Carotid Artery Stenosis

Surgical Aspects

BJÖRN KRAGSTERMAN

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Abstract

Randomised controlled trials (RCT) have demonstrated a net benefit of carotid endarterectomy (CEA) in stroke prevention for patients with severe carotid artery stenosis as compared to best medical treatment. Results in routine clinical practice must not be inferior to those in the RCTs. The carotid arteries are clamped during CEA which may impair the cerebral perfusion.

The aim of this thesis was to assess population-based outcomes from CEA, investigate risk factors for perioperative complications/late mortality and to evaluate effects of carotid clamping during CEA. In the Swedish vascular registry 6182 CEAs were registered during 1994-2003. Data on all CEAs were retrieved, analysed and validated. In the validation process no death or disabling stroke was unreported. The perioperative stroke or death rate was 4.3% for those with symptomatic and 2.1% for asymptomatic stenosis (the latter decreasing over time). Risk factors for perioperative complications were age, indication, diabetes, cardiac disease and contralateral occlusion. Median survival time was 10.8 years for the symptomatic and 10.2 years for the asymptomatic group.

Tolerance to carotid clamping during CEA under general anaesthesia was evaluated in 62 patients measuring cerebral oximetry, transit time volume flowmetry and stump pressure. High internal carotid artery flow before clamping and low stump pressure was associated with decreased oxygenation after clamping suggesting shunt indication.

In 18 patients undergoing CEA, jugular bulb blood samples demonstrated significantly altered levels of marker for inflammatory activation (IL-6) and fibrinolytic activity (D-dimer and PAI-1) during carotid clamping as compared to radial artery levels. This indicates a cerebral ischaemia due to clamping although clinically well tolerated.

In conclusion, the perioperative outcome after CEA in Sweden compared well with the RCTs results. Tolerance to carotid clamping may be evaluated by combining stump pressure and volume flow measurements. Although clinically tolerated clamping may induce a cerebral ischaemic response.

Keywords: carotid endarterectomy, carotid artery stenosis, carotid clamping, cerebral ischaemia

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MRA of a caroid artery stenosis.
The picture kindly provided by Johan Wikström,
Department of Radiology, Uppsala University Hospital.
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<tr>
<td>ACAS</td>
<td>Asymptomatic carotid atherosclerosis study</td>
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<td>ACST</td>
<td>Asymptomatic carotid surgery trial</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
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<tr>
<td>CEA</td>
<td>Carotid endarterectomy</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CCA</td>
<td>Common carotid artery</td>
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<td>DSA</td>
<td>Digital subtraction angiography</td>
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<td>ECA</td>
<td>External carotid artery</td>
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<td>ECST</td>
<td>European carotid surgical trial</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>GSM</td>
<td>Grey scale media</td>
</tr>
<tr>
<td>ICA</td>
<td>Internal carotid artery</td>
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<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>NASCET</td>
<td>North American symptomatic carotid endarterectomy trial</td>
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<td>NIRS</td>
<td>Near-infrared spectrometry</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>SBI</td>
<td>Silent brain infarction</td>
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<tr>
<td>SEP</td>
<td>Somatosensory evoked potentials</td>
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<tr>
<td>SP</td>
<td>Stump pressure</td>
</tr>
<tr>
<td>TIA</td>
<td>Transitory ischaemic attack</td>
</tr>
<tr>
<td>TCD</td>
<td>Transcranial Doppler</td>
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</table>
Introduction

Background
Stroke is the abrupt onset of focal neurological symptoms of a presumed vascular aetiology. These symptoms are the result of sudden death of brain tissue due to ischaemia subsequent to compromised blood flow. The cerebral blood flow may be impaired due to occlusion or rupture of the intra- and extracranial vessels. In the western world stroke is one of the leading causes of morbidity and mortality.

In Sweden stroke is one of the most common causes of hospitalisation and every year approximately 25-30 000 patients suffer from a stroke and an additional 5-6 000 suffer from a transitory ischaemic attack (TIA) [1, 2]. In the population approximately 20 000 patients are disabled by their neurological deficits and another 80 000 have non-disabling symptoms [3]. Hence, it is the most common cause of disability and the third leading cause of death in Sweden.

The aetiology of stroke includes both cerebral haemorrhage and cerebral infarction, and the majority of these strokes (~85%) are of ischaemic origin [1]. Approximately 15-25% of ischaemic strokes are due to lesions in the extracranial or major intracranial arteries[3-5]. Atherosclerotic plaques are predominantly located at arterial bifurcations, and if situated in the internal carotid arteries the circulation to the brain may be compromised. If a carotid atherosclerotic plaque ulcerates it may dislodge emboli, or stimulate to formation of thrombosis with subsequent embolism, most frequently into the area of distribution of the middle cerebral artery (MCA).

Stroke prevention is primarily based on medical treatment, but in some situations surgical treatment is the method of choice. Medical treatment to reduce the overall cardiovascular risk includes antiplatelet medications, statins (with several beneficial effects in addition to lowering lipids), anticoagulation for atrial fibrillation, smoking cessation, control of hypertension and metabolic control in the diabetic patients.

The role for surgical treatment of severe carotid artery stenosis in stroke prevention, both primary and secondary, has been established in large randomised controlled trials (RCT) [6-11]. However, the outcome both in short-(perioperative results) and long-term (durability and survival) must be optimised to achieve most overall benefit from the procedure. In Sweden 600-700 carotid endarterectomies (CEA) has been performed annually over the
last ten years. Approximately 90% of these have been for symptomatic lesions. During the last 2-3 years the numbers of patients undergoing CEA, especially for severe stenosis without recent neurological symptoms, has increased [12].

It seems very important to analyse the results of CEA, when implemented as a widespread treatment modality in the general population, for both symptomatic and asymptomatic indication.

Definitions of neurological events

Stroke is by the World Health Organisation (WHO) defined as clinical symptoms of focal and/or global disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than vascular.

Transitory ischemic attack (TIA) is defined as a reversible event with symptoms lasting up to 24 hours.

Stroke can be classified into different subgroups, with regard to duration or severity of functional impairment, but there are great inconsistencies in the terms used.

In Swedvasc stroke duration is divided into transient stroke with symptoms from 24 hours to 30-days, and permanent stroke with neurological deficits still persistent at 30-days.

After CEA the term perioperative stroke is frequently used, but can vary both regarding type and duration of the event. However, it mostly includes ipsilateral neurological deficits persisting for more than 24 hours and presenting during the period from surgery to 30-day follow-up.

Regarding the functional impairment after stroke, many different scales and definitions have been suggested. Classification into non-disabling or disabling stroke is one commonly practised. Non-disabling stroke may be defined as minimal focal neurological deficit, persisting for more than 24 hours but not leading to disability or significant impairment in activities of daily living. Disabling stroke may be defined as a neurological deficit lasting for more than 30 days and inducing a change of lifestyle. In the often cited modified Rankin scale non-disabling stroke represents grade ≤ 2 and disabling stroke grade ≥ 3 [13, 14].
Table 1. The modified Rankin scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Disability</th>
<th>Stroke definition used in the thesis</th>
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<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities.</td>
<td>Non-disabling stroke</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability requiring some help, but able to walk without assistance</td>
<td>Disabling stroke</td>
</tr>
<tr>
<td>4</td>
<td>Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.</td>
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Another stroke classification is based on the origin or possible source of embolism, usually divided into four different categories; cardiac (e.g. atrial fibrillation), large artery strokes (lesions in the aortic arch, extracranial vessels or the major intracranial branches), small vessel disease / lacunar infarctions (occlusion of minor intracranial branches) and others (e.g. carotid dissection or sinus thrombosis).

Among the large artery strokes, which may represent 15-25% of all ischemic strokes, carotid artery lesions are the dominant source of origin [4]. Some confusion may exist with regard to the definition of relevant vessel and affected side. The relevant vessel is selected based on the location of atherosclerotic lesions, the clinical features of the neurological deficit and/or imaging of the ischaemic lesion. Neurological deficits due to carotid artery stenosis (carotid territory events) are mainly embolisations in the distribution of the (middle) cerebral artery, whereas vertebrobasilary events are those localised in the posterior circulation. An ipsilateral event refers to an ischemic lesion on the same side as the relevant vessel, and is to be distinguished from the side affected with neurological deficits.

Ocular symptoms such as amaurosis fugax or retinal embolism are attributed to the ipsilateral carotid artery stenosis due to direct embolisation to the ophthalmic artery.
Symptomatic versus asymptomatic carotid artery stenosis

A patient classified as having a symptomatic carotid artery stenosis has recently, in most definitions suffered a central neurological event with symptoms within the last 6 months (and often imaging of cerebral ischemia), corresponding to the relevant vessel [7-9, 11].

Patients with an asymptomatic carotid artery stenosis have either never had any symptoms or had symptoms at least 6 months previously, corresponding to the side of the carotid artery stenosis [6, 10]. There is a group of patients often referred to as having non-hemispheric symptoms and this may include vertebrobasilary events (ie posterior circulation events) and non-specific symptoms (eg dizziness or vertigo). In the literature the classification of these patients varies widely, and they may be included in the symptomatic or asymptomatic cohort with or without specific definitions.

Imaging

Internal carotid artery (ICA) stenosis can be measured using different imaging modalities. The “golden standard” used in the majority of the large randomised trials is (selective) digital subtraction angiography (DSA). However, different measurement methods have been used for grading the degree of stenosis. The two most referred methods are the ones used in the ECST and NASCET, which have different measuring points of the stenosis and are therefore not directly comparable. In Figure1 the two methods are demonstrated and correlated.
Degree of internal carotid artery stenosis with different measuring methods

<table>
<thead>
<tr>
<th>NASCET (%)</th>
<th>ECST (%)</th>
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<tr>
<td>40</td>
<td>70</td>
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<tr>
<td>50</td>
<td>75</td>
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<td>60</td>
<td>80</td>
</tr>
<tr>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>80</td>
<td>91</td>
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\[
\text{NASCET(\%)} = \frac{1-B}{A} \times 100 \\
\text{ECST(\%)} = \frac{1-B}{C} \times 100
\]

Figure 1. Carotid stenosis defined according to NASCET or ECST methodology, the differences in measurement technique and comparisons of grading.

