

Carotid Stenosis

Elias Johansson



Institution for Public Health and Clinical Medicine
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To my wife

“Speed is the key”
Captain Richard Winters

Talking about the operation “Pegasus”, aimed at rescuing British paratroopers after the Market Garden disaster in the autumn of 1944.

(As acted by Damian Lewis in the 5th episode of the 2001 HBO miniseries “Band of Brothers”, written by Erik Jendresen)

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Abstract

Carotid stenosis is one of several causes of ischemic stroke and entails a high risk of ischemic stroke recurrence. Removal of a carotid stenosis by carotid endarterectomy results in a risk reduction for ischemic stroke, but the magnitude of risk reduction depends on several factors. If the delay between the last symptom and carotid endarterectomy is less than 2 weeks, the absolute risk reduction is >10%, regardless of age, sex, or if the degree of carotid stenosis is 50–69% or 70–99%. Thus, speed is the key. However, if many patients suffers an ischemic stroke recurrence within the first 2 weeks of the presenting event, an additional benefit is likely be obtained if carotid endarterectomy is performed even earlier than within 2 week after the presenting event.

Carotid endarterectomy for asymptomatic carotid stenoses carries a small risk reduction for stroke. Screening for asymptomatic carotid stenosis requires a prevalence of >5% in the examined population, i.e., higher than in the general population; however, directed screening in groups with a prevalence of >5% is beneficial.

The aims of this thesis were to investigate the length of the delay to carotid endarterectomy, determine the risk of recurrent stroke before carotid endarterectomy, and determine if a calcification in the area of the carotid arteries seen on dental panoramic radiographs is a valid selection method for directed ultrasound screening to detect asymptomatic carotid stenosis.

Consecutive patients with a symptomatic carotid stenosis who underwent a preoperative evaluation aimed at carotid endarterectomy at Umeå Stroke Centre between January 1, 2004–March 31, 2006 (n=275) were collected retrospectively and between August 1, 2007–December 31, 2009 (n=230) prospectively. In addition, 117 consecutive persons, all preliminarily eligible for asymptomatic carotid endarterectomy and with a calcification in the area of the carotid arteries seen on panoramic radiographs, were prospectively examined with carotid ultrasound.

The median delay between the presenting event and carotid endarterectomy was 11.7 weeks in the first half year of 2004, dropped to 6.9 weeks in the first quarter year of 2006, and had dropped to 3.6 weeks in the second half year of 2009.

The risk of ipsilateral ischemic stroke recurrence was 4.8% within 2 days, 7.9% within 1 week, and 11.2% within 2 weeks of the presenting event. For patients with a stroke or transient ischemic attack as the presenting event, this risk was 6.0% within 2 days, 9.7% within 1 week, and 14.3% within 2 weeks of the presenting event. For the 10 patients with a near-occlusion, the risk of ipsilateral ischemic stroke recurrence was 50% at 4 weeks after the presenting event.

Among the 117 persons with a calcification in the area of the carotid arteries seen on panoramic radiographs, eight had a 50–99% carotid stenosis, equalling a prevalence of 6.8% (not statistically significantly over the pre-specified 5% threshold). Among

men, the prevalence of 50–99% carotid stenosis was 12.5%, which was statistically significantly over the pre-specified 5% threshold.

In conclusion: The delay to carotid endarterectomy was longer than 2 weeks. Additional benefit is likely to be gained by performing carotid endarterectomy within a few days of the presenting event instead of at 2 weeks because many patients suffer a stroke recurrence within a few days; speed is indeed the key. The finding that near-occlusion entails an early high risk of stroke recurrence stands in sharp contrast to previous studies; one possible explanation is that this was a high-risk period missed in previous studies. The incidental finding of a calcification in the area of the carotid arteries on a panoramic radiograph is a valid indication for carotid ultrasound screening in men who are otherwise eligible for asymptomatic carotid endarterectomy.

