used during the operation, and this may reduce the perioperative stroke risk. When carotid endarterectomies are performed under local anaesthesia (LA), 7-16% of patients develop neurological deficit during carotid clamping, due to insufficient collateral blood flow.[129-134] Under such circumstances, most surgeons prefer using a shunt to restore blood flow. More controversial is shunting in CEA under general anaesthesia (GA).

Selective or routine shunting

Shunt placement can be technically difficult and limits the exposure of the operation field. Additionally, shunting has potential risks such as; artery dissection, plaque embolization, air embolism, and shunt thrombosis.[135, 136] On the contrary, in a shunt-all policy, the surgeons become more familiar with the practice, minimizing technical problems and the endarterectomy can be carried out without stress. It has not been proven which is best, a shunt-all policy, selective shunting, or non-shunting. Only a few randomized controlled trials have compared the use of selective and routine shunting, and no one has demonstrated any significant differences in patient related outcomes.[137, 138] Several large clinical trials have demonstrated excellent results with routine shunting. [139-141] In contrast, excellent results have also been reported from centre using a no-shunt policy.[142-144] All these results have led to substantial difference in shunt policy between countries and units.[145] In Sweden most units use selective shunting (i.e. based on symptoms (LA) or indirect measures of cerebral ischemia (GA)), and in 2015, 31 % of the patients treated with carotid endarterectomy were performed using a shunt.[38]

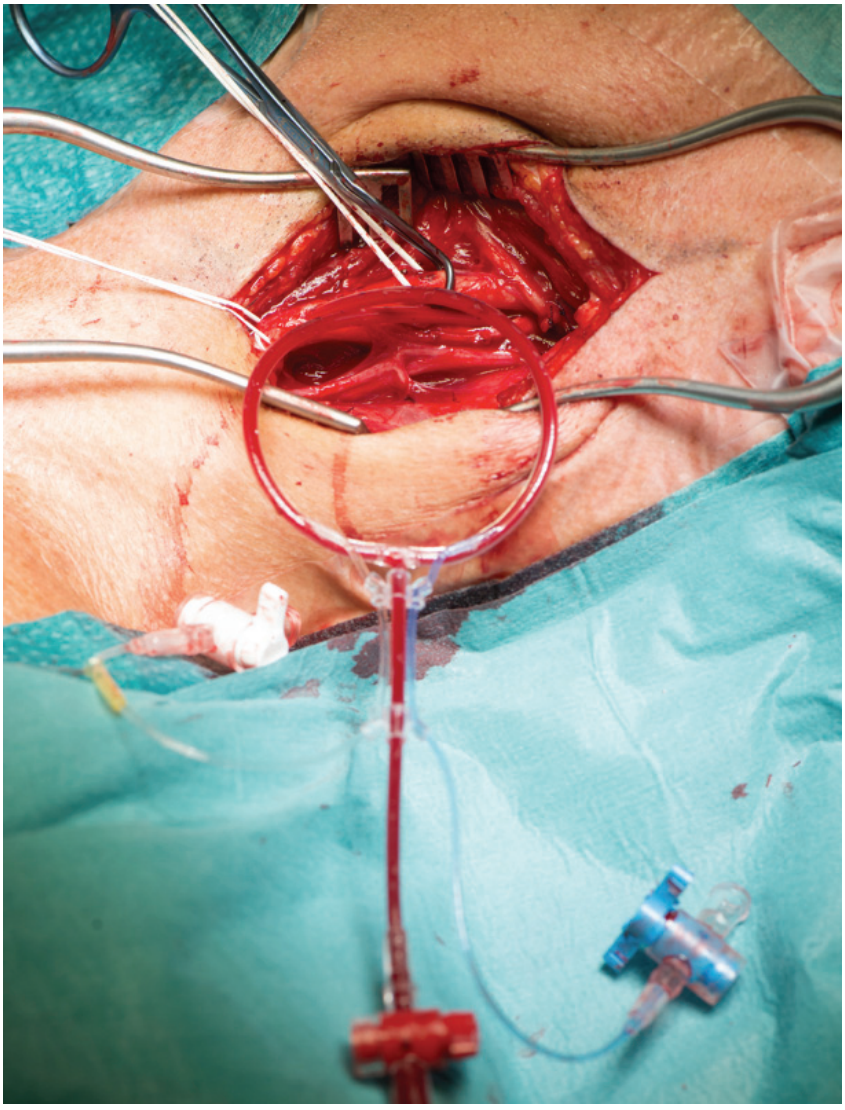

Figure 5. *Use of shunt (Pruitt-Inahara® (LeMaitre, Burlington, Massachusetts, USA)) during CEA.*

Anaesthesia during CEA

The debate whether to perform CEA under LA or GA is on-going. Evidence is lacking to favour either of the methods. The randomized controlled GALA trial (GA vs. LA) presented similar perioperative risks of stroke and death after CEA.[134] LA has some possible advantages. Patients operated under LA are in general shunted less frequent than patients operated under GA (14% versus 43%).[146] In the CREST trial, patients operated under LA had similar rate of myocardial infarctions as patients undergoing CAS, whereas patients operated under GA were more likely to have a postoperative myocardial infarction.[147]. In contrast, in the GALA trial, there was no difference in rate of myocardial infarctions between patients operated under LA and GA.[134] A Cochrane analysis reported a trend towards lower 30-day mortality in the group operated under LA, but no statistical significance in major outcomes.[146] However, for CEA done in LA the patient should be alert enough to do awake neurological testing during carotid clamping, and occasionally, the administration of local anaesthesia could affect deeper structures (such as intravasal injection, nerve damages), and cause a haematoma.[148] GA has the advantage of a perfectly still operation field, and no problems with patient discomfort. Other potential advantages with LA include avoiding of intraoperative hypotension and postoperative hypertension with the need of vasoactive medication. To summarize, since major outcomes between GA and LA do not differ, the type of anaesthesia chosen (local or general) should be based on the preference of the surgeon and the comfort of the patient.

Methods to predict cerebral ischemia

Less than one out of five patients require a shunt during CEA under LA. Consequently, in a shunt-all policy more than 80% of the patients are shunted unnecessarily. In the GALA trial, 43% of patients operated under general anaesthesia were shunted as compared to 14% under local anaesthesia (in the latter group, only 8.7% were shunted due to neurological symptoms, the others due to other reasons). To reduce the number of shunts in patients operated in GA, various methods have been used to predict cerebral ischemia during carotid clamping, but no study has identified a perfect method.

Stump pressure

The theory behind stump pressure is that the back bleeding from the internal carotid artery varies with the adequacy of the collateral circulation and that this back bleeding can be quantified by measuring the back pressure of the internal carotid artery, distal to an occluding clamp. This is called the stump pressure, and is widely used for predicting cerebral ischemia and thus to indicate shunt use. The cut-off pressure when shunting is mandated is debated, and different thresholds have been advocated. Some studies have reported stump pressure as mean arterial pressure, whilst others as systolic pressure. The method suffers from low specificity, but the reported sensitivity is relatively high. Still, 10-20% of the patients who required a shunt due to neurologic deficit have had a stump pressure of more than 50 mmHg. [129, 132, 133, 137] Studies performed on stump pressure in awake patients are presented in table 3

Other methods used for predicting cerebral ischemia during carotid clamping are Electroencephalogram (EEG), transcranial Doppler (TCD) and somatosensory evoked potentials (SSEP).

Table 3. Major studies of stump pressure under local anaesthesia

Author (year)	No. of carotid endarterectomies	Shunt requency	SP > 50 mmHg and neurologic symptoms	SP < 50 mmHg	Symptomatic patients
Moore et al (1969)[130] **	48	10%	0/48 = 0%	35/48 = 73%	42%
Evans et al (1985)[131] *	134	9.7%	3/13 = 23%	40/121= 33%	68%
Calligaro et al(2005)[129] *	474	7.2%	3/34 = 9%	139/474 = 29%	25%
Hans et al (2007)[132] **	314	10%	3/32 = 9%	98/314 = 31%	23%

*Systolic SP

**Mean SP

Near-infrared Spectroscopy

Near-infrared Spectroscopy (NIRS) is a relatively new method to detect and predict cerebral ischemia. NIRS is using the fact that the scalp and skull are relatively transparent to light in the near infrared spectrum (700-1000 nm), and that oxygenated and deoxygenated haemoglobin reflect light differently in this spectrum. NIRS enables continuous monitoring of changes in regional cerebral oxygenation (rSO2) in the frontal cortex. It is non-invasive, easy to use, and applicable in all patients. Compared to EEG and TCD, that require specialist technician service, NIRS is more cost effective.[133] NIRS has been proven to correlate to SP, EEG and TCD in patients operated under GA.[149-154]

NIRS is increasingly being used in cardiothoracic surgery to monitor cerebral perfusion to reduce the risk of malpositioning of cannula, and to reduce postoperative stroke in patients undergoing cardiac surgery.[155, 156]

Several different NIRS devices are available commercially, but no specific device has been proven to detect cerebral ischemia more accurately than the other. All use similar technology, but differ in a number of properties. For instance, different devices have different cut off values for rSO2. Two of the most used new devices are Foresight-Elite® (CAS Medical Systems Inc., Branford, CT, USA) and INVOS 5100C® (Medtronic, Minneapolis, MN, USA). A comparison between the two showed that Foresight-Elite might have less extracranial contamination than INVOS 5100C, but the clinical significance of this remains unknown.[157]

Little is known about the ability of NIRS to detect cerebral ischemia during carotid clamping. Only a few small studies of NIRS and CEA under local anaesthesia have been performed (see table 4). Thus, there is a need to analyse if NIRS has the ability to predict shunt need for units using selective shunting during carotid endarterectomy, to reduce the risk of ischemic induced perioperative strokes.

Table 4. Major studies of NIRS and CEA under local anaesthesia

Author (year)	No. carotid endarterectomies	Shunt frequency	PPV /NPV	Sens/ spec(%)	Cut-off value	Device	Symptomatic patients	ROC analysis-AUC
Ali et al (2010)[149]	49	16%	86/95	75 / 97.5	>20 %	Invos	NA	NA
Ritter et al (2010)[133]	81	11%	82/100	100 / 96	≥19%	Invos 4100	63%	0.986
Samra et al (2000)[158]	99	10%	33/97	80 / 82	>20 %	Invos 3100	NA	NA
Stilo et al (2012)[159]	100	5%	NA/NA	60 / 25	20 %	Invos 4100	40 %	NA
Rigamonti et al (2004)[154]	50	5%	NA/94	44 / 82	15 %	Invos 4100	NA	NA
Moritz et al (2007)[160]	48	17%	NA/NA	83/83	20 %	Invos 3100	50 %	0.905

3 Participants and Methods

3.1 Study design

The study designs of the four papers are summarized in table 5.