Since angiography is an invasive technique with a periprocedural risk for neurological events of up to 1.2% (ACAS) [6], other non-invasive modalities have been established such as magnetic-resonance-tomography angiography (MRA), computed-tomography (CT) angiography and duplex ultrasonography. With MRA and CT angiography the stenosis is measured with similar morphological criteria as DSA, whereas duplex classification of the degree of stenosis is based upon measuring blood flow velocities (as shown in Figure 2), which is then related to defined stenosis criteria [15]. Duplex has been established as an easy accessible and reliable [16] method that in addition to stenosis grading also may define plaque morphology (further discussed below) [17-19].
CEA of symptomatic carotid artery stenosis

Patients with carotid territory neurological events within the last 6 months, who have a severe internal carotid artery stenosis, should be considered for CEA given that they are medically fit for surgery and have functional benefit. RCTs have demonstrated an overall benefit for CEA compared to the best medical treatment for this group of patients.

The absolute risk reduction (ARR) of stroke or death in the two largest and most influential trials was in the European Carotid Surgery Trial 8.5% at 5 years and 19.4% at 3 years in the North American Symptomatic Carotid Endarterectomy Trial (in both trials 70-99% stenosis) [7-9, 11].

However, as the trials differed in measurement of the degree of stenosis as well as the outcome, the results are not possible to directly compare. In a re-analysis of these trials together with the Veterans Affairs trial (VA309) [20], with reassessments of original angiograms and using the same criteria for stenosis (NASCET-method) and for outcome, the overall effect of CEA was investigated. In these pooled data the 5-year ARR of ipsilateral ischemic stroke and/or operative stroke or death was 5.9% (60-69% stenosis), 15.8% (70-79% stenosis), 17.7% (80-89% stenosis) and 32.4% (90-99% stenosis, not including near-occlusion) [21]. The “number needed to treat” (NNT) to prevent one event at 5 years is ≤6 for a stenosis ≥70%. The perioperative stroke or death rate was 7.1% in pooled data.

It is essential in routine clinical practise to assess complication rates and to continually evaluate patient selection, in order to guarantee that the results
of CEA are at least as good when performed outside strictly controlled clinical trials.

CEA of asymptomatic carotid artery stenosis

Patients with a stenosis of the internal carotid artery, but without any medical history of neurological events from the artery’s distribution area within the last 6 months, have also been the subject for large RCTs. In these trials a net benefit for CEA over the best medical treatment has been demonstrated, but the risk reduction was less compared to trials on symptomatic stenoses [6, 10, 22-24].

The estimated ARR at 5 years for ipsilateral stroke (including operative stroke or mortality) was in the Asymptomatic Carotid Artheriosclerosis Study (ACAS) 5.9% (5.1% vs 11.0%) and in the Asymptomatic Carotid Surgery Trial (ACST) 5.4% (6.4% vs 11.8%), or a little more than 1% per year [6, 10]. The NNT to prevent one event at 5 years were 17 in ACAS and 19 in ACST.

One parameter that has a pronounced impact on the net benefit for these patients is the perioperative combined stroke or death rate, which was 2.3% in ACAS and 2.8% in ACST, with the same caveats as for CEA of symptomatic stenosis about the generalisation of these results in routine clinical practice.

Technical considerations of CEA

Patch angioplasty is one of the technical aspects of CEA that has often been debated and studied during the last decade. In a Cochrane review [25] it was shown that routine patching conferred a reduction in perioperative stroke/thrombosis and late stroke/restenosis compared to routine primary closure. However, many surgeons use patch angioplasty selectively, the rationale for this based on their own experience and peroperative judgements (which are difficult to standardise in an RCT).

The technique of eversion endarterectomy (EEA) has also been the focus in several trials. In a recent Cochrane review a possible decrease in restenosis was found but no association with early or late stroke or mortality risks could be identified [26].

An important issue is the possible impact of anaesthesia techniques on the outcomes from the procedure. A Cochrane meta-analysis of non-randomised trials showed a benefit for CEA under local anaesthesia (LA) vs general
anaesthesia, but this was not demonstrated when analysing the previous randomised trials [27]. Thus, this uncertainty has motivated a large ongoing randomised trial (GALA).

One of the obvious advantages with LA is the direct possibility to assess tolerance of carotid clamping and the need for shunting. If the procedure is done under general anaesthesia with selective shunting, other methods for determining shunt indication are used depending upon availability and preferences of surgical centres and individual surgeons.

Tolerance of carotid clamping

The intolerance of carotid clamping during CEA may result in reversible or irreversible cerebral ischaemia depending on the degree and the duration of inadequate cerebral perfusion. Factors which can contribute to the extent of impairment caused by the clamping are the collateral blood circulation (e.g. circle of Willis) and various other compensatory mechanisms (e.g. blood pressure and oxygenation). As mentioned above, when CEA is performed under general anaesthesia and with the use of selective shunting, an indirect method to assess an adequate cerebral perfusion is essential.

Well established methods for neuromonitoring include transcranial Doppler (TCD) with blood velocity measurements in the middle cerebral artery and detection of (micro)embolisation [28, 29], electroencephalography (EEG) measuring cerebral activity [30], somatosensory evoked potentials (SEP) with measurement of cerebral responsiveness [31] and cerebral oximetry with near-infrared spectroscopy (NIRS) which monitors changes in cerebral oxygenation [32, 33].

Another method used for deciding on shunt indication is carotid artery stump pressure, which indirectly assesses the capacity of the collateral circulation [34]. A method less well documented is transit time flowmetry, which measures volume blood flow in the carotid arteries with readings evaluating the ICA flow before clamping and after reperfusion [35, 36]. This method also offers a possible quality assessment of the CEA.

Cerebral ischaemia and reperfusion during CEA

Cerebral ischaemia induced by carotid clamping during CEA may induce an activation of inflammatory mediators and alterations in haemostasis [37-39]. Although the patient clinically may tolerate clamping well, a relative re-
gional ischaemia might develop due to inadequate perfusion and/or embolism, with resulting reversible or irreversible cerebral injury [40-42].

The patients with symptomatic carotid artery stenosis may also demonstrate altered levels of markers for the inflammatory and haemostatic systems after their cerebral insult [43-45]. What is less investigated is how the regional relative ischaemia during surgical clamping affects inflammatory and haemostatic markers, when measured in the local venous outflow from the intracranial structures.

Inflammation

Inflammation is the tissue response to injury which is mediated by a variety of factors. It may be characterised by an acute and a chronic phase. In both phases of inflammation a group of secreted polypeptides known as cytokines are key modulators in a complex network of interactions.

Among the cytokines, interleukin-6 (IL-6) is involved in both the acute phase (pro-inflammatory cytokine) and in mediating humoral response in chronic inflammation. IL-6 is a pleiotropic glycoprotein that in experimental and clinical studies has been a predictor of cerebral ischaemia/reperfusion injuries. Elevated levels have also been found in patients with acute stroke [46-48].

Another pro-inflammatory pathway is the CD40-CD40 ligand system. CD40 is an important activation receptor on many cells (e.g. lymphocytes, monocytes, macrophages, fibroblasts, dendritic-, smooth muscle- and endothelial cells) whose engagement via the ligand (CD40L or CD154) induces or upregulates inflammation, releases pro-inflammatory cytokines or connective tissue-degrading enzymes and procoagulant activity [49-51].

Increasing evidence also support the role for CD40-CD40L in atherogenesis and plaque instability [52-55]. Furthermore, the transmembrane protein CD40L is upregulated during acute stroke which persists for at least 3 months [56].

Coagulation and fibrinolysis

Coagulation is rapidly initiated when tissue factor (TF) is exposed to factor VII. The activated TF/VII complex activates factors IX and X. Factor Xa converts prothrombin to thrombin and prothrombin fragment 1+2 (F1+2),
which is greatly facilitated by the presence of coenzyme Va. F 1+2 with a t½ of 90 min is a stable marker of coagulation (factor Xa activity) and altered levels has been demonstrated for patients with carotid atherosclerosis and stroke [57-59]. Thrombin acts on fibrinogen to form soluble complexes (soluble fibrin). In Figure 3 the final steps of the coagulation pathway are shown (schematic presentation).

**Figure 3.** Schematic presentation of the coagulation pathway

Fibrinolysis (Figure 4) is initiated through the release of tissue plasminogen activator and urokinase from endothelial cells following injury and in response to thrombin. They cleave plasmin from plasminogen bound to fibrin within the clot. The control pathway is primarily set in motion by plasminogen activator inhibitor – 1 (PAI-1) which prevents tPA from activating circulating plasminogen to plasmin. PAI-1 is a marker of the fibrinolytic process and has a t½ of approximately 2 hours [60]. Plasmin degrades fibrin into D-dimers and fibrin degradation products (FDP). D-dimer acts as a marker of both fibrin generation (coagulation), degradation (fibrinolysis) and is also linked to the acute phase response.
Swedvasc

The Swedish Vascular Registry (Swedvasc) started as a regional registry in 1987 and has national coverage since 1994, thus the registry includes all surgical centres performing CEA in the country.

Prospective data on basic demography and risk factors, together with details of surgical techniques and postoperative outcome are registered. Follow-up includes perioperative (30-day) complications and outcome, as well as overall outcome and patency at one year (neurological events are not registered specifically after 30 days).