Sammanfattning på svenska (Swedish Summary)

Karotisstenoser är åderförmalknings-förträngningar av de blodkärl som förser främre halvan av hjärnan med blod. Dessa förträngningar kan släppa ifrån sig små bitar som orsakar blodproppar i hjärnan med stroke (slaganfall) som följd. Dock är inte alla stroke orsakade av karotisstenoser. Karotisstenoser kan opereras bort för att minska risken ett återinsjuknande i stroke. Hur stor denna riskminskning är beror på flera faktorer, men om operationen utförs inom 2 veckor från senaste symtom så minskar risken med mer än tio procentenheter oavsett kön, ålder eller om stenosgraden är mycket tät (70-99 %) eller måttligt tät (50-69 %); således är snabbhet nyckeln till framgång. Om många patienter återinsjuknar i stroke tidigare än inom två veckor från deras alarmsymtom (sista symtomet innan de söker vård), är det troligt att nyttan med en karotisoperation ökar om den utförs ännu tidigare än inom 2 veckor från alarmsymtomet.

Karotisstenoser kan också opereras bort innan de gett symtom. Att screena för sådana asymtomatiska karotisstenoser är enbart lämpligt om >5% av de undersökta har sjukdomen, men så pass vanlig är inte sjukdomen i allmänna befolkningen. Dock är riktad screening av grupper med >5% sjukdomsförekomst av nytta.

Målsättningarna med denna avhandling är att kartlägga hur lång fördröjningen till karotisoperationer är, att beräkna risken att drabbas av en ny stroke inom 2 veckor från alarmsymtomet samt att avgöra om personer, hos vilka förmalkningar vid halskärlen setts då de undersöks med panorama-tandläkarröntgen, bör genomgå riktad screening med ultraljud av halskärlen, i syfte att hitta asymtomatiska karotisstenoser.

Konsekutiva patienter med symtomgivande karotisstenos som utreddes inför en eventuell karotisoperation mellan 2004-01-01 och 2006-03-31 (275 patienter) samt mellan 2007-08-01 och 2009-12-31 (230 patienter) studerades i två studier. 117 konsekutiva personer, samtliga friska nog för en eventuell karotisoperation och med förmalkningar i området för halskärlen sedda på panorama-tandläkarröntgen, undersöktes med ultraljud av halskärlen.

Mediantiden mellan alarmsymtom och karotisoperation var 11,7 veckor under första halvåret 2004. Denna hade sjunkit till 6,9 veckor under första kvartalet 2006 och hade sjunkit till 3,6 veckor under andra halvåret 2009.

Risken för att återinsjukna i stroke var 4,8 % inom två dagar, 7,9 % inom en vecka och 11,2 % inom två veckor från alarmsymtomet i hela studiegruppen. För patienterna som sökte vård för en stroke eller TIA (men inte för ögonsymtom) var risken högre: 6,0 % inom två dagar, 9,7 % inom en vecka och 14,3 % inom två veckor från alarmsymtomet. För de tio patienter som hade en subokklusion var risken för återinsjuknande i stroke 50 % inom 4 veckor från alarmsymtomet.

Av de 117 personer med förmalkningar i området för halskärlen som undersöktes med ultraljud hade åtta en karotisstenos – dvs. förekomsten var 6,8 % (vilket inte

var statistiskt säkerställt över 5 %). Dock hittades alla karotisstenoser hos män. Hos män var förekomsten 12,5 % - vilket var statistiskt säkerställt över 5 %.

Sammanfattningsvis, fördröjningen till karotisoperation var längre än 2 veckor. Det är troligt att nytta med karotisoperationer stiger om de utförs så tidigt som inom några dagar efter alarmsymtomet – dvs. snabbhet är sannerligen nyckeln till framgång. Fyndet att patienter med subokklusioner hade en hög risk för tidigt återinsjuknande i stroke står i skarp kontrast till tidigare studier. Detta kan förklaras av att denna tidiga risk kanske missades i tidigare studier då patienterna inkluderades i dessa studier efter att denna högriskperiod hade passerat. Män hos vilka man av en händelse noterat förkalkningar vid halskärnen på panoramataktlärarröntgen bör undersökas vidare med ultraljud av halskärnen, om de i övrigt är så pass friska att en asymtomatisk karotisoperation kan bli aktuell.