Table 5. Study design

	Study design	Participants	Data source	Outcome
Study I	Retrospective cohort study	Södersjukhuset CAS n = 208, CEA n = 552 National results CAS n = 258, CEA n = 6474	Local hospital quality register and Swedvasc	30-day outcome after CAS and CEA
Study II	Retrospective cohort study	National results CAS n = 323	Swedvasc	Perioperative outcome in relation to urgency of CAS
Study III	Matched cohort study	National results CAS n = 409, CEA n = 748	Swedvasc and In patient registry	Long-term outcome after CAS and CEA
Study IV	Observational Prospective Diagnostic Multi-center study	Södersjukhuset and Gävle hospital n = 185	Consecutive local hospital data	Diagnostic accuracy of predicting cerebral ischemia

3.1.1 Swedish National registry for Vascular Surgery, Swedvasc

The Swedvasc registry was created in 1987 and reached nationwide coverage by 1994. It covers all centres performing carotid endarterectomy and/or carotid artery stenting in the country. Swedvasc is web-based, and the data is registered locally at each center. Procedure data is recorded along with comorbidities, risk factors and demographic data. Follow up data at 30-days include morbidity, complications, and outcome.

Swedvasc is connected to the Swedish National Population Registry, and the mortality data is therefore 100% accurate. In general, the data derived from Swedvasc is highly accurate. One validation of the registry for the period year 2000-2004 showed an external validity on carotid procedures of 93.4%.[161] A more recent international validation of the registry for year 2012, showed an external validity (the carotid procedures registered in the hospital administrative data was compared to what was registered in Swedvasc) on carotid procedures of 98.8%, and

internal validity (data from hospital records was compared to what was registered in Swedvasc) of 97.4 %.[162] In May 2008, an updated version (2.0) of the registry was launched. The new version included minor changes of some of the risk factor definitions (see below).

3.1.2 In patient registry, IPR

The National Board of Health and Welfare register all in-hospital admissions. In Sweden, hardly any hospitals with in-patient care are private, which enables this registry to cover all in-patient health care provided in Sweden. Surgical procedures as well as diagnosis with ICD-10 codes are registered on a personal basis. Hospital reimbursement is based on registered diagnosis and surgical codes, which motivates the hospitals to do correct coding. The IPR was founded in 1964 when the National Board of Health and Welfare began collecting data on somatic in-patient care in six Swedish counties. Today, the national coverage of the IPR is currently almost 100%. The IPR has high validity, and the sensitivity for stroke diagnosis is about 95%.[163]

3.1.3 Definitions

In study I, II, and III we used the current criteria available from Swedvasc for risk factors and comorbidity.

Symptomatic stenosis was defined as all ipsilateral artery events within 180 days prior to the intervention of a patient with carotid stenosis. Non-hemispheric, vertebrobasilar and atypical symptoms, as well as hemispheric carotid symptoms prior 180 days, were regarded as asymptomatic.

Stroke within 30 days includes any new or worsened focal neurologic deficit lasting more than 24 hours, and also intracerebral bleedings.

Alarm symptom = Qualifying event = Index symptom is the neurological symptom resulting in the patient presenting to health care.

Time to intervention is the time period between the alarm symptom/qualifying event/index symptom, until treatment.

Renal insufficiency if serum creatinine ≥150 μmol/L (≥130 μmol/L in study IV).

Hypertension if on antihypertensive medication

Diabetes mellitus if treated with oral antidiabetics and/or insulin.

Pulmonary disease includes chronic obstructive pulmonary disease and asthma.

Heart risk is current heart failure, angina pectoris, or earlier acute myocardial infarction. In Swedvasc 1.0, but not in Swedvasc 2.0, atrial fibrillation was included in the definition.

Current smoker includes quitting within the last 4 weeks.

Smoking in study I includes quitting up to five years ago.

High risk for CAS in study I was defined as two or more risk factors out of: age > 70 years, pulmonary disease and renal insufficiency.

In study I. If a postoperative stenosis was > 50%, it was regarded to be a *restenosis*. A flow velocity of ≥ 1.5 m/s and a velocity quota for internal carotid artery/ common carotid artery of ≥ 2.2 measured at a flow angle of 50-60° was classified as restenosis.[164]

3.2 Purpose, study population, design and outcome

3.2.1 Study I

Tested the hypothesis of whether a high volume centre could achieve better results for CAS as compared to national results.

In this retrospective single-centre review of all consecutive patients treated with CAS at Södersjukhuset between November 25th 2004 and April 27th 2011 were compared to national data from Sweden. Södersjukhuset is, by Swedish numbers, a high volume centre; at that time 45% of all Swedish CAS was performed at Södersjukhuset. These data were compared to results from CEA performed at Södersjukhuset during the same time period, and also compared to patients treated with CAS and CEA elsewhere in Sweden. Comparison data were extracted from Swedvasc. Only procedures for internal carotid stenosis were included. Indications other then stenosis were excluded (trauma, dissections, aneurysms), as were percutaneous transluminal angioplasty without stenting. CAS performed on synchronous arch and or intracerebral stenosis were excluded.

Primary endpoint was 30-day stroke or death and 30-days stroke/death/AMI rate. The secondary endpoint was restenosis after CAS at 1 year.

3.2.2 Study II

Explored whether or not there was a correlation between time from alarm symptoms to CAS and perioperative results. In this retrospective nationwide cohort study, all patients registered in Swedvasc treated with CAS between January 1st 2005, and March 20th 2014 were included. Only procedures for ICA stenosis treated with bare metal stents were included. Patients operated on bilaterally were identified, and if procedures were more than 30 days apart, both operations were included in the analysis. In total 323 procedures were included. All patients were categorized into different groups depending on the interval between qualifying event and intervention: 0-2 days, 3-7 days, 8-14 days, and 15-180 days. To increase power and for comparison with other studies, we did two other time categorizations: 0-7 days, 8-14 day, 15-28 days, and 29-180 days; and 0-7 days, and 29-180 days respectively. Primary outcome was 30-day stroke or death rate. Secondary outcome was the composite endpoint of AMI, stroke, or death at 30 days.

3.2.3 Study III

Examined the long-term results after CAS. For comparative purposes we used a matched cohort treated with CEA. In this retrospective matched cohort study, we included all patients who had CAS performed for symptomatic or asymptomatic carotid stenosis from January 1st 2005, to December 31st 2012 and were registered in Swedvasc. Only primary CAS were included and we used a 7-year retrospective period to identify and exclude earlier operated patients. Excluded were also patients treated with covered stents, PTA solely, or combined procedures. In total 409 patients treated with CAS were included. For comparison with the study group, we used patients operated with CEA (n = 748), matched with respect to age, sex, procedure year, and indication (minor stroke, transient ischemic attack, amaurosis fugax, or asymptomatic). Since every patient in Sweden has a unique personal identification number, we could cross match the whole cohort with the in patient registry. We used International Classification of Diseases- codes I60-69 to identify all strokes during follow up, G45 and G46 for identifying transient ischemic attacks that had been misclassified, and eventually I48 to identify patients with atrial fibrillation. Charts and radiological reports from all in-hospital episodes were retrieved and thoroughly read by two investigators to assess the severity (measured by modified Rankin Scale) and brain territory of the stroke. The investigators were blinded to treatment type. Primary outcome was ipsilateral stroke or death from 31 days after index date to the end of follow up. Secondary endpoints were all causes of mortality, ipsilateral stroke, death, and any stroke or death more than 30 days postoperatively. Since many patients died during follow-up, we did a competing risk analysis, with death as competing risk to ipsilateral stroke after day 31.

3.2.4 Study IV

We compared Near-infrared Spectroscopy and stump pressure as predictor of cerebral ischemia in patients undergoing CEA under LA. In this prospective multicentre study from January 2013 - October 2016, 185 patients from two vascular units (Södersjukhuset and Gävle Hospital) were included.

The patients were evaluated neurologically throughout the operation by the anaesthesiologist and a nurse in collaboration with the vascular surgeon. An intraluminal shunt (Javid or Pruitt-Inahara) was used selectively only if the patient developed new neurological symptoms, or neurologic deterioration as compared to the preoperative state. All endarterectomies were performed or supervised by an experienced vascular surgeon.

The rSO_2 measurement was performed using the NIRS Foresight® oximeter (CAS Medical Systems Inc., Branford, Connecticut). See figure 6.

A 23-Gauge needle was inserted in the common carotid artery and used for stump pressure measurement (mean arterial pressure) after clamping the common carotid artery and external carotid artery. A test clamping for five minutes was performed, and the stump pressure was measured. The change in rSO_2 was measured continuously during the operation and six hours thereafter.

In order to evaluate the ability to predict cerebral ischemic symptoms we used receiver operating characteristic curve (ROC curve) and compared area under curve for the change in rSO2

(ΔrSO2) and stump pressure. An area under the curve (AUC) of 0.5 suggest no discrimination, a value of 1 suggest perfect discrimination. The ROC curve shows the possible sensitivity and specificity for different cut-off points. A cut-off point was chosen for each modality and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were then calculated from this optimal cut-off point with corresponding 95 % confidence intervals. Since missed cerebral ischemia could have fatal consequences, we prioritized high sensitivity for the cut-off point.

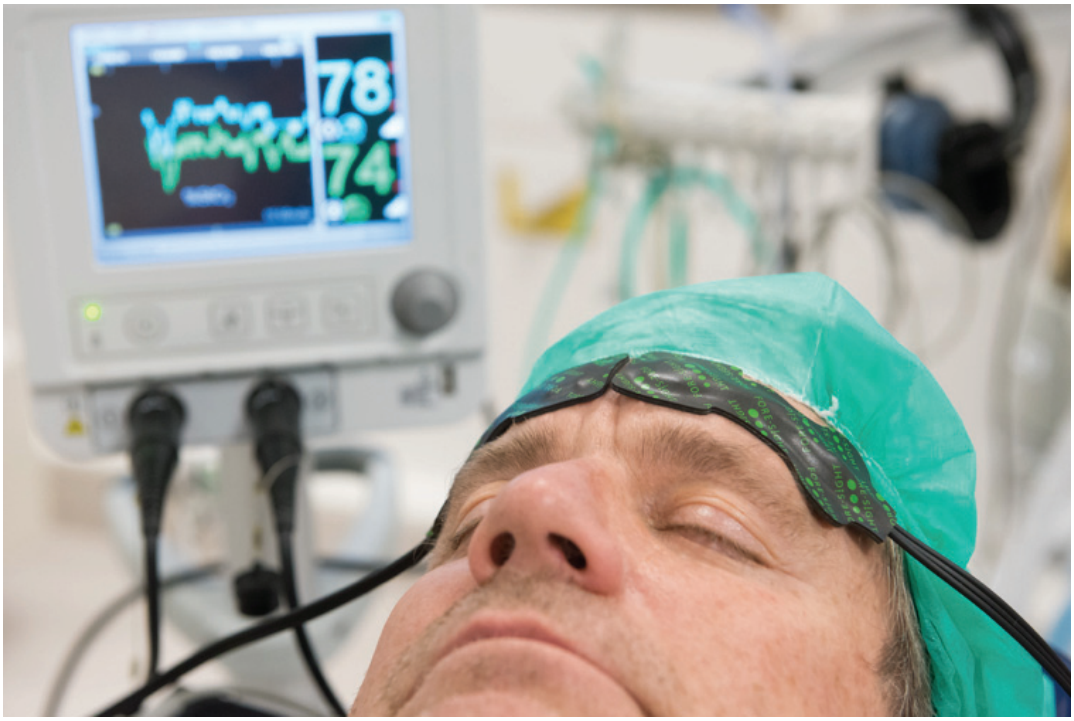

Figure 6. *Measurement with Foresight® oximeter. Two sensors are applied on the patient's forehead, and the rSO2 are registered continuously.*

3.3 Statistical methods

Statistical analysis was mainly performed using the IBM SPSS version 18.0-22.0 (SPSS Inc., Chicago, IL, USA). For competing risk analysis in study III, the software R 3.2.2 was used for competing risk analysis and bootstrap CI calculations.