The registry has been validated both internally and externally on several occasions [61]. A validated vascular registry with national coverage can provide population based data on outcome and alterations over time for vascular interventions, eg CEA.
Aims

In patients undergoing carotid endarterectomy;

- to demonstrate population-based results on perioperative morbidity and mortality after CEA (*paper I-II.*)
- to analyse risk factors for complications after CEA in a population (*paper I-II.*)
- to evaluate alterations over time in outcome after CEA for asymptomatic stenosis (*paper II.*)
- to assess the long-term survival for patients undergoing CEA for asymptomatic stenosis (*paper III*)
- to evaluate different methods for predicting the need for shunt during carotid clamping in patient undergoing CEA under general anaesthesia (*paper IV*).
- to characterise the effects of carotid clamping on regional cerebral perfusion and reperfusion, with regard to markers of the inflammatory, coagulation and fibrinolytic systems (*paper V*).
Subjects and methodology

Papers I-III:
Swedvasc has coverage of all centres performing CEA in Sweden since 1994. In retrospective reviews data on all registered CEAs were retrieved for two time periods. From January 1994 until December 1996 for a combined cohort and case-control study of perioperative outcome and risk factors (paper I). From January 1994 until December 2003 for studies with special focus on patients operated on for asymptomatic carotid artery stenosis concerning perioperative outcome (paper II) and long-term survival (paper III).

The studies were ethically approved by the registry review board, which according to Swedish law has the authority concerning registry data.

Swedvasc validation
Validation of the registry with regard to CEA registrations was performed with different methods;

1. a case-control review of neurological complications by independent observers (paper I)
2. a random sample of ~ 10 % of all procedures for asymptomatic stenosis (paper II)
3. a target validation of unclear complication registrations among the patients operated on for an asymptomatic stenosis (paper II)
4. a cross-match with the National Population-registry for accurate data on mortality and date of death (papers II-III)
5. an external validation by cross-match with the In-Patient Registry (IPR) for registrations of CEA during the year 2003 (papers II-III).
Schematic figure of the validation processes are shown in Figure 5.

Figure 5. The five different validation procedures of the Swedvasc registrations for CEA during 1994-2003.

Swedvasc definitions

Risk factors in Swedvasc have had the same definitions throughout the study-period:

- Cerebrovascular disease; all present or previous neurological events (stroke, TIA or AF).
- Diabetes mellitus; treatment with insulin, oral medication or diet.
- Hypertension; medication or a diastolic blood-pressure ≥ 110.
- Cardiac disease; previous myocardial infarction, atrial fibrillation, heart-failure, angina pectoris, coronary artery by-pass, operation for valvular disease or signs of ischemia on ECG.
- Previous vascular surgery; open or endovascular procedure or amputation for vascular disease.
- Renal insufficiency; a serum creatinine > 150 µmol/l.
- Smoking; regular smoking within five years.

Postoperative neurological deficits are classified as either:
A) Ipsilateral carotid territory events:
- Transitory ischemic attack (TIA) including amaurosis fugax (AF)
- Transient stroke (deficit >24 hours and < 30 days)
- Permanent stroke (deficit > 30 days)

B) Other perioperative neurological events
- Cerebrovascular event (all perioperative neurological events not classified as an ipsilateral carotid territory event, for example contralateral carotid territory events or posterior circulation events)

Definitions in the papers
In these papers the definition of asymptomatic stenosis excluded all ipsilateral carotid artery events and non-hemispheric symptoms within 6 months (non-hemispheric symptoms including posterior circulation events and non-specific symptoms).

In paper III the patients operated on bilaterally were identified and one of the CEAs was selected, as the index procedure, for analysis. As the focus of the study was the patients operated on for an asymptomatic lesion, these were primarily selected as index procedures. In case of one asymptomatic and one symptomatic carotid lesion, the CEA of the asymptomatic artery was defined as the index procedure. If both arteries were asymptomatic or symptomatic, the first operated vessel was defined as the index procedure.

Statistics
Statistical analyses were performed using the SPSS for Windows program package and R [62]. Continuous variables were summarized by the median (range or quartiles) while categorical variables were summarized by percentages. Continuous variables were compared with the Student’s t-test or Wilcoxon-Mann-Whitney test and categorical variables with the Pearson $\chi^2$-test or Fisher’s exact test depending on the distribution of the variable.

Preoperative variables that were positively associated with postoperative outcome at p<0.1 were selected for multivariate analysis using logistic regression. Relative risks (RR) for the cohort part of the study and odds ratio (OR) for the case-control part was calculated when possible (paper I).

Analyzes of risk factors for the different combined outcomes were performed using logistic regression with the presented model designed based on the number of (adverse event) AE, the completeness of the variables in the data-base and on the clinical relevance. As the numbers of AE were small, the numbers of variables that may be included in the model were limited (recommended to be 1 variable per $\geq 10$ events) (paper II).
Logistic regression models were fitted to estimate the relative odds (OR) of 5 year mortality for different risk factors, as well as for asymptomatic vs symptomatic patients adjusted for each of these risk factors one at a time. Kaplan-Meier curves were used to illustrate crude cumulative survival. Survival curve comparisons were done using logrank test and hazard ratios, but non-proportionality of the hazards limits the ability of analysis (paper III).

The odd ratios (OR) and relative risks (RR) are presented with 95% confidence intervals (CI). A statement of statistical significance implies a p-value < 0.05.

Papers IV-V
Prospective studies on patients undergoing CEA, assessing different effects of carotid clamping. Inclusion criteria were symptomatic stenotic lesions of the ICA of ≥ 70% as measured by Duplex ultrasonography.

All patients had given informed consent to participate and the medical ethics committee for Uppsala University had approved the study (Uppsala 99080).

CEA
All procedures were performed under normotensive, normocarbic general anaesthesia. An arterial line was inserted via the contralateral radial artery.

The CEA was performed with standard surgical technique by a longitudinal arteriotomy. A fabric patch was used selectively.

Intravenous unfractionated heparin (5000 IU) was given before clamping in all patients. Dextran 70 (50 ml/h, 10h) was started after arrival in recovery unit.

A postoperative duplex ultrasonography of the operated ICA was performed before the patients left the hospital. After 30 days the patient was examined by a neurologist.

Measurements
Stump pressure was measured, via a cannula in CCA connected to a calibrated pressure transducer, before and after clamping of CCA and ECA. A Javid shunt was inserted if the (mean) stump pressure was less than 40 mmHg (papers IV-V).
Volume blood flow was measured using a calibrated transit time ultrasonic perivascular probe, positioned on the proximal part of the prepared CCA (CardioMed flowmeter CM1005, Medistim A/S, Oslo, Norway). Measurements were recorded before clamping with separate readings of CCA, ICA and ECA. Following reperfusion, the probe was positioned at the same site and flow was separately measured in CCA, ECA and ICA, 5 and 10 minutes after declamping (paper IV).

Two cerebral oximeters (model Invos 4100A, Somanetics, MI, USA) were used for simultaneous bilateral rSO2 monitoring. Sensors from the dual-channel system were applied on the forehead bilaterally. The system monitored changes in cerebral saturation referred to as an rSO2 index, the absolute values being considered too relative within a given patient. The numerical rSO2 readings recorded at 1-min intervals were stored on computer discs. Percent change was calculated according to the formula (paper IV):

\[
\text{% change} = \frac{\text{mean RSO2 preclamp} - \text{min RSO2}}{\text{mean RSO2 preclamp}} \times 100
\]

Blood samples were drawn via a catheter inserted into the ipsilateral superior jugular bulb (via the common facial vein and affixed by suture ligature) and simultaneously from the contralateral radial artery; before clamping, during clamping (5, 15, 30 min) and after reperfusion (5 min). Baseline samples were taken the day before surgery from the cubital vein. The plasma was separated and snap-frozen (-70°C). All samples were analysed for fragment 1+2 (F1+2), plasminogen activator inhibitor -1 (PAI-1), fibrin degradation product (D-dimer), interleukin-6 (IL-6) and soluble CD40 ligand (CD40L).

Baseline median (and quartile) values were compared to a reference group of 50 healthy patients (paper V).

Statistics

Statistical analyses were performed using SPSS for Windows statistical package (SPSS Inc, USA). Results are presented with median and range or interquartile range (IQR). Non-parametric rank tests were used to compare rSO2 and flow values before, during clamping and after reperfusion. For analyses of associations Spearman’s correlation and linear regression were used (paper IV).
Comparison of data within groups were analysed with Wilcoxon signed rank test (two-tailed) *(Paper V)*.

Box plots with logarithmic scale were used to demonstrate the different measurements semi-graphically. Outliers are defined by SPSS as observations > 1½ box lengths from upper/lower quartile and extreme values if > 3 lengths.

Baseline parameters with skewed distribution were presented as plots of study patients together with median and quartiles for study and reference values.

A p-value of ≤ 0.05 was considered as statistically significant.
Results

Paper I-III

The preoperatively registered baseline characteristics for the patients included in papers I-III are listed in Table 2.

Table 2. Preoperative registered risk factors and indications for CEA. Comparison between the groups with symptomatic vs asymptomatic stenosis in papers II-III.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Paper I (%)</th>
<th>Papers II-III (%)</th>
<th>Papers II-III (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All indications</td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>66</td>
<td>67</td>
<td>64</td>
<td>0.16</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>45</td>
<td>45</td>
<td>47</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>60</td>
<td>65</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous vascular surgery</td>
<td>19</td>
<td>16</td>
<td>39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
<td>19</td>
<td>19</td>
<td>0.86</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>0.93</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>38</td>
<td>42</td>
<td>41</td>
<td>0.77</td>
</tr>
<tr>
<td>Indication for CEA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor stroke</td>
<td>34</td>
<td>40</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>34</td>
<td>37</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>18</td>
<td>20</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>11</td>
<td>NA</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Others (eg non-hemispheric)</td>
<td>3</td>
<td>2</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Paper I

A total of 1518 CEAs on 1411 patients were reported during a three year period (Jan 1994-Dec 1996). The mean patient age was 68.8 (range 53-90) years. Patch angioplasty was used in 29.1%. Baseline characteristics are presented in Table 2.
Registered 30-days complications were stroke (permanent and transient) in 4.9%, TIA/amaurosis fugax in 1.2% and the combined perioperative stroke or death rate in 5.9%. Causes of the 22 deaths were 13 cardiac, 7 strokes, 1 pneumonia and 1 ruptured aortic aneurysm.