Abbreviations and Glossary

These abbreviations and definitions are used throughout this thesis:

ACA	Anterior Cerebral Artery.
ACAS	Asymptomatic Carotid Atherosclerosis Study.
Acom	Anterior Communicating artery.
ACST	Asymptomatic Carotid Surgery Trial.
Amaurosis fugax	Monocular blindness of supposedly vascular origin lasting shorter than 24 hours.
ApoB/ApoA1 ratio	A measurement of lipid levels.
APP	Anterio-Posterior projection. A radiological examination used in the PtU study.
ARR	Absolute Risk Reduction. A statistical parameter for determining treatment effect. Calculated by subtracting the risk with treatment A with the risk with treatment B.
Atheroma	An atherosclerotic lesion regardless of size. In this thesis, this term is mainly limited to the presentation of the atherosclerotic process.
Carotid Angioplasty	A carotid stenosis intervention. With intra-arterial catheters the carotid stenosis is widened from the inside, often combined with a metal net – a stent.
Carotid Intervention	Either CEA or carotid angioplasty.
Carotid Plaque	An atherosclerotic lesion in the carotid artery that narrows the lumen. In this thesis, the term plaque is used to denote the atherosclerotic lesion that is not yet large enough to be classified as a stenosis.
Carotid Stenosis	A large atherosclerotic lesion in the carotid artery. In this thesis, a carotid stenosis is defined as a diameter reduction of $\geq 50\%$ according to the NASCET-method.
CCA	Common Carotid Artery.
CCA-method	One of three ways to measure the diameter reduction of a carotid stenosis.
CEA	Carotid Endarterectomy. “Carotid surgery”. A surgical procedure in which the carotid artery is opened and the atherosclerotic lesion is removed.
CEMRA	Contrast enhanced Magnetic Resonance angiography – MR angiography with intravenous contrast.
Conventional angiography	The classical invasive angiography technique. Entails injecting intra-arterial contrast with catheters.
CT angiography	Computed Tomography angiography – CT with intravenous contrast, the images are captured in the arterial phase.
ECA	External carotid artery.
ECST	European Carotid Surgery Trial.
ECST-method	One of three ways to measure the diameter reduction of a carotid stenosis.
EDV	End Diastolic Velocity. A measurement to describe flow velocities on ultrasound.
Hemodynamic	The physiological and pathophysiological concept for how the blood flows. When too little blood comes to the brain for any reasons (such as a flow limiting carotid stenosis) a hemodynamic stroke can occur.
ICA	Internal Carotid Artery.

Likelihood ratio	A statistical parameter for diagnosis. Combines sensitivity and specificity.
MCA	Middle Cerebral Artery.
Medical risk	The risk of an event in the group randomized to not receive the invasive procedure in a trial.
MR Angiography	Magnetic Resonance Angiography – MR angiography without intravenous contrast.
NASCET	North American Symptomatic Carotid Endarterectomy Trial.
NASCET-method	One of three ways to measure the diameter reduction of a carotid stenosis.
Near-occlusion	A special type of carotid stenosis that is not measured by the reduction in diameter, but by the severe hemodynamic effect the stenosis incurs.
NNT	Numbers Needed to Treat. A statistical parameter for determining treatment effect. Calculated by $1/ARR$. Denotes the number of patients that needs to be treated in order to prevent one event.
Non-invasive modality	An imaging technique that is none-invasive or minimally-invasive. Used in this thesis to designate ultrasound, CT angiography, MR angiography or CEMRA; but excludes conventional angiography.
Outcome	What a study is designed to measure, such as any stroke that occurs between time point A and B.
PCA	Posterior Cerebral Artery.
Pcom	Posterior Communicating artery
Perioperative risk	The risk of any stroke or death within the first 30 days of CEA.
Periprocedural risk	The risk of any stroke or death within the first 30 days of carotid angioplasty.
PET	Positron Emission Tomography. An advanced radiological imaging method.
Predictive value	A statistical parameter for diagnosis. The percent of patients with a positive test that actually have the disease and vice versa for negative.
Prevalence	A statistical parameter for diagnosis. The percent of a population that has the disease.
Pseudo outcome	What a (small) study is designed to study. A pseudo outcome is by itself unimportant, such as reduction in microemboli; but the pseudo outcome is known to be associated to an important outcome, such as stroke recurrence.
PSV	Peak Systolic Velocity. A measurement to describe flow velocities on ultrasound.
PtU	Panorama to Ultrasound – one of the studies in this thesis.
Retinal artery occlusion	Monocular blindness of supposedly vascular origin lasting longer than 24 hours.
Risk factor	A parameter that marks an increased risk of an unwanted outcome and if altered, changes the risk of the outcome.
Risk marker	A parameter that marks an increased risk of an unwanted outcome but when altered, does not change the risk of the condition.
RRR	Relative Risk Reduction. A statistical parameter for determining treatment effect. Calculated by dividing the difference in risk between treatment A and treatment B with treatment A.
Sensitivity	A statistical parameter for diagnosis. The percent of patients with the disease that have a positive test.
Significant stenosis	A concept of when a plaque becomes a stenosis. This might be defined as when the hemodynamic situation is altered or by when