3.3.1 Study I and II

Continuous data with normal distribution were presented with mean and standard deviation and non-normally distributed data with median and interquartile range. For categorical data a two-sided Fisher´s or Chi square test was used. Student's t-test was used for continuous data. Mann-Whitney U test was used for non-parametric data. The 95% confidence intervals were calculated with the modified Wald method. Statistical significance was set at p-value < 0.05.

3.3.2 Study III

In addition to the statistical analysis used in study I and II, we used the Wald-Wolfowitz test to compare distributions of modified Rankin Scale scores. We calculated cumulative incidences of outcomes from Kaplan-Meier estimates and compared CAS and CEA with the Mantel-Haenszel log-rank test. Standard Cox proportional hazards model was used for outcomes, and models were adjusted for pre-specified covariates known to affect the outcome after CEA and CAS: diabetes mellitus, hypertension, cardiac disease, atrial fibrillation, current smoking, pulmonary disease, and renal insufficiency. Patients who survived without an event were censored.

3.3.3 Study IV

In addition to the statistical analysis used in study I and II we used receiver operating Characteristic curve (ROC curve) and compared the area under the curve for changes in rSO2 and stump pressures. A cut-off value was chosen to prioritize high sensitivity for each modality, and for stump pressure 50 mmHg. Sensitivity, specificity, positive predictive value and negative predictive value with corresponding 95 % confidence intervals were then calculated. We used the Hanley and McNeil´s method to compare ROC curves for NIRS and SP.[165]

4 Results

4.1 Study I

During the study period, 208 CAS and 552 CEA procedures were performed in Södersjukhuset. During the same period, 258 CAS procedures, and 5922 CEAs were performed elsewhere in Sweden.

CAS at Södersjukhuset

In Södersjukhuset, 38% of all carotid procedures were CAS. Comparing the CAS groups, the patients in Södersjukhuset were slightly older and had less heart disease (see table 6).

The most common indications for using CAS were severe comorbidity (27%) or randomization within *ICSS* or *ACST-2* (25 %). All indications for using CAS in Södersjukhuset are presented in table 7.

A protection device was used in all CAS patients in Södersjukhuset. In 57% of the cases, flow reversal (Neuro protection system (NPS); W. L. Gore and Associates, Flagstaff, Ariz, US) was used. The rest were treated with a standard filter. Any stroke or death occurred in 3/118 patients (2.5%) when reversed flow was used and in 3/90 (3.3%) when filter was used, (p = 1.0). When comparing symptomatic vs. asymptomatic carotid stenosis, the stroke or death, the frequency was 2.7% (3/111) and 3.1% (3/97) respectively (p = 1.0).

Ninety percent of the patients had a one year duplex follow up. One patient had an asymptomatic occlusion, 16 patients (10%) had a restenosis at one year, six patients were revascularized, two of whom were symptomatic.

CAS elsewhere in Sweden (Södersjukhuset excluded) and comparison with CAS in Södersjukhuset

CAS was performed at nine other centres. On average 29 CAS (range 1-119) were performed per center (Södersjukhuset excluded). Comparing Södersjukhuset with national Swedvasc data (Södersjukhuset excluded) as shown in table 8, 2.9 % of patients treated at Södersjukhuset had a stroke or died, compared to 7.4 % (p= 0.04). Among asymptomatic patients registered in Swedvasc, 10.9 % (11/101) had a stroke within 30 days, as compared to 2.7 % in Södersjukhuset.

CEA in Södersjukhuset and in Sweden (Södersjukhuset included)

In patients operated with CEA in Södersjukhuset, 4.0% had a stroke or died within 30 days. Stroke and death rates among asymptomatic patients was 3.7%, and for symptomatic patients it was 5.0 %. Corresponding values for CEA registered in Swedvasc including Södersjukhuset was 4.4%, 4.4%, and 4.0% respectively. There were no significant differences between the local and national results with respect to perioperative outcome after CEA (see table 8).

Table 6. Baseline characteristics for CAS patients treated at Södersjukhuset and national Swedvasc data

	Södersjukhuset (n=208)	Swedvasc (n=258)*	p-value †
Male Sex	68% (141)	74% (192)	NS
Age mean (SD)	71 (8.5)	69 (8.3)	0.01
Symptomatic TIA Ischemic stroke Amaurosis fugax Asymptomatic	53% (111) 47% (52) 38% (42) 15% (17) 47% (97)	58% (149) 35% (52) 43% (64) 22% (33) 42% (109)	NS
Days from index symptom until CAS‡,	8 (IQR 5-28)	13 (IQR 6-25)	NS
Smoking	37% (66)	43% (81)	NS
Diabetic	29% (61)	29% (61)	NS
Pulmonary disease	11% (22)	18% (28)	NS
Renal dysfunction (creatinine>150µmol/L)	4% (8)	5% (11)	NS
Heart disease	46% (94)	61% (108)	<0.01
Treated hypertension	81% (169)	81% (173)	NS
High risk CAS # Average risk CAS	35% (72) 65% (132)	41% (56) 59% (80)	NS

NS indicates Non significant; CAS indicates Carotid artery stenting, CEA indicates Carotid endarterectomy; TIA indicates Transient Ischemic Attack.
* Södersjukhuset excluded from national data. † Fisher's test for dichotomous data and t-test for continuous data, Mann Whitney test for waiting time variable. ‡Data available only in swedvasc 2.0. # High risk defined as two or more risk factors out of: age>70 years, heart disease, pulmonary disease, renal dysfunction.

Table 7. Indications for CAS at Södersjukhuset

	% (n)
Randomized within ICSS/ACST2	25 (51)
Restenosis after previous CEA/CAS	11 (22)
Severe comorbidity	27 (56)
Post-radiation therapy	6 (12)
Surgically inaccessible stenosis	7 (15)
Contralateral laryngeal nerve injury	0.5 (1)
Patients preference	8 (17)
Previous neck surgery	1 (2)
No specified reason	15 (32)
Total	100.0 (208)

Table 8. 30-day outcomes in patients treated with CAS at Södersjukhuset compared to Swedish national CAS data, and CEA at Södersjukhuset compared to Swedvasc.

	Carotid Artery Stenting, CAS			Carotid endarterectomy, CEA		
	Södersjukhuset CAS %, (n)	Swedvasc CAS† %, (n)	p-value*	Södersjuk-huset CEA %, (n)	Swedvasc CEA %, (n)	p-value*
Patients, n	208	258		552	6474	
Any stroke	1.9 (4)	5.4 (13/242)	NS	3.8 (21/549)	4.0 (250/6322)	NS
Death	1.0 (2)	2.3 (6)	NS	0.5 (3/552)	0.8 (53/6472)	NS
AMI	1.4 (3)	2.9 (7/242)	NS	2.7 (15/548)	1.8 (113/6314)	NS
Stroke or death	2.9 (6)	7.4 (18/243)	0.04	4.0 (22/549)	4.4 (277/6322)	NS
- Among symptomatic	2.7 (3/111)	4.9 (7/142)	NS	3.7 (16/428)	4.4 (220/5007)	
- Among asymptomatic	3.1 (3/97)	10.9 (11/101)	0.0495	5.0 (6/121)	4.0 (53/1315)	NS
- Among high risk	5.6 (4/72)	16.7 (9/54)	NS			
- Among average risk	1.5 (2/132)	3.9 (3/76)	NS			
Stroke or death or AMI	3.4 (7)	9.5 (23/243)	0.01	6.2 (34/548)	5.8 (368/6321)	NS

NS Non significant; CAS Carotid artery stenting, CEA Carotid endarterectomy; TIA Transient Ischemic Attack.
* Fisher´s exact test. † SÖS excluded from national data

4.2 Study II

During the study period, 323 patients with an average age of 71 years underwent CAS due to symptomatic carotid stenosis. The qualifying neurologic event was TIA (42.7%), minor stroke (36.5%), amaurosis fugax (18.9%), major stroke (1.5%) and crescendo TIA (0.3%). Looking at the median, the intervention was performed 13 days after qualifying event (IQR 7-29). An embolic protection device was used in 90.6% of the patients, most often filter (58%) followed by reversed flow (Neuro Protection System, WL Gore®). Thirteen patients were treated within 2 days from qualifying event, 85 between 3-7 days, 80 patients between 8-14 days, and 145 patients between 15-180 days. There were no major differences between the different groups with respect to comorbidities, protection device used, degree of stenosis, reason for CAS, or postoperative medical treatment (see table 9).

The combined stroke or death rate were similar in the different time periods; 0% in the group treated 0-2 days, versus 4.7% at 3-7 days, 6.3% at 8-14 days, and 4.1% for the patients treated at 15-180 days (p = 0.76). Also in our secondary analysis, with four different time periods the combined stroke and death rate were similar for all subgroups; 4.1% for the group treated 0-7 days, versus 6.3 % treated at 8-14 days, 4.8 % at 15-28 days, and 3.6 % at 29-180 days (Table 10 and 11).

Table 9. Baseline characteristics in relation to time to CAS for 323 patients.