In the analysis of predictors for different outcomes, the independent factors for combined permanent stroke and death (4.3%) are shown in Table 3, and were the indication for surgery (minor stroke vs. other indications) (RR=1.4), diabetes mellitus (RR=1.4), cardiac disease (RR=1.4) and operation at a university hospital (RR=1.4).

Table 3. Risk factors for combined permanent stroke or death N=65/1518 (4.3%. *=-2, †Mann-Whitney-U test, ‡ Fisher’s exact test)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Indication (stroke vs others)</td>
<td>0.02‡</td>
<td>1.41 (1.06-1.87)</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>0.09*</td>
<td>1.56 (0.93-2.63)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.51*</td>
<td>1.18 (0.71-1.99)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.09*</td>
<td>2.05 (1.19-3.53)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.03‡</td>
<td>1.69 (1.03-2.78)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>&lt;0.01*</td>
<td>1.98 (1.22-2.73)</td>
</tr>
<tr>
<td>Previous vascular surgery</td>
<td>0.13</td>
<td>1.51 (0.88-2.59)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.79‡</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.0‡</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.05*</td>
<td>0.58 (0.31-1.00)</td>
</tr>
</tbody>
</table>

There was no significant correlation between the annual caseload of the centres and complication rates (p=0.17). Patch angioplasty did not influence the complication rate (p=0.70).

Case-control study

The 65 cases of permanent stroke or death were compared with 130 controls (without serious complications but matched for operating centre, indication and age).

Results of comparison for the chosen variables are presented in Table 4. Contralateral occlusion, present in 15/65 cases and 7/130 controls, was the only statistically significant factor (OR=5.3) and remained as a risk factor also after correction for the use of shunt.
Table 4. The impact of different variables on perioperative permanent stroke or death risk. *=Students-test, **Fisher’s exact test, ***=X2, ****=Mann-Whitney-U test

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis degree, mean 84.5±11.8 (SD)</td>
<td>0.61*</td>
</tr>
<tr>
<td>Contralateral occlusion N=22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Infarct on CT preoperatively N=83</td>
<td>0.47***</td>
</tr>
<tr>
<td>Bleeding: ml (case; median=200 (0-1600), controls; median=150 (0-700))</td>
<td>0.16****</td>
</tr>
<tr>
<td>Shunt N=79</td>
<td>0.61***</td>
</tr>
<tr>
<td>Occlusion time; min (case; mean=29.7 (SD 25.6), controls; mean=26.6 (SD 21.4))</td>
<td>0.41*</td>
</tr>
<tr>
<td>Operation time; min (case; median 128 (60-314), controls; median 120 (59-200))</td>
<td>0.18****</td>
</tr>
<tr>
<td>Tacking suture N=67 (24 case vs 43 controls)</td>
<td>0.59***</td>
</tr>
<tr>
<td>Local anaesthesia vs general anaesthesia (cases; 16 vs 49, controls; 39 vs 91)</td>
<td>0.43***</td>
</tr>
</tbody>
</table>

Paper II

A total of 6182 carotid endarterectomies were registered during this ten-year period (1994-2003), among these 10.9% had indication asymptomatic stenosis. Bilateral CEAs were performed on 6% of the patients.

Mean age was 70 years (quartiles 64; 75) for both the symptomatic and asymptomatic group. Baseline characteristics are presented in Table 2.

Patch closure was performed in 34% for asymptomatic vs 32% for symptomatic lesions (p=0.20).

The perioperative morbidity and mortality rates are shown in Table 5, with a combined stroke (permanent and transient) or death rate of 2.1% for asymptomatic vs 4.3% for the symptomatic group (p<0.01) over the whole time period. There were two fatal strokes (of 3 deaths) among the procedures for asymptomatic and 17 (of 74 deaths) among those for symptomatic stenosis.
Table 5. Perioperative complications after CEA for the whole time period (symptomatic vs asymptomatic stenosis) and the two 5-year periods (asymptomatic stenosis 1994-1998 vs asymptomatic stenosis 1999-2003).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=5511</td>
<td>N=671</td>
<td>x^2</td>
<td>N=330</td>
<td>N=341</td>
<td>x^2</td>
</tr>
<tr>
<td>Permanent stroke</td>
<td>2.1%</td>
<td>0.9%</td>
<td>0.04</td>
<td>1.5%</td>
<td>0.3%</td>
<td>0.09</td>
</tr>
<tr>
<td>Transient stroke</td>
<td>1.3%</td>
<td>1.0%</td>
<td>0.54</td>
<td>1.5%</td>
<td>0.6%</td>
<td>0.24</td>
</tr>
<tr>
<td>TIA</td>
<td>1.3%</td>
<td>0.3%</td>
<td>0.02</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.98</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>2.0%</td>
<td>1.7%</td>
<td>0.54</td>
<td>1.8%</td>
<td>1.5%</td>
<td>0.72</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>2.5%</td>
<td>4.2%</td>
<td>0.01</td>
<td>4.6%</td>
<td>3.8%</td>
<td>0.64</td>
</tr>
<tr>
<td>Death</td>
<td>1.4%</td>
<td>0.4%</td>
<td>0.05</td>
<td>0.9%</td>
<td>0.0%</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke or death</td>
<td>4.3%</td>
<td>2.1%</td>
<td>&lt;0.01</td>
<td>3.3%</td>
<td>0.9%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data from the asymptomatic cohort was divided into two 5-year periods (1994-1998 and 1999-2003). During the first period 330 operations were performed (12.6% of the total number of CEAs during that time period), compared to 341 procedures (11.7%) during the second.

Baseline characteristics were comparable between the two periods except that hyperlipidaemia (p<0.01) and hypertension (p=0.02) were more frequent in the second period.

Patch closure was more frequently used during the second period (28% vs 40%, p=0.01). The frequency of eversion endarterectomy increased over time (0.3% vs 5.9%, p<0.01).

Perioperative morbidity and mortality rates are shown in Table 5. There was no mortality and only one permanent (non-disabling) stroke during the second period.

Logistic regression analysis was performed on the asymptomatic group testing the factors age, gender and patch for different combinations of outcome. When all stroke, TIA, cardiovascular complications and death were used as outcome in the model, the only significant variable identified was age with an OR=2.8 (1.4-5.6) for those older than 75 years. In the same model, women had an OR=1.4 (0.7-2.8) and patch OR=0.8 (0.4-1.6).
Paper III

During the ten-year period 1994-2003 a total of 5808 patients were registered in Swedvasc for a primary carotid endarterectomy. In 10.8% of the patients the index CEA was for asymptomatic stenosis. The total proportion of patients operated on bilaterally with CEA was 6%, and among patients with an asymptomatic stenosis 24% (bilateral asymptomatic lesions in 6%).

Median age was 70 years (quartiles 64; 75), equal for the symptomatic and asymptomatic cohort. Baseline characteristics are presented in Table 2.

Patch closure was performed in 34% of patients with asymptomatic vs 32% with symptomatic lesions (p= 0.15). Eversion CEA was used in 3.3% for asymptomatic vs 1.9% for symptomatic stenosis (p=0.01).

The median (range) time at risk was 5.1 (0.1-11.8) years. The Kaplan-Meier curves in Figure 6 display the crude cumulative survival rate with respect to indication for CEA.

The median survival for the asymptomatic cohort was estimated to 10.2 (9.0-*) years and for the symptomatic 10.8 (10.5-11.6) years (* the upper limit of the 95% confidence interval for the curve has not yet crossed the 0.5 level). The average hazard did not differ significantly between the symptomatic and asymptomatic groups (p=0.12; HR=0.89 (0.76-1.03)).
Figure 6. Kaplan-Meier curve for crude cumulative survival of the asymptomatic (solid line) and symptomatic (dotted line) cohort. Numbers of patients at risk listed for every second year of follow-up.

The analyzed data on all patients with a completed 5-year follow-up, with respect to the risk factors registered at baseline, are presented in Figure 7. Previous vascular surgery (OR=1.8), cardiac disease (OR=1.7), diabetes (OR=2.3) and age (OR=1.5) were predictors of decreased 5-year survival.
Figure 7. Risk factors for 5-year mortality in asymptomatic patients. The circles and lines represent crude relative odds and 95% confidence intervals.
Validation results (papers I-III)

**Paper I**

In the process of reviewing patient reports in the control group an independent observer found one patient (1/130) with a transient stroke not registered and one patient (1/130) with a permanent stroke misjudged as a local neurological complication (a central, not peripheral, facial paresis with mild symptoms persisting 30 days).

**Paper II**

Complete medical records were obtained for 84/92 (91%) of the random sample and target validation. In reviewing the records we found; a) two permanent strokes and three transient strokes incorrectly registered, b) one transient stroke and one TIA not registered (Table 6).

The two incorrectly registered permanent strokes were non-disabling.