	Time to CAS, days				
	0 to 2	3 to 7	8 to 14	15 to 180	*p*-value
Patients, n	13	85	80	145	
Male sex, n (%)	10(76.9)	58(68.2)	60(74.1)	98(67.6)	0.620
Age, y (SD)	69(6.4)	71(8.7)	72(9.3)	70(8.7)	0.306*
Octogenarians, n (%)	2(15.4)	14(16.5)	17(21.3)	24(16.6)	0.811
Current smokers (N=257), n (%)	2(16.7)	19(30.6)	19(31.1)	27(22.0)	0.350
Co morbidities, n (%)					
Cardiac disease (N=265)	4(30.8)	32(37.6)	29(35.8)	64(44.1)	0.321
Pulmonary disease (N=259)	3(23.1)	9(10.6)	11(13.6)	15(10.3)	0.597
Diabetes Mellitus (N=304)	5(38.5)	21(24.7)	21(25.9)	35(24,1)	0.880
Hypertension (N=303)	10(76.9)	62(73.8)	61(75.3)	108(75,0)	0.939
Renal insufficiency (N=314)	2(16.7)	5(6.0)	5(6.4)	7(5.0)	0.445
Neurologic event, n (%)					
Amaurosis fugax	2(15.4)	15(17.6)	9(11.1)	35(24.1)	0.119
TIA	2(15.4)	37(43.5)	37(46.3)	62(42.8)	0.221
Minor stroke	8(61.5)	30(35.3)	32(39.5)	48(33.1)	0.194
Crescendo TIA	0(0.0)	0(0.0)	1(1.3)	0(0.0)	0.384
Major stroke	1(7.7)	3(3.5)	2(2.5)	0(0.0)	0.052
Ipsilateral stenosis**					0.110
<50%	1(7.7)	4(4.7)	4(4.7)	4(2.8)	
50-69%	2(15.4)	25(29.4)	27(33.8)	46(31.7)	
>=70%	9(69.2)	56(65.9)	49(61.3)	94(64.8)	

Contralateral stenosis (N=316)**					0.961
<50%	9(75.0)	57(67.9)	55(68.8)	92(65.7)	
50-69%	0(0.0)	12(14.3)	9(11.3)	20(14.3)	
>=70%	1(8.3)	8(9.5)	8(10.0)	13(9.3)	
Occlusion	2(16.7)	7(8.3)	8(10.0)	15(10.7)	
Indication for endovascular approach					0.154
RCT	1(7.7)	10(11.8)	10(12.5)	18(12.4)	
Restenosis	0(0.0)	2(2.4)	3(3.8)	18(12.4)	
Previous neck radiation or neck surgery	1(7.7)	9(10.6)	13(16.3)	22(15.2)	
Comorbidity	2(15.4)	28(32.9)	22(27.5)	36(24.8)	
Surgical inaccessible stenosis	3(23.1)	13(15.3)	14(17.5)	16(11.0)	
Patients choice	0(0.0)	3(3.5)	3(3.8)	9(6.2)	
Not specified reason	6(46.2)	20(23.5)	15(18.8)	25(17.2)	
Protection device (N=322), n (%)					0.047
None	2(15.4)	9(10.6)	9(11.3)	10(6.9)	
Occlusion balloon	0(0.0)	5(5.9)	6(7.5)	7(4.8)	
Filter	9(69.2)	38(44.7)	37(46.3)	99(68.3)	
Reversed Flow	2(15.4)	32(37.6)	26(32.5)	26(17.9)	
Postop medication					
Statins (N=303), n (%)	11(84.6)	72(84.7)	64(80.0)	122(84.1)	0.885
Antiplatelet therapy (N=311)					0.603
Single antiplatelet n (%)	2(15.0)	5(5.9)	3(3.8)	15(10.3)	
Dual antiplatelet n (%)	10(76.9)	71(83.5)	67(83.8)	108(74.5)	
Anticoagulation, n (%)	1(7.7)	7(8.2)	4(5.0)	6(4.1)	

CAS indicates carotid artery stenting; TIA indicates Transient Ischemic Attack; RCT indicates randomized controlled trial
P-values were calculated by chi square and t-test(*).**Degree of stenosis according to the NASCET criteria.

In the first half of the study period (Jan 2005 - Aug 2009), 4.9% of the symptomatic carotid stenoses in Sweden were treated by CAS (n = 187) which decreased to 3.4% in the second part. The time from qualifying event to intervention decreased from 15 to 10 days during the study period. The 30-day stroke and death rate increased from 4.9% to 5.9%. In the first half of the study period, nine centres performed CAS, seven of them continued in the second period. None of these differences were statistically significant.

The 30-day stroke and death rate for the whole cohort was 5.9% in patients without EPD, 4.2% with the use of filter and 4.0% in patients with reversed flow (p=0.895). Corresponding rates for patients treated within 7 days (n=98) was 16.7%, 2.1% and 2.6% respectively (p=0.062).

Table 10. Procedural adverse events

	Time to CAS (days)				
	0-2, N = 13 n (%)	3-7, N = 85 n (%)	8-14, N = 80 n (%)	15-180, N = 145 n (%)	p-value*
Stroke	0 (0.0)	3 (3.5)	5 (6.3)	5 (3.5)	0.626
AMI	0 (0.0)	3 (3.5)	2 (2.5)	2 (1.4)	0.602
Deaths	0 (0.0)	0 (0.0)	3 (3.8)	1 (0.7)	0.126
Stroke/death (95%CI)	0 (0.0) (0-26.6)	4 (4.7) (1.5-11.9)	5 (6.3) (2.4-14.1)	6 (4.1) (1.7-8.9)	0.757
Stroke/death/AMI (95%CI)	0 (0.0) (0-26.6)	7 (8.2) (3.8-16.3)	6 (7.5) (3.2-15.7)	8 (5.5) (2.7-10.7)	0.640

AMI indicates Acute Myocardial Infarction; CAS indicates Carotid Artery Stenting; CI indicates Confidence intervals.
*p-values were calculated by Chi square

Table 11. Procedural adverse events (secondary time classification)

	Time to CAS (days)				
	0-7, N=98 n (%)	8-14, N=80 n (%)	15-28, N=62 n (%)	29-180, N=83 n (%)	p-value*
Stroke	3 (3.1)	5 (6.3)	2 (3.2)	3 (3.6)	0.706
AMI	3 (3.1)	2 (2.5)	1 (1.6)	1 (1.2)	0.688
Deaths	0 (0.0)	3 (3.8)	1 (1.6)	0 (0.0)	0.091
Stroke/death (95%CI)	4 (4.1) (1.3-9.0)	5 (6.3) (2.4-14.2)	3 (4.8) (1.1-13.8)	3 3.6(0.1-10.5)	0.864
Stroke/death/AMI (95%CI)	7 (7.1) (3.3-14.3)	6 7.5(3.2-15.7)	4 6.6.5(2.1-15.9)	4 4.8(1.5-12.1)	0.900

AMI indicates Acute Myocardial Infarction; CAS indicates Carotid Artery Stenting; CI indicates Confidence intervals.
*p-values were calculated by Chi square

4.3 Study III

The final study population in study III consisted of 1157 patients: 409 CAS and 748 CEA (control group matched with respect to indication, sex, age and procedure year), see flow chart below (figure 8). The majority (69%) was treated due to symptomatic stenosis. During follow up, the cohort had 394 hospitalization episodes with stroke or TIA diagnosis registered in the in patient registry. After retrieving 393 out of 394 charts, 133 postprocedural strokes were identified, and 12 patients had more than one stroke. Within 30 days, 3.4% in the CAS group and 3.2% in the CEA group had a stroke or died, p = 0.86. After the perioperative phase, 96/409 patients treated with CAS and 121/748 with CEA had a new ipsilateral stroke or died, corresponding to a rate of 7.25 (95% CI 5.91 – 8.82) per 100 person-years in CAS-patients compared to 4.53 (95% CI 3.78 – 5.40) in CEA-patients. In the Cox regression analyses, patients treated with CAS had an overall higher risk, HR 1.63 (95% CI 1.24-2.13), for ipsilateral stroke or death after day 30 compared to those treated with CEA in crude analysis. The matching of the control group was close, and the groups were fairly similar with respect to comorbidities (see Table 12). We adjusted the Cox regression analysis for known confounding factors. The adjusted risk was essentially unchanged, HR 1.59 (95% CI 1.16-2.19), see Table 13. All outcomes regarding stroke after 30 days showed higher risk for CAS, whereas all cause mortality was similar for CAS and CEA. We also performed a competing risk analysis (with death as competing risk to ipsilateral stroke), which showed an even more pronounced increased risk for stroke. The severity of stroke, measured by modified Rankin Scale was similar in both groups. The Kaplan Meier curves for major outcomes are presented in Figure 7a-7d.

Table 12. Baseline characteristics

	Type of intervention						
	CAS	(%)	(95%CI)	CEA	(%)	(95%CI)	P-value
Patients, n	409			748			
Male sex, n (%)	300	73.3	(68.9 – 77.7)	552	73.8	(70.6 – 76.9)	0.889
Age, years (SD)	70.0	8.7	(69.4 – 70.6)	70.3	7.8	(69.7 – 70.9)	0.628*
Current smokers	96	23.5	(19.5 – 27.8)	190	25.4	(22.4 – 28.7)	0.477
Co morbidities, n (%)							
Cardiac disease	164	40.1	(35.4 – 44.9)	257	34.4	(31.0 – 37.8)	0.055
Pulmonary disease	47	11.5	(8.7 – 14.9)	59	7.9	(6.1 – 10.0)	0.055
Diabetes mellitus	105	25.7	(21.6 – 30.1)	149	19.9	(17.2 – 22.9)	0.026
Hypertension	298	72.9	(68.4 – 77.0)	554	74.1	(70.8 – 77.1)	0.676
Renal insufficiency	13	3.2	(1.8 –5.2)	30	4.0	(2.8 – 5.6)	0.520
Indication, n (%)							0.953†
Asymptomatic	133	32.5	(28.1 – 30.2)	231	30.9	(27.7 – 34.3)	
Amaurosis fugax	44	10.8	(8.0 – 14.1)	82	11.0	(8.9 – 13.4)	
TIA	122	29.8	(25.5 – 34.4)	227	30.3	(27.1 – 33.7)	
Minor stroke	110	26.9	(22.8 – 31.4)	208	27.8	(24.7 – 31.1)	

CAS = carotid artery stenting; CEA = carotid endarterectomy; TIA = Transient Ischemic Attack. CI = confidence interval. P-values were calculated by Fisher´s exact test, * t-test, and † chi square. Confidence intervals were computed with Mid-P Exact test for proportions and t-test for age.

Table 13. Cumulative incidence at 5 years and hazards for stroke and death in patients treated with carotid stenting (CAS) compared to carotid endarterectomy (CEA)

	CAS (n=409)		CEA (n=748)		Hazard ratio (95% CI) of CAS relative to CEA	
Outcome	*n*	Cum inc (%)* (95% CI)	*n*	Cum inc (%)* (95% CI)	Unadjusted†	Adjusted for confounders‡
Ipsilateral stroke from day 31	28/398	9.4 (6.2 – 14.1)	20/733	2.9 (1.7 – 5.1)	3.22 (1.67 – 6.21)	3.40 (1.53 – 7.53)
Ipsilateral stroke or death from day 31	95/394	30.8 (25.3 – 37.1)	120/724	20.7 (17.2 – 24.7)	1.71 (1.26 - 2.31)	1.59 (1.15 - 2.18)
Any stroke or death from day 31	105/391	34.2 (28.5 – 40.8)	135/722	23.6 (19.8 – 27.8)	1.62 (1.22 – 2.16)	1.49 (1.10 – 2.00)
Death from day 31	76/404	25.7 (20.5 – 31.9)	106/737	18.61 (15.3 – 22.6)	1.36 (0.99 – 1.87)	1.20 (0.84 – 1.72)

All patients alive without an event at 30 days after procedure are included in the analysis. Time starts at day of procedure.
*Cum inc=cumulative incidence at 5 years. † Cox model stratified on matching pairs. ‡ Cox model adjusted for smoking, pulmonary disease, diabetes, hypertension, heart disease, renal disease, atrial fibrillation, and stratified on matching pairs.
CI=confidence interval.

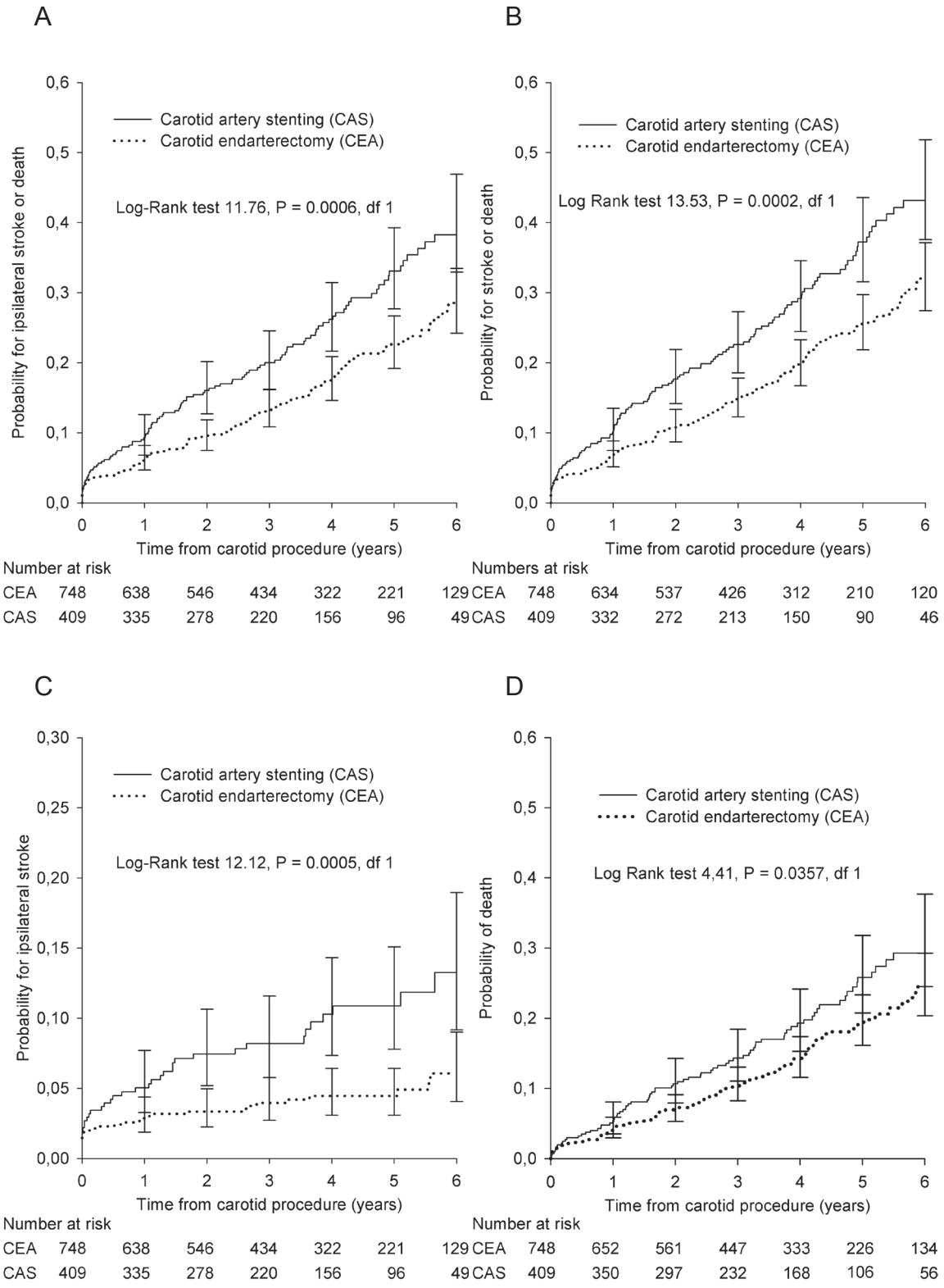

Figure 7. *Kaplan-Meier curves for major outcomes. A. Ipsilateral stroke or death for > 30 days after treatment. B Any stroke or death for > 30 days after treatment. C Ipsilateral stroke for > 30 days after treatment. D Death. The numbers below the panels are the numbers of patients in each group that are event free and still at risk.*

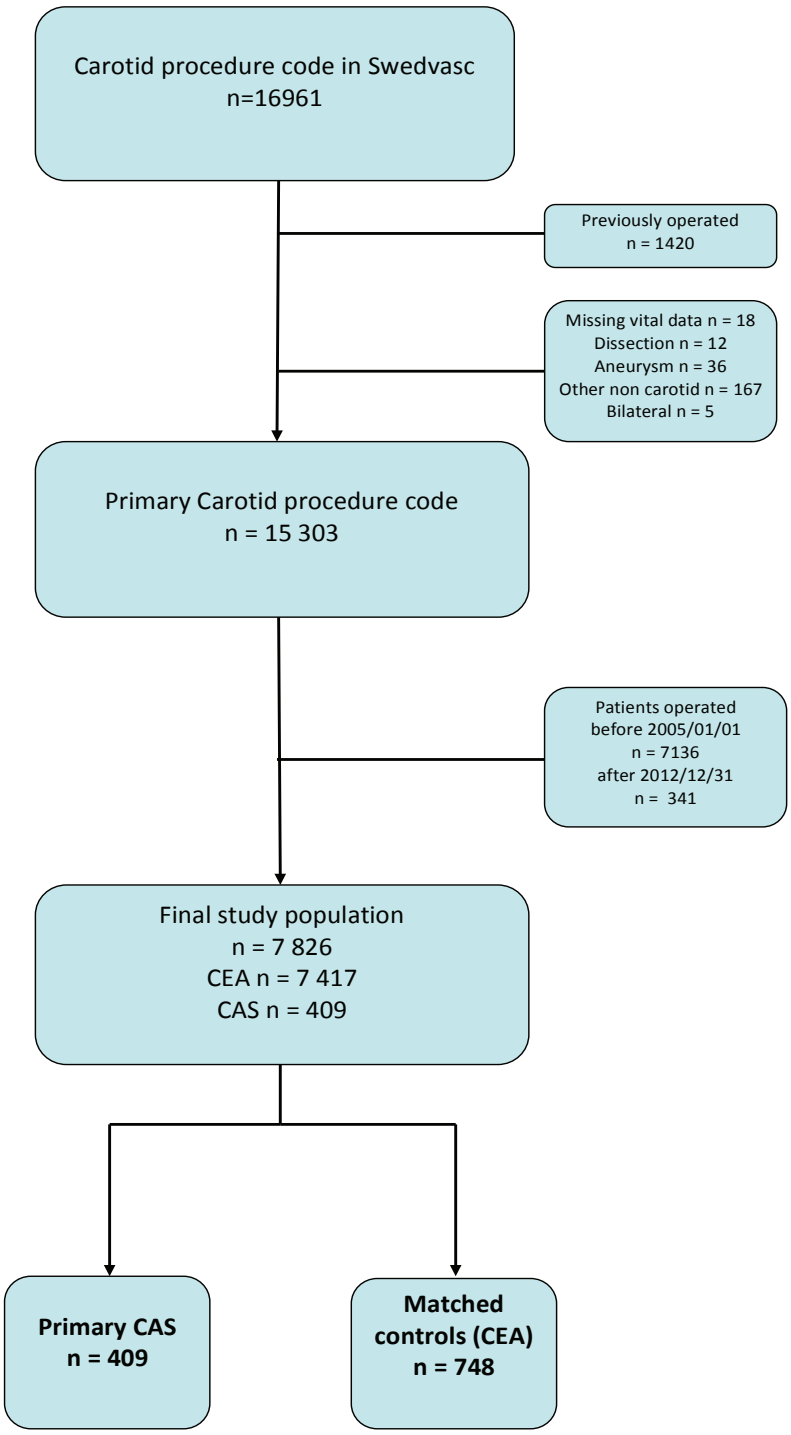

Figure 8. *Flow chart*

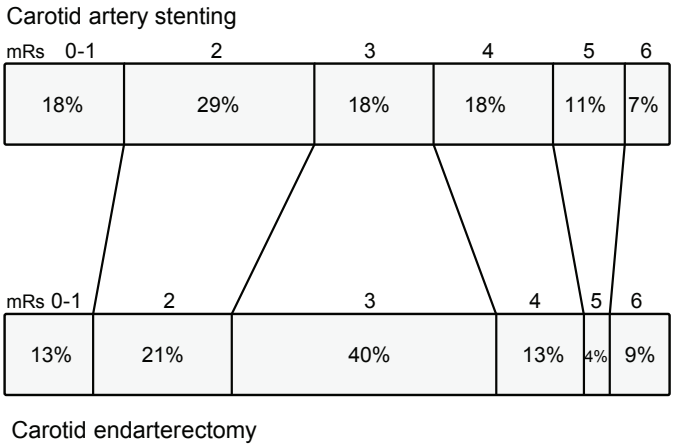

Figure 9. *Modified Rankin Scale when admission to hospital during follow up*

4.4 Study IV

We prospectively included 185 patients. During carotid clamping, twenty patients developed neurologic symptoms (10.8%). Baseline characteristics were similar for those who developed neurological symptoms and those who did not (Table 14). Mean stump pressure (MAP) was lower in the group that developed neurologic symptoms than in those who did not, 34 ± 19 mmHg versus 55 ± 17 mmHg ($p < 0.01$). A box plot of all SP is presented in figure 10. The relative change in rSO2 on the operated side (ΔrSO2 ipsi) decreased more after clamping in the group that developed neurologic symptoms than in those who did not, -15 ± 7% versus -4 ± 6% ($p<0.01$). The change in rSO2 during the endarterectomy is presented in Figure 11 and the operative data in Table 15. After shunt insertion, the rSO2 on the ipsilateral side returned to equivalent level as before clamping, ΔrSO2 increased with 12 ± 7% after 1 minute; and 14 ± 8% after 5 minutes, as compared to measurements during clamping. The AUC for ΔrSO2 and SP was 0.92 (95 % CI 0.87-0.95) and 0.81 (95 % CI 0.74-0.86) respectively. Pairwise comparison of ROC curves using Hanley and McNeil´s method was difference between areas 0.11(95% CI -0.02-0.24). See figure 12 for the ROC curve.

Using SP ≤ 50 mmHg as the cut-off value, we found an 85% (95% CI 64-95) sensitivity and 54% (95% CI 46-61) specificity for SP to detect cerebral ischemia. The PPV was 19% (95% CI 12-28) and NPV 96% (95% CI 90-99). We prioritized high sensitivity when choosing a cut-off value for ΔrSO2. A value of 9% decrease was identified to be optimal for detecting cerebral ischemia. With this cut-off value, the sensitivity was 95 % (95% CI 76-99) and specificity 81 % (95% CI 75-86). The PPV was 38% (95% CI 26-52) and NPV 99% (95% CI 96-100%). See table 16.

Neurologic deterioration during carotid clamping was detected in one patient with a ΔrSO2 ≥ 9%, and three patients with a SP > 50 mmHg. The ROC curve is presented in figure 12.

Three patients (15%) in the group that developed neurologic symptoms during clamping had a stroke within 30 days, compared to 1 patient (0.6%) among those who did not develop neurological symptoms during clamping ($p = 0.004$). See table 17 for 30-day outcome.