<table>
<thead>
<tr>
<th>Validation</th>
<th>N patient-records obtained / requested</th>
<th>N incorrect registrations</th>
<th>Neurological deficit in registry</th>
<th>Classification in validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sample</td>
<td>65/71 (93%)</td>
<td>2</td>
<td>1) Minor contralateral finger dysfunction (IV-V)</td>
<td>Transient stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Contralateral facial paresis (corner of mouth)</td>
<td>Local neurology</td>
</tr>
<tr>
<td>Target Validation</td>
<td>1) Thrombosis or occlusion; 2/3</td>
<td>1</td>
<td>Contralateral arm dysfunction (minutes duration)</td>
<td>Not registered</td>
</tr>
<tr>
<td></td>
<td>2) Peripheral embolization; 2/2</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3) Cerebrovascular event; 8/9</td>
<td>3</td>
<td>1-2) Ipsilateral (worsening) arm dysfunction (3 and 7 days duration)</td>
<td>Cerebrovascular event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3) Contralateral hand/arm dysfunction (&lt;7 days duration)</td>
<td>Cerebrovascular event</td>
</tr>
<tr>
<td></td>
<td>4) Missing 30-day registration; 7/7</td>
<td>1</td>
<td>Contralateral hand dysfunction and aphasia (&lt;5 days duration)</td>
<td>Not registered</td>
</tr>
<tr>
<td>Total</td>
<td>84/92 (91%)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Contralateral carotid territory symptoms but with contralateral occlusions, according to the (new) Swedvasc definition should these have been registered as transient strokes.*
Papers II-III

In the cross-match with the National Population-registry all perioperative deaths had been reported to the Swedvasc.

During 2003, 771 CEAs were registered in Swedvasc and 782 patients in the IPR. Three hospitals had exactly the same number of procedures in both registries; ten had more in Swedvasc and eight more in the IPR. In those latter eight hospitals a surplus of 32 operations were registered in the IPR. A total of 4.1% (32/782) of those in the IPR were unregistered in Swedvasc.

Comments to papers I-III

In analysing registry data the reliability of the results may be discussed, one potential weakness is the completeness of registrations and another is self-auditing. The completeness of the registrations for CEA has been evaluated previously with good validity [61].

Concerning the problem of self-reported data [63] Swedvasc strongly recommends independent neurological evaluation. Another factor that may contribute to the validity is that the results of the individual surgeons are confidential and that much of the data are registered prospectively.

To overcome some of these inherent problems with register data we performed several different validation procedures, and the results demonstrate good accuracy with few missed and incorrect registrations. Furthermore, none of these missed or incorrectly registered events were disabling strokes and there was no death unreported.

Papers IV-V

Patient demographics and indication for CEA are demonstrated in Table 7.
Table 7. Preoperative registered risk factors and indications for CEA.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Paper IV (%)</th>
<th>Paper V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>71 (51-84)</td>
<td>69 (58-75)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>70</td>
<td>83</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>45</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>67</td>
</tr>
<tr>
<td>Previous vascular surgery</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Current smoker</td>
<td>38</td>
<td>39</td>
</tr>
</tbody>
</table>

**Indication for CEA**

- Minor stroke: 30, 39
- TIA: 60, 17
- Amaurosis fugax: 10, 33
- Others (eg non-hemispheric): 11

---

**Paper IV**

Sixty-two patients were included. The median clamping time was 42 (32-57) minutes. Eight patients (13%) were operated upon using a Javid shunt (based on stump pressure <40mm Hg). Patch angioplasty was used for arteriotomy closure in 82% of the patients.

One patient developed an intraoperative stroke but no other neurological deficits developed perioperatively, resulting in a stroke or death rate of 1.6%. Duplex follow up within 30 days revealed no major pathology of the ICA.

**Transit time volume blood flow**

Transit time volume flow measurements increased after the CEA in CCA (p<0.05) and ICA (p<0.001) as demonstrated in Table 8. Patients with contralateral ICA occlusion had higher ipsilateral ICA flow before clamping (p=0.04).
Table 8. Results of median flow (ml/min) before clamping and after reperfusion in the CEA. CCA and ICA flow increased significantly after the procedure. ** p<0.05

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>ECA</th>
<th>ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before clamping</td>
<td>164 (102-412)</td>
<td>102 (38-190)</td>
<td>78 (39-222)</td>
</tr>
<tr>
<td>5 min after reperfusion</td>
<td>238 (141-460)</td>
<td>79 (55-116)</td>
<td>122 (90-194)</td>
</tr>
<tr>
<td>10 min after reperfusion</td>
<td>297 (174-430)**</td>
<td>81 (40-148)</td>
<td>162 (80-436)**</td>
</tr>
</tbody>
</table>

Cerebral oximetry

Cerebral oximetry decreased (rSO$_2$) after clamping in patients requiring a shunt (based on stump pressure < 40 mmHg), after shunt placement the rSO$_2$ was reversed (49% vs 58%), shown in Table 9. No significant changes were registered in the contralateral hemisphere.

Table 9. Results of cerebral oximetry (rSO2) during CEA. Correlation between decreases in rSO$_2$ and need for shunt (stump pressure < 40 mmHg), reversed by shunt placement. * p<0.01.

<table>
<thead>
<tr>
<th></th>
<th>Before clamping</th>
<th>At clamping</th>
<th>5 min after reperfusion</th>
<th>10 min after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Shunt</td>
<td>63 (59-65)</td>
<td>62 (57-67)</td>
<td>66 (63-73)</td>
<td>65 (63-71)</td>
</tr>
<tr>
<td>Shunt</td>
<td>65 (62-71)</td>
<td>49 (42-54)*</td>
<td>61 (57-70)</td>
<td>62 (61-70)</td>
</tr>
<tr>
<td>After shunt</td>
<td></td>
<td>58 (57-61)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Measurement associations

The associations between the different measurements are demonstrated in Figure 8.

Associations were found between:
- A high ICA volume flow before clamping and low stump pressure (r=-0.45, p=0.03).
- A high ICA volume flow before clamping and decreasing rSO$_2$ during clamping (r=-0.41 p=0.01).
- A low stump pressure and decreasing rSO$_2$ during clamping (r=-0.61 p=0.002), the rSO$_2$ changes was reversed by shunt insertion.
Figure 8. Scatter plots and curve estimations for associations between stump pressure, transit time volume flow and cerebral oximetry.

Comments to paper IV
The results in this paper are based on the preset shunt indication of stump pressure < 40mmHg, and as the only complication occurred in a patient operated on with a shunt, other means of comparisons were not possible. However, there was reasonable number of patient included and the measurement association was relatively strong (eg stump pressure vs cerebral oximetry) which strengthen the results.
Paper V
Twenty-two patients scheduled for elective CEA for symptomatic internal carotid artery (ICA) stenosis were prospectively included in the study. Four patients needed a perioperative shunt (based on stump-pressure <40 mmHg) and were excluded before the analysis, leaving eighteen patients completing the study.

The contralateral ICAs were occluded in two patients, one had a stenosis of > 70% and the remaining fifteen had stenosis < 70% on duplex ultrasonography.

Seventeen patients received aspirin and of these four had additional treatment with dipyridamole. The remaining patient was on clopidogrel. Five patients were on warfarin, but all had INR < 1.5 on the day of the CEA.

Median (range) clamping time was 56 (29-87) min. Patch angioplasties were used in 89%.

No patient suffered any perioperative central neurological event.

Levels of biomarkers
The patterns for the jugular bulb (JB) levels during the procedure in relation to radial artery (RA), baseline (BL) and to the previous value are shown in Table 10.

Interleukin-6
IL-6 was elevated compared to baseline levels throughout the CEA. The jugular bulb values increased prominently directly after clamping and then again after reperfusion. Throughout the procedure the jugular bulb levels were higher than in the radial artery.

Soluble CD40L
During CEA the levels of soluble CD40L did not change from baseline or between the measurement intervals. All samples, both jugular bulb and radial artery, showed a similar pattern.

Fragment 1+2
The jugular bulb levels of F1+2 increased from baseline during the initial part of the CEA, until clamping with heparinisation when it rapidly decreased (5 min after clamping) and then levelled out. There were no differences between jugular bulb and radial artery levels.

Plasminogen activator inhibitor-1
PAI-1 levels did not change from baseline until after reperfusion when it increased, but not in relation to the previous (30min after clamping) levels.
The jugular bulb levels were lower than in the radial artery during the procedure until after reperfusion.

**Cross-linked fibrin degradation product (D-dimer)**

Jugular bulb D-dimer levels were increased throughout the procedure in comparison with peripheral and baseline levels, with a significant increase at clamping.

Table 10. *Comparisons between the cerebral (jugular bulb (JB)), peripheral (radial artery (RA)) and baseline (BL) levels at the different moments of the procedure. Arrows indicating the cerebral (JB) samples in regard to increased or decreased level as compared to the RA, BL or previous JB samples. Test used Wilcoxon Signed Rank Test.*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Comparisons between cerebral (JB), peripheral (RA) and baseline (BL) mean levels</th>
<th>Before clamping</th>
<th>5min after clamping</th>
<th>15min after clamping</th>
<th>30min after clamping</th>
<th>After reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JB vs RA</td>
<td>↑ p=0.019</td>
<td>↑ p=0.036</td>
<td>↑ p=0.011</td>
<td>↑ p=0.016</td>
<td>↑ p=0.001</td>
<td></td>
</tr>
<tr>
<td>JB vs BL</td>
<td>↑ p=0.036</td>
<td>↑ p=0.004</td>
<td>↑ p=0.008</td>
<td>↑ p=0.001</td>
<td>↑ p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>JB vs JB</td>
<td>↑ p=0.050</td>
<td>↑ p=0.088</td>
<td>↑ p=0.001</td>
<td>↑ p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD40L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JB vs RA</td>
<td>p=0.551</td>
<td>p=0.586</td>
<td>p=0.469</td>
<td>p=0.279</td>
<td>p=0.056</td>
<td></td>
</tr>
<tr>
<td>JB vs BL</td>
<td>p=0.245</td>
<td>p=0.407</td>
<td>p=0.737</td>
<td>p=0.244</td>
<td>p=0.272</td>
<td></td>
</tr>
<tr>
<td>JB vs JB</td>
<td>p=0.712</td>
<td>p=0.426</td>
<td>p=0.865</td>
<td>p=1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>F 1+2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JB vs RA</td>
<td>p=0.127</td>
<td>p=0.602</td>
<td>p=0.099</td>
<td>p=0.125</td>
<td>p=0.205</td>
<td></td>
</tr>
<tr>
<td>JB vs BL</td>
<td>↑ p=0.003</td>
<td>p=0.959</td>
<td>p=0.299</td>
<td>p=0.378</td>
<td>p=0.910</td>
<td></td>
</tr>
<tr>
<td>JB vs JB</td>
<td>↓ p=0.002</td>
<td>p=0.234</td>
<td>p=0.938</td>
<td>p=0.589</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PAI-1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JB vs RA</td>
<td>↓ p=0.009</td>
<td>↓ p=0.004</td>
<td>↓ p=0.001</td>
<td>↓ p=0.004</td>
<td>p=0.155</td>
<td></td>
</tr>
<tr>
<td>JB vs BL</td>
<td>p=0.205</td>
<td>p=0.394</td>
<td>p=0.469</td>
<td>p=0.326</td>
<td>↑ p=0.046</td>
<td></td>
</tr>
<tr>
<td>JB vs JB</td>
<td>p=0.315</td>
<td>p=0.629</td>
<td>p=0.315</td>
<td>p=0.875</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D-dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JB vs RA</td>
<td>↑ p=0.011</td>
<td>↑ p=0.003</td>
<td>↑ p=0.003</td>
<td>↑ p=0.006</td>
<td>↑ p=0.005</td>
<td></td>
</tr>
<tr>
<td>JB vs BL</td>
<td>↑ p=0.006</td>
<td>↑ p=0.001</td>
<td>↑ p=0.001</td>
<td>↑ p=0.001</td>
<td>↑ p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>JB vs JB</td>
<td>↑ p=0.004</td>
<td>p=0.307</td>
<td>p=0.495</td>
<td>p=0.642</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comments to paper V

Although a small number of patients, the activation of inflammation and fibrinolysis in the jugular bulb samples demonstrated a consistent pattern. The regional pattern of biomarkers after carotid clamping was suggestive of cerebral ischaemia. This effect was clear despite the fact that all patients received unfractionated heparin, however, with regard to coagulation (and possibly also fibrinolysis) the alterations of marker for thrombin generation (eg F1+2) would probably have been increased.
General discussion

After the publication of the large randomised trials on CEA of carotid artery stenosis, this treatment modality was implemented and is now one of the most common vascular procedures which are performed in Sweden [12]. However, some concerns have been raised about the results in routine clinical practice.

A validated registry, with coverage of all centres performing CEA in the country can provide population-based data on the national outcome of the procedure. In analysing the overall benefit of the procedure both the short- and long-term outcomes are important.

The perioperative results are influenced by intra- and postoperative complications, and as the aim of the surgery is to decrease the future stroke risk, the combined stroke or death rate is an important and commonly reported outcome measure. Most perioperative strokes occur within the first days after the procedure, so tolerance of carotid clamping and surgical technique among other factors have impact on outcome [64].

Long-term outcome of CEA is dependent both on the durability of the procedure and the late mortality, especially for the patients with asymptomatic stenosis. Some patients with certain risk factors may benefit less from CEA than others, and these factors may differ between short- or long-term outcomes.

CEA for symptomatic stenosis

The two most influential trials of CEA for recent symptomatic severe carotid stenosis are ECST and NASCET, a third (Veteran Affairs VA309) was stopped early when the results from the first two studies were published [7-9, 11, 20].

Although differences in the definition of complications and the degree of stenosis make comparison difficult, the rate for perioperative stroke or death were in ECST 7.0% and in NASCET 6.7%. When analysing these studies
pooled (including also VA309) and with the data reassessed for degree of stenosis and outcome, the stroke or death rate was 7.1 % for stenosis ≥ 70% (NASCET-method) [21].

In a systematic review of all studies on perioperative results after CEA the pooled estimate of stroke or death risk was 5.1% (for studies published after 1994, including 18885 CEAs) [65].

The corresponding risk of perioperative stroke (permanent and transient) or death was 5.9% in Swedvasc during 1994-1996 (paper I) and 4.3% during 1994-2003 (paper II).

Comparisons between the results from randomised trials and vascular registries (or single centres) should be interpreted with caution, although extensive register validations can make such comparisons more reliable. Following the present analysis, it seems reasonable to suggest that the population-based perioperative results for CEA of symptomatic stenosis in Sweden compares well with the results from the RCTs.

Timing of CEA

Timing of CEA after the qualifying event is an important factor to consider since the net benefit decreases over time due to an initially high stroke recurrence rate [7, 9, 66].

In patients with large artery atherosclerosis the risk of recurrent stroke in population based studies was 4.0% at 7 days, 12.6% at one month and 19.2% at 3 months [4]. With TIA as the presenting symptom there was a high risk of recurrent TIA or stroke in a population based study with 2.5% (TIA) vs 1.4% (stroke) at 2 days, 6.2% vs 6.7% at 1 month and 7.9% vs 9.5% at 3 months, respectively [2]. Approximately 15-26% of patients with an ischemic stroke have had a preceding TIA and 43% had the event within 7 days prior to the stroke (92% in the same vascular territory) [67].

However, there are some concerns about the risk for reperfusion complications (i.e. hemorrhagic transformation) in early CEA after cerebral infarctions. This is not well investigated in controlled trials but it has been a common practice to defer the surgery 4-8 weeks after a larger infarction [68, 69]. In a recent prospective study of CEA within 15 days of preceding symptom, the authors concluded that there was no association with increased perioperative risk related to CT/MR cerebral infarctions [70]. The size of the cerebral infarction was not evaluated in this study but relatively large infarction volumes on imaging in combination with residual neurological disability are suggested as factors to consider when deciding on the timing for CEA [71, 72]. Large volume infarctions may constitute a group where special considerations should be taken into account, the choice being either to defer
the procedure or to perform early revascularisation with intense postoperative blood pressure regulation.

In a systematic review of the literature on stroke or death risk after CEA the pooled estimates for “urgent” surgical indication (i.e., stroke in evolution, crescendo TIA) demonstrated an OR=4.9 (3.4-7.1) vs nonurgent surgery. However, when comparing neurological stable patients there was no difference between early (<3-6 weeks) and late (>3-6 weeks) CEA (OR=1.1 (0.8-1.6) early vs late CEA) [65].

In summary, it seems reasonably that the majority of patients with TIA or minor stroke should benefit most if the CEA can be performed as soon as possible after the event (hence, the logistics for such an organisation being an issue by itself).

### CEA for asymptomatic stenosis

In the two largest trials on CEA for asymptomatic stenosis the combined perioperative stroke or death rate were 2.3% in ACAS and 2.8% in ACST, as compared with 2.1% in the Swedvasc registry (1994-2003) [6, 10].

When analysing this registry data for the two 5-year periods, the perioperative stroke or death rate decreased in the later time period (1999-2003) to 0.9%. This is consistent with other series of CEA for asymptomatic stenosis [73, 74] and also with a recently published meta-analysis where the pooled estimate of the absolute risk of stroke or death decreased for the asymptomatic indication in the later time period [65]. Many different factors may have contributed to this improvement in outcome including patient selection, surgical technique, pre- and postoperative medical treatment. No major single factor was possible to identify in the present papers (further discussed later).

Although the perioperative results are promising, the net benefit of the procedure is not statistically evident in the RCTs until 2-3 years after the CEA, and this makes the long-term outcome an important issue. The long-term follow-up of ACST is still ongoing (~2 years) and other series on late outcome (>5 years) of CEA for asymptomatic stenosis are from a few single centres reporting 10-year survival of approximately 60%. In Table 11 some series on long-term survival are listed for patients with asymptomatic carotid stenosis, both for natural history and after CEA (with asymptomatic indication ranging from 33% to 100%).
Table 11. Studies on long-term survival for patients with severe asymptomatic carotid artery stenosis, both for surgically and medically treated patients.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patient group studied</th>
<th>N Pat</th>
<th>% Asympt</th>
<th>Mean / median age</th>
<th>5-year survival %</th>
<th>10-year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper III [75]</td>
<td>CEA asymptomatic stenosis</td>
<td>631</td>
<td>100</td>
<td>70</td>
<td>78.2</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td>CEA asymptomatic stenosis (+ combined and non-hemispheric)</td>
<td>312</td>
<td>100</td>
<td>69 (SD 5.3)</td>
<td>74.6 (SD 5.3)</td>
<td>59.4 (SD 8.6)</td>
</tr>
<tr>
<td></td>
<td>CEA asymptomatic stenosis (with/without silent brain infarction)</td>
<td>103</td>
<td>100</td>
<td>67 (SD 4.6)</td>
<td>78.3 (SD 4.6)</td>
<td>60.6 (SD 7.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>198</td>
<td></td>
<td></td>
<td>86.0 (SD 2.8)</td>
<td>69.3 (SD 6.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.8</td>
<td>87.2</td>
</tr>
<tr>
<td>[77]</td>
<td>CEA</td>
<td>1000</td>
<td>33</td>
<td>72</td>
<td>72.4</td>
<td>44.7</td>
</tr>
<tr>
<td>[78]</td>
<td>CEA</td>
<td>1897</td>
<td>64</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[79]</td>
<td>CEA</td>
<td>540</td>
<td>47</td>
<td>68</td>
<td>92 (SD 1)</td>
<td>89 (SD 2)</td>
</tr>
<tr>
<td>[80]</td>
<td>Asymptomatic carotid stenosis (&gt;60%) and contralateral occlusion</td>
<td>82</td>
<td>100</td>
<td>66 (SD 5.6)</td>
<td>83 (SD 5.6)</td>
<td>67 (SD 16)</td>
</tr>
<tr>
<td>[81]</td>
<td>Asymptomatic carotid stenosis (&gt;60%)</td>
<td>216</td>
<td>100</td>
<td>66</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>[82]</td>
<td>Asymptomatic carotid stenosis (50-79%)</td>
<td>426</td>
<td>100</td>
<td>74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The median survival time was 10.2 years for the asymptomatic patient in the present paper (paper III). The survival time is thus reduced compared to the life expectancy of an average 70-year old person in Sweden (12.3 years for men vs 15.4 years for women (1995) and 13.7 years for men vs 15.5 years for women (2004)). However, it is important to bear in mind that these patients represent a selected group and one should therefore not make any general conclusions for all patients with asymptomatic stenosis based on these results.