Table 14. Baseline characteristics for the 185 patients

Variable	Neurologic symptoms during CEA n, (%) N=20	No-neurologic symptoms during CEA n, (%), N=165	p-Value
Sex, male	11 (55.0)	115 (68.5)	0.313
Side, Right	11 (55.0)	79 (47.9)	0.638
Age (years; Mean; sd)	74; 7	71; 8	0.631*
Diabetes Mellitus	3 (15.0)	27 (16.4)	1.000
Hypertension	18 (90.0)	127 (77.0)	0.254
Heart disease	7 (35.0)	50 (30.3)	0.798
Pulmonary disease	3 (15.0)	18 (10.9)	0.706
Renal insufficiency	3 (15.0)	13 (7.9)	0.389
Current smoker	0 (0.0)	27 (16.4)	0.049
Symptomatic	19 (95.0)	138 (83.6)	0.206
Indexsymptom			0.145
Amaurosis fugax	1 (5.0)	40 (24.2)	
TIA	11 (55.0)	56 (33.9)	
Crescendo TIA	0 (0.0)	2 (1.2)	
Minor stroke	7 (35.0)	40 (24.2)	
Asymptomatic	1 (5.0)	29 (17.6)	
Time from symptom to operation (days); median; IQR	5.0; 8.0	7.0; 8.0	0.306†
Degree of ipsilateral stenosis			0.872‡
20-49%	1 (5.0)	12 (7.3)	
50-69%	4 (20.0)	38 (23.0)	
70-99%	15 (75.0)	115 (69.7)	
Degree of contralateral stenosis			0.357‡
<20%	11 (55.0)	91 (55.2)	
20-49%	2 (10.0)	34 (20.6)	
50-69%	5 (25.0)	18 (10.9)	
70-99%	2 (10.0)	18 (10.9)	
Occlusion	0 (0.0)	4 (2.4)	

CEA indicates Carotid endarterectomy; IQR, Interquartile Range; TIA, transient ischemic attack; sd, standard deviation

Fisher exact test if other method is not presented *T test, †Mann Whitney U test, ‡Chi-square test

Table 15. Operative data; mean value and standard deviations (sd).

No- neurologic symptoms during clamping, N = 165	Pre clamp- Mean (sd)	Clamp 1 min Mean (sd)	Clamp 5 min Mean (sd)	Post Clamp 1 min Mean (sd)	Post Clamp 5 min Mean (sd)
MAP (mmHg)	95 (15)	100 (15)	101 (15)	95 (14)	92 (14)
rSO2ipsi (%)	72 (5)	69 (6)	69 (6)	72 (5)	73 (10)
ΔrSO2 ipsi* (%)	Ref	-4 (6)	-4 (5)	1 (5)	1 (5)
rSO2kontra (%)	73 (5)	72 (5)	72 (5)	73 (5)	73 (5)
SP (mmHg) range		55 (17) 3-110			

Neurologic symptoms during clamping, N = 20	Pre clamp- Mean (sd)	Clamp 1 min Mean (sd)	Shunt inserted 1 min (n=16) Mean (sd)‡	Shunt inserted 5 min (n=16) Mean (sd)‡	Post Clamp 1 min Mean (sd)	Post Clamp 5 min Mean (sd)
MAP (mmHg)	88 (11)	92 (20)			96 (15)	96 (18)
rSO2ipsi	71 (5)	61 (6)	67 (6)	68 (5)	72 (5)	73 (5)
ΔrSO2 ipsi (%)	Ref.	-15 (6)*	12 (7)†	14 (8)†	1 (6)*	2 (6)*
rSO2kontra (%)	73 (5)	71 (7)	71 (6)	72 (6)	73 (8)	71 (6)
SP (mmHg) range		34 (19) 0-73				

MAP indicates Mean arterial pressure (systemic blood pressure); SP, Stump pressure; sd, standard deviation

*Relative change in rSO2 compared to pre clamp †Relative change in rSO2 compared to during clamping 1 min ‡Twenty patients developed neurological symptoms during clamping, 16 of whom received a shunt.

Table 16. Results of NIRS and stump pressure to detect cerebral ischemia compared to awake testing.

	Neurologic symptoms during CEA (n=20)	No-neurologic symptoms during CEA (n=165)	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV(%) (95% CI)
ΔrSO2 < 9.0 %*	1	134	95 (76-99)	81 (75-86)	38 (26-52)	99 (96-100)
ΔrSO2 ≥ 9.0 %*	19	31				
SP > 50 mmHg	3	84	85 (64-95)	54 (46-61)	19 (12-28)	96 (90-99)
SP ≤50 mmHg	17	73				

CEA indicates Carotid endarterectomy; SP, stump pressure; NPV, Negative predicted value; PPV, Positive predicted value.

*Relative change in rSO2 after carotid clamping compared to before carotid clamping

Table 17. 30-day results

Outcome within 30 days	All patients N=185 n (%)	Neurologic symptoms during clamping, N=20 n (%)	No-neurologic symptoms during clamping, N=165 n (%)	p-value*
AMI	3 (1.6)	0 (0.0)	3 (1.8)	1.000
TIA	5 (2.7)	0 (0.0)	5 (3.0)	1.000
Stroke	4 (2.2)	3 (15.0)	1 (0.6)	0.004
Death	1 (0.5)	0 (0.0)	1 (0.6)	1.000
Stroke/death	5 (2.7)	3 (15.0)	2 (1.2)	0.009

AMI indicates acute myocardial infarction; TIA, transient ischemic attack

*Fisher exact test. P-value for comparing patients with and without neurologic symptoms.

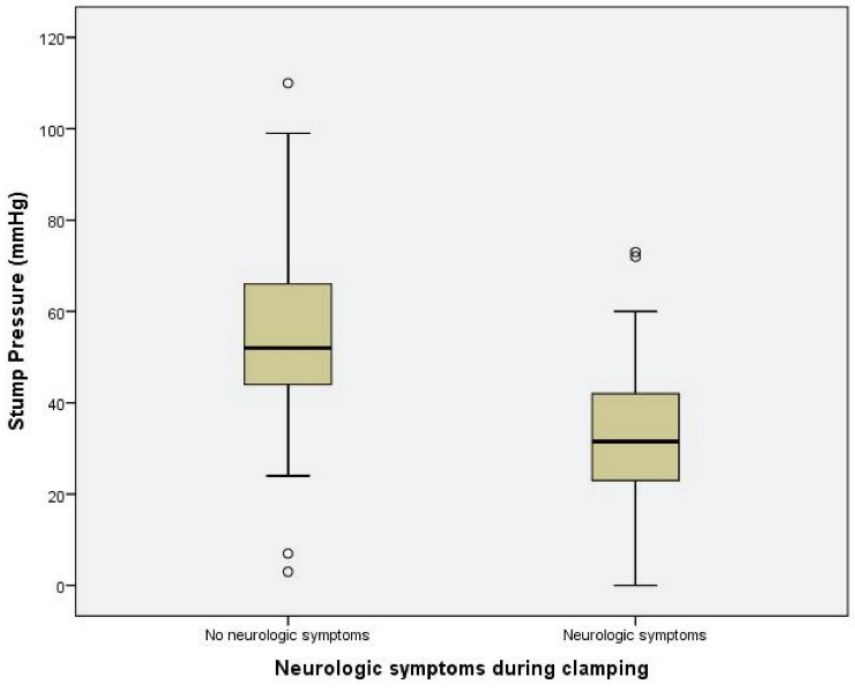

Figure 10. *Box plot of stump pressure*

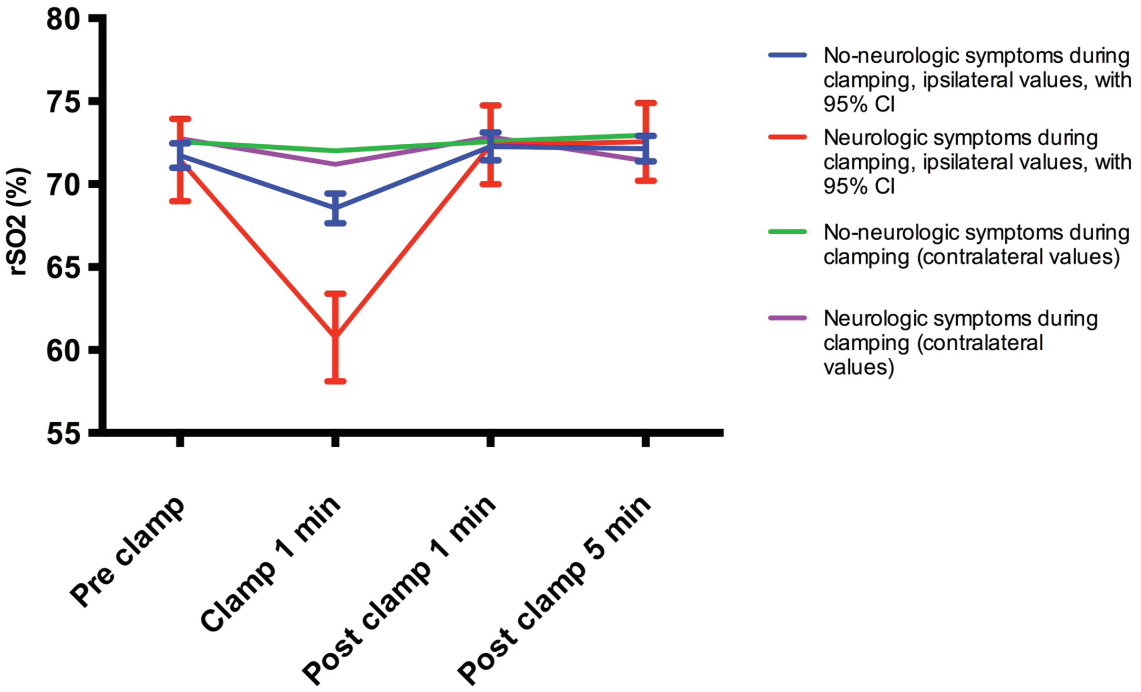

Figure 11. *Change of rSO2 during different stages of endarterectomy*

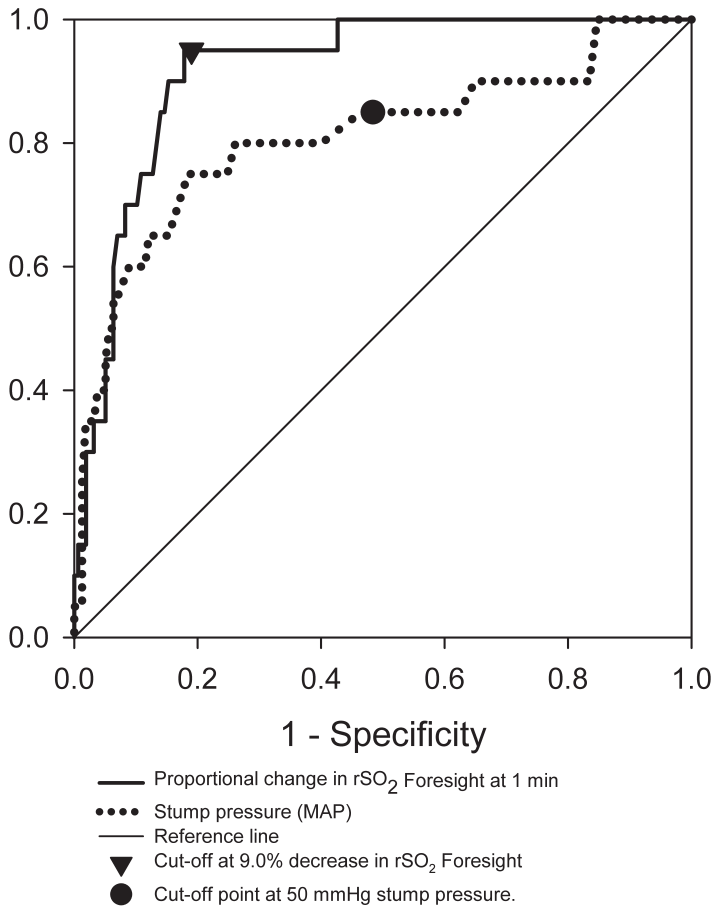

Figure 12. *ROC curve to evaluate the ability of NIRS and stump pressure to predict cerebral ischemia during carotid clamping. Cut-off value for ΔrSO2 ≥ 9.0 %, cut-off value for stump pressure ≤ 50mmHg*

5 Discussion

5.1 General discussion and main findings

5.1.1 The relevance of patient volume

Our results in study I show that in a centre with experienced staff and high volumes of CAS, you can produce comparatively good results. But the nationwide stroke or death rates at 30 days are higher among patients treated with CAS than CEA. This is not unique for Sweden, as similar findings are reported from several registry studies where it has been shown that the 30 day results for CAS is not as good as in the randomised controlled trials.[78] A significant observation in our study is the 10.9% stroke or death rate at 30 days for patients treated with CAS for asymptomatic stenosis outside Södersjukhuset.