In summary, this extensively validated Swedvasc data for CEA of the asymptomatic cohort demonstrates perioperative complication rates well comparable with those from the randomised trials. Concerning the long-term outcome it seems reasonable to select patients based on risk-benefit considerations in regard to risk factors (discussed in the following) and the patients’ own preferences.
Plaque morphology

Patient selection for CEA is primarily based on the degree of ICA stenosis derived from the results of the RCTs. However, although the degree of stenosis correlated well with the stroke rate in patients with asymptomatic stenosis, 34% of all ipsilateral neurological events and 35% of the ipsilateral strokes occurred in patients with a stenosis <60% (NASCET-method) [83].

Several other factors are involved in the development of an unstable carotid artery plaque [84]. Morphological characteristics of vulnerable plaques can be demonstrated by different imaging modalities, such as duplex classification by computed grey scale media (GSM), pixel distribution analysis and fibrous cap thickness [17-19, 85]. Another developing technique is high resolution MRA with characterisation of lipid content and fibrous cap [86, 87].

However promising the studies of carotid plaque imaging may seem they are not yet fully assessed for implementation in routine clinical practice [84, 88].

Registry data

Registry data have several inherent limitations but Swedvasc has been validated on several occasions with >90% report rate and reproducibility concerning CEA [61, 89]. During 2003 (the last year in this series), a cross-match for all patients who had an operation code for CEA, was compared to the in-hospital registry of the National Board of Health and Welfare with a 96% accuracy.

Four different validations; a case-control study (1994-1996), a cross-match of death dates with the National board of Health and Welfares population registry (1994-2003), a random sample of asymptomatic patients and a review of all unclear complications registered in the asymptomatic patients (1994-2003) were performed in the present studies. During this validation process we did not find any disabling stroke or death unreported.

Baseline risk factors are prospectively registered in Swedvasc but the reliability depends on the accuracy of the responsible surgeon while completing the protocol. When analysing the registrations of these risk factor for CEA during the time period 1994-2003, the percentage of missing fields (including “unknown” registrations) are shown in Table 12.
Most of the risk factors have more than a 95% registration rate and the accuracy of these registrations has previously been validated with a 60% reproducibility (probably mainly due to the poor registration of hyperlipidaemia) [61].

Table 12. Baseline risk factors among patients registered for CEA during 1994-2003 in Swedvasc. Percentage of registrations marked as unknown or missing fields.

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>Registration; unknown or missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>5.1%</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>39%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.9%</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>4.5%</td>
</tr>
<tr>
<td>Previous vascular surgery</td>
<td>4.2%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>5.3%</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6.3%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Risk factors

It is essential to evaluate the individual patient when deciding upon CEA, as it is a prophylactic procedure in which all different risk-benefit considerations have to be taken into account. Several risk factors have been identified in the literature and some have also been demonstrated in the present papers (I-III) as potential predictors of negative outcome from the procedure. Many of the publications on risk factors are subgroup analyses (sometimes small subgroups), single centre series or register based studies with low level of evidence. However, reports on pooled data from the RCTs, meta-analyses and systematically reviews may better contribute to the management decisions. Some important factors to consider in the clinical situation are discussed below.

Gender

In the RCTs females had less benefit from the CEA compared to men, this due to a higher operative risk and a lower risk for stroke on medical treatment [6-11].

In a pooled analysis (remeasured stenosis with NASCET-method) of the large symptomatic trials, CEA was clearly beneficial in women with >70%
stenosis (ARR 9.9% (1.8-18.0)) but not in those with < 70% stenosis (ARR -2.7% (-8.8-3.5)) [66].

A meta-analysis of the asymptomatic trials (ACAS/ACST) demonstrated a considerable uncertainty with regard to the benefit of CEA for women, the OR for stroke or death being 0.96 (0.63-1.45), based on events during a mean follow-up of 2-3 years [90]. The long-term net benefits might be underestimated but this should be disclosed with the stroke incidence in the coming years of follow-up.

In the Swedvasc data analysed (paper I-III), gender did not influence either perioperative stroke/death risk (all indications) or 5-year mortality (asymptomatic indication). Long-term survival was 10.2 years in all patients but due to the small numbers with this follow-up specific gender analysis was not meaningful, however the expected survival was longer for women than for men. This may be interpreted either as a possible increased long-term benefit due to longer survival or as a reduced late survival after CEA with perhaps a reduced stroke risk on medical treatment alone.

In summary, it seems clear that the majority of women benefit from CEA for symptomatic carotid artery stenosis ≥70%. A dilemma is concerning women with asymptomatic stenosis where (level 1) evidence has not yet clearly demonstrated a benefit of CEA. However, it seems reasonable not to exclude all women with asymptomatic stenosis but to perform CEA with appropriate selection and continuous focus/follow-up on the perioperative results.

Age

A subgroup analysis of the RCTs demonstrated an increased benefit of CEA for symptomatic stenosis (≥70%) in patients older than 75 years, with a 5-years ARR=37.2%, this mainly due to the relatively high stroke risk on medical treatment [66]. Noteworthy is that the trials included approximately only 10% of patients ≥75 years of age (and very few patients ≥80 years) and that the elderly patients in the trials might represent a selection of generally fit individuals [91].

In a systematic review of all publications reporting data on association between age and procedural risk of stroke or death following CEA, the pooled results showed an OR=1.2 (1.0-1.4) for patients ≥75 years and an OR=1.2 (0.9-1.5) for those ≥80 years of age [92].

In the present paper (I) age > 75 years was an independent predictor for perioperative mortality (RR=1.6 (1.0-2.4)) but not for permanent/fatal stroke or the combined (stroke or death) outcome.

For patients with asymptomatic stenosis CEA is more of a long-term investment, as it will take 2-3 years to statistically compensate for the perioperative risk and even 2-3 more years to gain the absolute stroke risk reduction from the procedure. In ACAS and ACST the projected aggregated 5-
year ARR of stroke or procedural morbidity was 5.5% (6.0 vs 11.5) [10]. In subgroup analysis of those older than 75 years no significant benefit after successful CEA was demonstrated (ACST: ARR 3.3% (-1.9-8.4)) but due to the small number of patients these results are less conclusive [10].

In the present studies of CEA for asymptomatic stenosis (paper II-III) age was a predictor of combined perioperative morbidity and mortality with an OR=2.8 (1.4-5.6) for age >75 years and also for decreased 5-year survival with an OR=1.5 (1.1-2.1) per 10 years.

In summary, it seems reasonable not to withhold CEA for symptomatic stenosis in patients older than 75 years, although consideration must be taken with regard to other risk factors/comorbidity. This is supported by the substantial early stroke risk on medical treatment alone and consequently less influenced by the late outcome/expected survival after the procedure. On the contrast, patient with asymptomatic stenosis who are older than 75 years do not generally seem to be good candidates for a prophylactic CEA, as the net benefit may be of limited duration.

**Contralateral carotid artery occlusion**

In the analyses of the RCTs, occluded contralateral internal carotid arteries have had conflicting impact on the outcome, this mainly due to different medical and surgical risks.

In the pooled data of the trials on symptomatic lesions the surgical (stroke or death) risk after CEA for the patient with a contralateral occlusion was 18.0% (8.4-27.7) vs 7.0% (5.6-8.3) for those with a patent contralateral artery. The medical (ipsilateral stroke) risk of a contralateral occlusion was 25.8% (15.5-36.0) vs 20.9% (18.4-23.3) at 5 years. Although the wide CIs indicates that there were limited numbers of patients studied within this group, the CI for surgical risk with contralateral occlusion was separated from the overall surgical risk ((8.4-27.7) vs (6.1-8.8)) predicting increased stroke or death risk after CEA for this group [66].

However, when performing a subgroup analysis of the patients with contralateral occlusion in NASCET, it was demonstrated that despite a higher surgical risk, CEA conferred a significant reduction in the 2-year risk of ipsilateral stroke (ARR=43.3% (22.1% surgical vs 69.4% medical risk) [93].

In a systematic review of CEA with risk factor analyses, a trend towards increased perioperative stroke or death risk with contralateral occlusion was found with an OR=1.9 (1.3-2.7). In this review the prevalence was low (4.7%) and only two studies reached significance [94].

In the present case-control study (paper I) contralateral occlusion was the only identified factor predicting increased perioperative stroke or death risk with an OR=5.3 (2.0-13.1). In the control group 5.4% (7/130) had contralateral occlusion.
In the randomised trials of CEA for asymptomatic stenosis the impact of contralateral occlusion is difficult to analyse because of the considerable difference in the risk-benefit calculations. In ACAS there was a 5-year ARR= -2.0% (5.5% surgical vs 3.5% medical risk) for contralateral occlusion, which was a result of the benign course of medically treated subjects [95]. In contrast the findings in ACST demonstrated a 5-year ARR=8.6% (1.5% surgical vs 10.1% medical risk) [10].

In summary, patients that have severe symptomatic disease and contralateral occlusion seem to benefit from CEA in spite of a higher perioperative risk. However, for the patients with an asymptomatic stenosis and a contralateral occlusion, the level of evidence seems too uncertain for general management guidelines.

Carotid shunt indications

Tolerance of carotid clamping during CEA is obviously best tested in an awake patient, however not all vascular centres practice local anaesthesia, and so far no level 1 evidence on perioperative outcome clearly favouring either local or general anaesthesia has been demonstrated [27].

CEA under general anaesthesia confers the problem with assessing the patients’ tolerance to clamping and if selective shunting is practiced, some indirect method for deciding on the need for shunting is necessary [96, 97]. Various methods are available, including intracerebral circulation monitoring (eg TCD) [28], activity (eg SEPS or EEG) [98, 99] or oxygenation (NIRS) [100, 101] with intermittent or continuous measurements during the clamping.

Other methods predict the need for shunt on measurements before the arteriotomy, such as carotid stump pressure and transit time volume flow measurement. Carotid stump pressure (SP) is the “back pressure” in the clamped ICA and measuring SP indirectly assesses the capacity of the cerebral collateral blood flow [34]. Recently SP was investigated in patients undergoing CEA under local anaesthesia and the threshold of ≥ 40mmHg was considered reliable (false-negative rate 1.0%) [102].

Transit time volume flow measurements might be used for different purposes during CEA, first in combination with SP to decide on shunt indication, as low SP in combination with a high volume flow decreases the cerebral oxygenation during clamping (paper IV). Secondly, measuring the volume flow and wave form during reperfusion offers completion control (absolute flow and/or decreasing flow). Furthermore, the differences between the volume flow before and after the CEA may indicate of possible risk of hyperperfusion [103, 104]. Hyperperfusion syndrome is a rare but potentially serious complication after CEA that confers a high risk for neurological morbidity and mortality [105].
Considering that none of the methods used to predict the patients’ tolerance to clamping during CEA under general anaesthesia is in all aspects superior to the others, decisions on which method to use will be based on availability, technical issues, local experience or expertise with the methods and the interpretation of the measurements.

Cerebral ischemia

Carotid clamping during CEA impairs the cerebral perfusion to various degrees, and although the patient clinically tolerates clamping a relative ischaemia may result in subclinical reversible or irreversible damage. In response to the clamped induced regional hypoperfusion other investigators have identified different markers for cerebral ischaemia such as inflammatory mediators [38], metabolites or anti-oxidants [39, 106, 107] and markers for cellular brain damage [40-42]. These markers of cerebral ischaemia is detected in mixed venous blood samples collected from the ipsilateral jugular bulb, which has been demonstrated to be of predominantly intracerebral origin [108].

In the present paper (V) a pattern suggestive of regional ischaemic response after carotis clamping during CEA were demonstrated by the jugular bulb levels of IL-6, D-dimer and PAI-1. These markers for the inflammatory and fibrinolytic systems were most prominently altered directly after clamping and reperfusion, although almost all of the jugular bulb (cerebral) levels differed from the radial artery (peripheral) levels throughout the procedure. The marker for the coagulation system or more specific the thrombin generation, F1+2, rapidly decreased after systemic heparinisation which was administered at the time of clamping. Unfractionated heparin has t½ of approximately 2 hours and since it was not reversed the effect on antithrombin III persisted during the procedure. This heparin effect is in agreement with a previous report on haemostasis during CEA [109].

Several investigators have identified altered levels of inflammatory and haemostatic markers in stroke patients, both in the acute face and during follow up [44, 46, 47, 56, 58, 110-116]. Furthermore, in association with carotis plaques various markers of these systems have been demonstrated [52, 57, 59, 117-122].

With the advances in stroke research regarding plaque instability and ischaemia/reperfusion injury, there may be a potential for therapeutic modulations during CEA [48, 123-125].
Conclusions

We conclude that;

- the population-based perioperative complication rates for CEA in Swedvasc compares well with the large randomised trials (paper I-II).
- the risk factors in Swedvasc for preoperative complications after CEA were the indication for surgery (minor stroke vs. other indications), age, diabetes, cardiac disease and contralateral occlusion (paper I-II).
- the perioperative outcome after CEA for patients with asymptomatic severe carotid artery stenosis improved over time (paper II).
- the long-term survival was reduced for the patients undergoing CEA for asymptomatic stenosis. Predictors of decreased late survival were age, diabetes, cardiac disease and previous vascular surgery (paper III).
- the shunt indication during carotid clamping may be evaluated by a combination of stump pressure and transit time volume flow measurements (paper IV).
- the altered levels of markers for the inflammatory and fibrinolytic systems induced by carotid clamping during CEA suggested development of regional cerebral ischemia (paper V).
Summary in Swedish (svensk sammanfattning)

Bakgrund
Slaganfall (stroke) är en av de vanligaste orsakerna till sjukhusvård, handikapp och mortalitet i Sverige. Äderförkalkning med förträngning av halspulsådern, karotisstenos, beräknas orsaka ~ 15 % av alla stroke. Patienterna med karotisstenoser delas in olika kategorier, asymptomatiska respektive symtomatiska. En patient med en symtomatisk stenos har inom de senaste 6 månaderna haft en TIA/stroke som härrört från denna kärlförträngning.

Stora randomiserade studier har visat att operation av karotisstenoser, karotis endartärektomi (CEA), minskar risken för att insjukna i ett nytt stroke jämfört med bästa medicinska behandling. Den totala riskreduktionen av detta profylaktiska ingrepp är dock direkt avhängig komplikationsfrekvensen, ifa avseende bestående stroke och/eller mortalitet. Operationsresultaten i allmän klinisk praxis får inte vara sämre än i de randomiserade studierna för att den sammantagna vinsten av ingreppet skall kvarstå.

Vid CEA stängs ena halspulsådern av, vilket påverkar hjärnans cirkulation och syresättningen i varierande grad. Olika metoder för att bedöma påverkan av kärlavstängningen används, för att avgöra behovet av att under operationen använda en shunt för att säkerställa cirkulationen.

Om hjärncirkulationen lokalt får otillräckligt med syresatt blod leder detta till olika grad och omfattning av hjärncellsskada, sk cerebral ischemi. Cerebral ischemi leder också till aktivering av inflammation, koagulation och fibrinolys, vilket kan ytterligare påverka omfattningen av den ev skadan.

Syfte
Målsättningarna med avhandlingen var att undersöka de populationsbaserade resultaten för patienter som opererats med CEA i Sverige, och hur de har utvecklats över tiden, även avseende långtidsöverlevnad; att utvärdera olika metoder för att bedöma när shunt bör användas under karotis operationen; att undersöka hjärnans aktivering av inflammation, koagulation och fibrinolys vid kärlavstängning under CEA.
Delarbeten 1-5

Riskfaktorer för komplikationer efter CEA – en populationsbaserad studie.

Material/metod
Data från Svenska kärlregistret (Swedvasc) för alla registrerade CEA (n=1518) under 1994-1996 insamlades. En kombinerad kohort- och fallkontrollstudie genomfördes. Totalt 43 patienter med permanent stroke och 22 dödsfall (65/1518) var registrerade och jämfördes med två slumpmässigt valda kontroller per fall. Registret validerades.

Resultat
Komplikationsfrekvensen för permanent stroke och/eller död var 4.3 %. Oberoende riskfaktorer var operationsindikation minor stroke, diabetes och hjärtsjukdom. Kontralateral ocklusion var enda riskfaktorn i fallkontrollstudien. Registrets validitet var god.

Resultaten av karotisendartärektomi för asymptomatiska stenoser i Sverige förbättras – analys från ett populationsbaserat register.

Material/metod

Resultat

Långtidsöverlevnad efter karotisendartärektomi för asymptomatisk stenos
Material/metod

Resultat
Totalt 5808 patienter var opererade för CEA under tidsperioden, av dessa var 10.8% opererade för en asymptomatisk stenos. Medianuppföljningen var 5.1 år. För gruppen opererade för asymptomatisk karotisstenos var medianöverlevnad 10.2 år. Riskfaktorer för sämre 5-årsöverlevnad var ålder, tidigare kärlkirugi, hjärtsjukdom, diabetes mellitus.

Lokala hemodynamiska förändringar vid karotisendartärektomi – hur påverkas den cerebrala syresättningen.

Material/metod
Prospektiv studie av 62 patienter med symtomgivande täta förträngning av A carotis interna (ICA) opererade i generell narkos. Mätningar av stumptryck, volymflöde samt cerebral oxygenering (rSO2).

Resultat
Lågt stumptryck var associerat med både högt ICA-flödet före, samt med en sänkning av rSO2 under kärlavstängning, det senare reverserades vid shuntinsättning. Ett högt ICA-flödet före kärlavstängning var också associerat med en sänkning av rSO2 under kärlavstängning.

Cerebral ischemi vid karotisendartärektomi – analys an markörer för aktivering av inflammation, koagulation samt fibrinolys

Material/metod

Resultat
D-dimer,IL-6 och PAI-1 visade signifikanta skillnader mellan jugularis (JB) och radialis (RA) proverna, med en markant jugularisaktivering vid kärlavstängningen/påsläpp som tecken på cerebral ischemi.
Sammanfattning
De nationella resultaten för perioperativa komplikationer efter CEA var väl jämförbara med de randomiserade studiernas. Resultaten för operation av asymtomatisk karotisstenos förbättrades över tiden, dock var långtidsöverlevnaden minskad.
Vid bedömningen av patientens tolerans för kärlavstängning under CEA kan kombination av stumptryck och volymsflödesmätning vara användbart.
Karotisavstängning leder till förändrade nivåer av markörer för regional inflammations- och fibrinolysaktivitet som tecken på cerebral ischemi.
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