Comparing the stroke and death rate among symptomatic patients treated with CAS in Södersjukhuset and Sweden (2.7% and 4.9% respectively) with CAS patients in earlier randomised controlled studies SAPPHIRE (29% symptomatic patients) was 5.5%[79], EVA-3S 9.6%[80], SPACE 7.7%[81], ICSS 8.5%[82] and among symptomatic patients in CREST 6.0%[83] the Swedish national results are not so extreme.

Very few centres in Sweden performed CAS before 2004, and Södersjukhuset started with CAS in November 2004, thus our data includes a learning curve. Nine centres performed CAS in 2004-2008, seven centres after 2008 and only six after 2010. In the early phase the total stroke and death rate after all CAS was 6.4 %. There has probably been an adaption to the early poor results, and some of the smaller units have stopped performing CAS, and the results for CAS improved during the study period. A possible explanation of the low frequency of complications in our single centre is due to high volume and experience of the team (only two operators performed all interventions). Also, the 10.9% stroke and death rate among asymptomatic patients in Sweden outside Södersjukhuset were on a very limited number of patients (11 out of 101 patients) in 5 different centres.

Limited experience among interventionists participating in some of the randomised controlled trials has been proposed as an explanation for the high rate of complications in e.g. EVA-3S and ICSS as compared to CREST, where 30 CAS was required for credentialing. It has been shown in several studies that the stroke and death rate among experienced operators was lower than for inexperienced operators, and an annual volume of at least 6 CAS/operator has been proposed.[166-169] A systematic review confirms that the results of CAS have improved over time, and a learning curve is likely to exist, and in active CAS units it may take around two years before stroke and death rate declines to around 5%.[170] In contrast to this, analysis within EVA-3S, patients treated by investigators that had done more than 50 carotid stent procedures had higher rate of stroke and death than those who had experience of fewer than 50 carotid stentings. Likewise, in the ICSS, the more experienced centres had a higher stroke or death rate.[171]

However, this could be 'chance', or possibly due to the treatment of more diseased patients. It is unlikely, that centres performing very few stenting procedures per year could achieve similar results to high volume centres. With the low number of CAS being performed every year in Sweden, they should be centralized into only a very few centres.

In previous meta-analyses, the superiority of CEA disappeared for patients younger than 70 years[172-174] We also found CAS to be better in younger patients in Södersjukhuset, but the difference was small (2.4% vs 4.0% for stroke/AMI/death, p = 0.7) .

The alarming 10.9% stroke or death rate among CAS for asymptomatic stenosis raises questions, as well as the stroke or death rate of 4.0% among 1315 asymptomatic CEA patients, thus questioning the benefits of this operation.

This study has some limitations. The sample size on CAS procedures is small and does not allow us to compare outcome adjusted for comorbidities with national data. The data from Swedvasc has high validity, but is not as complete as the single centre series, and have missing values on baseline characteristics and 30-day outcome. But the missing outcome data in Swedvasc would probably increase the frequency of complications since missing data in general tends to have less favourable results.

The strength of our single centre cohort is that it is a consecutive series. We have no missing cases for the 30-day follow-up, and the combination with the population registry makes the validity for the stroke and death variable very reliable.

5.1.2 Timing of carotid intervention

-The time relation between neurologic symptoms and intervention.

In our nationwide study, we did not find any differences between patients who underwent CAS within two days or within one week from alarm symptom. Although relatively few patients were treated within the first two days after alarm symptom, no major peri-procedural complication or death occurred among those patients.

The available data regarding risk of CAS stratified for time between neurologic symptoms and intervention is very limited. The CAPTURE registry reported an increased rate of stroke and death when CAS was performed within two weeks after onset of neurologic symptoms compared to other symptomatic patients (OR 2.15, 95%CI 1.14-4.08).[166] Small single-centre series have reported disparate results: Setacci et al., showed a stroke and death rate of 3.8% if patients were treated within 48 hours,[123] Wach et al., 7.1% for patients treated within 48 hours[119], whereas Topakian et al., reported a 26% stroke and death rate for patients treated within 14 days, compared to 1.9% if treated after 14 days.[121] The largest analysis of stenting and time relation from qualifying event to treatment is pooled data from SPACE, ICSS, and EVA 3-S with data on a total of 1434 CAS procedures, where only 138 of those were within 1 week. They found that the risk of CAS, compared to CEA, was especially high within the first week after symptoms, RR 3.44 (95% CI 1.0-11.8).[120]

For CEA the results diverge as well: a meta-analysis and a large cohort study could not identify a higher perioperative stroke- and death rate for CEA in the subacute phase.[116, 175] Some single-

centre series have demonstrated good results for CEA in the acute phase [177-180] whereas other have shown inferior results in the acute phase.[112,176] One Swedvasc study showed very high incidence of perioperative complications for patients operated with a CEA within 48 hours.[113] In contrast, two recent studies could not support that time after index event influenced the perioperative stroke or death rate.[114, 115]

However, since the early risk of recurrent stroke for patients with symptomatic stenosis with recent neurologic event with medical therapy solely is so high, [93, 94, 97, 103-105, 181-183] there might be justification in urgent treatment, even if the complication rate would be increased. [184, 185]

Possibly the diverging results between studies regarding time relation between neurologic symptoms and carotid intervention is due to different study populations, inconsequent terminology and low power.

The strength of our study is that it is a large population-based study investigating the risks of urgent CAS. It has national coverage and reflects the clinical reality in a country. Data quality on outcomes is good with few missing values. Small numbers of patients that had undergone a procedure within 2 days from onset of symptoms limits our report with respect to this urgent group. Still, it illustrates that the complication rate after CAS, performed within 1 week from alarm symptom, is within acceptable limits.

5.1.3 Embolic protection device

The flow reversal system has some potential advantages compared to filters and the early reports had low stroke rate.[186, 187] Proximal balloon occlusion systems produce less micro emboli registered with TCD than filters.[188] But on the other hand, proximal occlusion is reported to produce more emboli than filters on post op MR in a small trial.[189]

In study I, we could not detect any difference in outcome stroke or death at 30 days if reversed flow or filter was used among patients treated in Södersjukhuset (2.5% vs 3.3%, p=1.0).

In the acute phase after a stroke and TIA, the plaques are in general unstable, and it takes around two weeks for the plaque to stabilize. In this acute phase, reversed flow would be even more appealing, than passing a fresh thrombus with a stiff guide wire. Patients treated without EPD had an increased rate of stroke or death within 30 days compared to filter and reversed flow. In the group treated with no EPD and within 7 days from onset of symptoms (n=12), the stroke and death rate was 16.7% compared to filter 2.1% and reversed flow 2.6% (p=0.062). Due to low numbers, none of these differences were statistically significant.

5.1.4 Long-term results after carotid artery stenting

In our nationwide cohort study, including all primary CAS procedures in Sweden, we observed an increased risk for late stroke or death after CAS as compared to CEA. There were no differences with respect to death between the groups, and the increased risk in the CAS group was mainly due to an increased risk of ipsilateral stroke. The matched design, the similar mortality rate and the small changes in hazard ratios after adjusting for confounders indicate a low degree of confounding and bias.

The two year follow up after SPACE, the five-year results of the EVA3-S and the 7.4 year follow up from CREST trial study showed no significant difference between CAS and CEA with respect to ipsilateral stroke in the post-procedural period.[87, 89, 92] However, in the ICSS long-term follow-up, where patients were followed for a median of 4.2 years, there was a higher incidence of total stroke after 30 days in the CAS group, HR 1.53 (95% CI 1.02-2.31). In the ICSS, the difference was, mainly driven by strokes occurring in the contralateral or vertebrobasilar territory.[190] This could be explained by chance, but as can be seen in the ACST-1, the risk of contralateral stroke was reduced after CEA, and probably some hypoperfusion strokes could be avoided.

The CAVATAS trial, SPACE and EVA 3-S have all reported an increased rate of restenosis after CAS compared to CEA.[86-88] In the ICSS long-term follow-up, no difference in the long-term rates of severe restenosis or occlusion was found.[190] While restenosis in general was a significant risk factor for recurrent ipsilateral stroke in the CREST trial, there was no difference in rate of restenosis between CAS and CEA (12.2% and 9.7%) after 7.2 years.[89, 90]

There is no uniform protocol for follow-up after CEA or CAS in Sweden, and the Swedvasc registry does not include information about surveillance details after treatment. Accordingly, the natural course of recurrent stenosis after CEA and CAS cannot be studied or adjusted for in our study. Nevertheless, restenosis may be one explanation for the inferior results of stenting shown here.

The present study has some limitations. The two groups, although matched, cannot compete with data from randomized controlled trials. The baseline characteristics were fairly similar in the two groups, but both measured and unmeasured differences between the groups may have affected the results.

Another limitation is the lack of information on the rationale behind the chosen treatment method. Indications, such as hostile neck or anatomically high stenosis, may confound our results. On the other hand, it is likely that such confounding factors would affect the short-term more than long-term outcomes.

The strengths of this study are the nationwide, real-world nature of the data combined with high reliability of mortality data and low number of missing data on stroke outcomes (1/394). In addition, the size of the study makes the risk of a type II statistical error less likely.

Adjusting for possible confounders at baseline, such as diabetes, heart disease, pulmonary disease and atrial fibrillation did not alter the hazards substantially. The CEA group was matched with respect to age, sex, procedure year, and indication (minor stroke, transient ischemic attack, amaurosis fugax, or asymptomatic). The all-cause mortality did not differ between the groups, which supports the suggestion that CAS patients were comparable to CEA patients at baseline. Moreover, there were no differences in antithrombotic medication or history of atrial fibrillation between the CAS and the CEA groups at the time of stroke events > 30 days after surgery, thus a difference in strokes caused by cardio-embolism is not likely.

Our results differ from the long-term results in the RCTs and one can only speculate on the mechanisms behind this. One concern with the RCTs is that patients and centers are highly selected, causing questionable generalizability. Regarding the long-term results from CREST,

only 64% of the patients gave consent for the long-term follow up, and 52% were asymptomatic.[89] A systematic review of registry data found higher stroke/death rates after CAS than after CEA in the perioperative period. The adverse events after CEA were similar in the registries to the RCTs, whereas CAS had a significantly higher proportion of adverse events, compared to the RCTs.[78] Although the mechanism is unclear, the "real world" long-term results after CAS could be inferior to those in the RCTs.

5.1.5 Shunting during carotid endarterectomy

In this prospective multicentre trial, decrease in rSO2 was more accurate than stump pressure in predicting cerebral ischemia during clamping of the carotid artery. With a 9% decrease in ΔrSO2 as compared to pre-clamping, the sensitivity was 95%, and specificity 81%, and a NPV of 99%. Corresponding values for stump pressure with a cut-off value of ≤ 50 mmHg was 85%, 54%, and 96%. It is possible to increase the sensitivity, but with the disadvantage of lower specificity. With a 5% decrease in rSO2, the sensitivity is 100%, specificity 51%. To achieve 95% sensitivity with SP, the specificity would have been unacceptably low, 16% (cut-off 73mmHg).

The use of shunting in CEA is debated. Some surgeons prefer routine shunting while others advocate selective use. Not more than 10-15% of all patients undergoing endarterectomy develop neurological symptoms as a sign of cerebral ischemia when operated on under local anaesthesia. Thus, in a shunt-all policy 85-90% of the patients are shunted unnecessarily.[129-133, 149, 154, 158-160]

Our results show that if 50 mmHg is used as cut-off level for shunt use, nearly half of the patients would have been shunted, and still, three patients, with neurologic deterioration during clamping would have been missed (false negative). Three missed patients out of 20 may imply that 15% of the patients that would have needed a shunt would not have gotten it! That is similar to the results from Evans et al.,[131] who found 3/13 shunt cases had a SP > 50 mmHg, while Calligaro et al., and Hans et al., reported less false negative results (3/34 and 3/32 respectively).[129, 132] The lower incidence of false negative results presented by Calligaro et al., and Hans et al., is probably due to the low rate of symptomatic patients in their series since symptomatic patients are probably more susceptible to cerebral ischemia during clamping.

Only a few small studies have been published comparing NIRS with awake testing. Depending on the cut-off value different sensitivities and specificities have previously been reported.[133, 149, 154, 158-160] In our study, we only had one false negative (0.5%) with NIRS, and the sensitivity was 95%. This is an important benefit of the method compared to SP. Ritter et al., had similar sensitivity with a cut-off value of 19 % measured with INVOS 4100®(Troy, MI, USA).[133] The high sensitivity and negative predictive values are further supported by findings of Pennekamp et al., and Mauermann et al., in patients operated under general anaesthesia compared to EEG.[151, 152] We did not have enough power to prove a statistically significant difference for the ROC curves for NIRS and SP (95%CI -0.02-0.24). However, to achieve 95% sensitivity for SP, which is a clinically acceptable level, the specificity would have been 16% (95% CI 10-47). An additional advantage with the NIRS compared to SP is the possibility of continuous monitoring during endarterectomy and of shunt function dur-

ing clamping. After shunt insertion, the rSO2 increased by 14 ± 8 % five minutes after shunt insertion as compared to during clamping.

The study-population consisted of 84% symptomatic patients, and the median time from symptom to operation was six days. Taking this into account, we present good perioperative results with an overall 30-day stroke or death rate of 2.7%. Interestingly, in the group that developed neurologic symptoms during carotid clamping, three patients (15%) had a stroke, as compared to only one patient (0.6%) amongst those who did not develop symptoms ($p = 0.004$). None of the strokes were caused by a known shunt problem. Although these results should be interpreted with caution due to the small numbers, patients who develop neurological symptoms during carotid clamping might have an increased risk of suffering a perioperative stroke despite the use of a shunt. Calligaro et al., also observed an increased risk of perioperative stroke in this group: 5.9% versus 0.9%.[129]

To our knowledge, this is the largest study of NIRS in patients under LA and also the largest cohort comparing SP and NIRS. Compared to earlier studies of SP we present a high proportion of symptomatic patients that were treated shortly after an alarm symptom.

An existing occlusion of the contralateral carotid artery has been reported to be a risk factor for low SP and consequently shunt need.[132, 191, 192] In the present study, only four patients (2.2%) had a contralateral occlusion. None of them developed neurological symptoms, but using 9% cut-off value for NIRS, two out of four would have been predicted falsely positive. Using SP ≤ 50 mmHg as cut-off for shunting, three out of four would have been falsely predicted as positive. The numbers are too small to draw any conclusions, but in this subgroup with contralateral occlusion, it seems to be difficult to predict cerebral ischemia. Some patients with contralateral occlusion may have been chosen for operation under general anaesthesia with routine shunt use by the treating surgeon. The same could be true for patients with larger structural infarcts found on preoperative CT scans.

There are some limitations in our study. One concern is if our findings could be extrapolated to patients under general anaesthesia since autoregulation is lost. One shortcoming with the NIRS technique is the sole measurement of rSO2 of the superficial brain cortex, thus ischemia in deeper brain structures could be missed. On the other hand our results do not show any shortcoming of NIRS compared to stump pressure in this respect. Several different NIRS devices are available commercially, all employing similar technology, but differ in a number of properties. Accordingly, alternative devices will probably show variability in different optimal cut-off values. Only a small number of patients developed neurological symptoms during clamping, which makes our results uncertain, and there is a need for larger studies to confirm our results.

5.2 Methodological considerations

Random errors cause imprecise results whereas systematic errors affect the validity and lead to wrong conclusions.

Bias is a process at any stage of inference that produces results that systematically deviates from the true values.

Bias and errors may have, to some extent, affected our studies.

5.2.1 Selection bias

If the association between exposure and outcome differs between the subjects in a study and subjects not in the study, the study population, fails to represent the population for which the study is intended to target, there is a selection bias.

In study I, there is an obvious risk for selection bias. In a high volume centre with more experienced personnel, the experience of choosing cases suitable for CAS (with less risk for complications) is obviously higher as compared to in less experienced centres.

In study III, the indication for choosing treatment with CAS or CEA is lacking. Previous radiation therapy could be associated with poorer outcome and risk of restenosis and could have been selected for CAS therapy.

In study IV, only 2.2% of the patients had an occlusion of the contralateral carotid artery, most likely a selection bias, since these patients are reported to be at a higher risk for the need of a shunt. Patients with larger infarcts on CT scan might have been operated under general anaesthesia with a routine shunt. Patients with severe neurologic symptoms could have problems to understand study information and thus not be able to give informed consent. This selection would probably not affect the internal validity of the test but may affect the external validity (generalizability) of the test.

5.2.2 Information bias

Information bias occurs when the study variables are falsely measured or the data is badly collected. *Misclassification* is a common information bias measurement error, which in turn is divided into differential and non-differential misclassification. *Differential misclassification* is when the misclassification in the compared groups differs, which could bias the estimate. In *non-differential misclassification*, the proportion of data with error is the same between the groups that are compared, and the results would not be biased but could be hidden or diluted.

Outcome after carotid surgery that is reported by the surgeon who performed the operation tends to be better than if follow-up is performed by someone without any relation to the surgeon.[193]

In study II, we measured the time from qualifying event to operation to see whether it is safe to perform CAS early after neurologic symptoms. The date for the qualifying event or alarm symptom is defined as the date the patient had the neurological event for which he/she sought

medical advice, and not the latest neurologic event. More informative for this type of study would have been time from latest event to CAS but this information was not registered in Swedvasc earlier.

In study III, we cannot rule out the possibility that some patients could have had a stroke at home or in an institution, not being admitted to a hospital. If so, the number would probably be low and not related to treatment (i.e. non-differential misclassification).

In study IV, there were instructions for how to measure stump pressure, but in some case there might have been an error in the measurements (e.g. clamp might not occlude the artery properly). Also, the NIRS technique solely measures rSO2 in the superficial brain cortex, and ischemia in deeper brain structures could be missed.

5.2.3 Confounding

Factors that causes mixing of effects and that are associated with both exposure and outcome and not in the causal pathway are called confounding factors.

In study I, risk factor profile between patients treated with CAS at Södersjukhuset and elsewhere in Sweden differed. The sample size of CAS at Södersjukhuset was relatively small, and we were not able to adjust for these confounders.

In study III we adjusted for most of the known confounders. Although the two groups were closely matched with similar comorbidities, and the fact that we adjusted for confounders, there might still be some unmeasured hidden variables and thus residual confounding.

5.2.4 Precision

A type I error is an incorrect rejection of the null hypothesis; a type II error is incorrectly accepting the null hypothesis.

In study I, the low number of complications makes it difficult to exclude that the differences between CAS in Södersjukhuset and those reported in Swedvasc for stroke or death were due to chance alone, and thus the interpretation of the result could be a type I error.

In study II, only 13 patients were intervened upon within 48 hours, and 85 patients within 3-7 days. These small numbers limits the report, and a type II error cannot be excluded.

6 Conclusions

- ✓ Carotid artery stenting is not as safe as carotid endarterectomy from a national perspective. Nevertheless, our data shows that it is possible to achieve acceptable results in a consecutive selective case series.

- ✓ Carotid artery stenting performed within 1 week after onset of a neurologic event is not associated with an additional risk of suffering from a perioperative complication as compared with those treated subsequently.

- ✓ Carotid artery stenting has an increased long-term risk of stroke and death as compared to carotid endarterectomy. This increased risk is mainly explained by an increased rate of ipsilateral stroke following the peri-procedural period indicating that carotid artery stenting is not as durable as carotid endarterectomy for the long-term treatment of carotid artery stenosis.

- ✓ Near-infrared spectroscopy is a highly sensitive monitoring tool with acceptable specificity in predicting cerebral ischemia and the need for shunting during carotid endarterectomy, and clearly superior to stump pressure.

7 Future Perspectives

Even though few surgical procedures are as examined as treatment for carotid stenosis, there are several areas in which further research can lead to improvements for patients with symptomatic and asymptomatic carotid artery stenosis:

Could development of CAS technology such as new embolic protection devices and stents (e.g. biodegradable stents covered with ultrathin membrane) and CAS technique (e.g. direct puncture of the CCA) lead to improvement of the perioperative results and long-term efficacy and even out the gap between CAS and CEA?

What is best treatment for asymptomatic carotid stenosis and what subgroup will benefit from intervention?

When is “optimal timing” for carotid intervention, and how soon after neurologic event should CEA/CAS be performed?

Will general health improvement and future advances in medical therapy require that the RCTs for symptomatic stenosis will be repeated?

Will future NIRS, after technical improvement, be the method of choice for selective shunting in CEA under general anaesthesia?

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