	treatment is beneficial – thus, this concept means different things for different doctors.
Specificity	A statistical parameter for diagnosis. The percent of patients without the disease that have a negative test.
Stroke	A disease caused by disturbance in the blood flow to the brain leading to sudden decrease in neurological functions that with symptoms lasting longer than 24 hours. Can be either ischemic or haemorrhagic.
TCD	TransCranial Doppler. Ultrasound of the intracranial arteries.
TIA	Transient Ischemic Attack. A disease caused by disturbance in the blood flow to the brain leading to sudden decrease in neurological functions that with symptoms lasting shorter than 24 hours. Is most often ischemic, but can be haemorrhagic.

Original papers

Paper I: Johansson EP, Wester P. Delay from symptoms to Carotid Endarterectomy. *J Int Med.* 2008;263:404-11.

Paper II: Johansson EP, Arnerlöv C, Wester P. Risk of recurrent stroke before carotid endarterectomy: The ANSYSCAP study. *Submitted.*

Paper III: Johansson EP, Öhman K, Wester P. Risk of recurrent ipsilateral ischemic stroke in patients with symptomatic carotid near-occlusion. *Manuscript.*

Paper IV: Johansson EP, Ahlqvist J, Garoff M, Karp K, Levring Jäghagen E, Wester P. Ultrasound screening for asymptomatic carotid stenosis in subjects with calcifications in the area of the carotid arteries on panoramic radiographs: A cross-sectional study. *BMC Cardiovascular Disorders.* 2011;11:44.

Foreword

Not knowing the first thing about carotid stenoses, I approached my to-be supervisor after a lecture and asked for a job over the summer. This was in the late spring of 2006. I had recently been turned down for a summer job four times by researchers in other fields because they had made no plans to take on a summer researcher that year. Fortunately, he agreed. This was the beginning of my journey into stroke and, more specifically, into carotid stenosis. It has all been most interesting.

Although the process of atherosclerosis development and cap rupture is well understood, it is hard to determine if a certain atherosclerotic stenosis is unstable in a certain patient (and has caused the recent symptoms); and even harder to know if an unstable stenosis will lead to more symptoms. Thus, when we treat a patient by removal or bypass or with angioplasty of the atherosclerotic stenosis, we do not know if the intervention is necessary for this specific patient. Some procedures, such as coronary interventions (but not carotid interventions), can relieve ischemic symptoms. All of these invasive atherosclerosis treatments carry a periprocedural risk for the patient so that there is always uncertainty about specific individual benefit. For this reason, the concepts of risk and risk management have been created. A treatment can be considered as very beneficial if the absolute risk reduction (ARR) is 20%, dictating a number needed to treat (NNT) of 5. Roughly, this means that four out of five receiving the intervention do not benefit from it. Only if the ARR is $>50\%$ is it likely that a particular individual will benefit from the treatment. Although we seldom know if a treatment will benefit a particular patient, we can often know that treating a group of patients will result in a reduced number of symptom events and assess if the treatment is likely to be of more benefit than harm in the individual patient.

I have been fortunate to have observed about 700 pre-operative evaluations for carotid endarterectomy. Through my article reading, discussion with peers, and these observations, many questions have arisen. Some have been answered, some have not, and many simply led to more questions. In addition to the traditional introduction and presentation of the studies here, I also try to provide insight into some of the questions surrounding carotid stenosis, I hope offering something of interest both for the beginner and the advanced reader. Carotid imaging, especially the translation of flow velocities on carotid ultrasound to percent stenosis, and the patient selection for carotid intervention, especially subgroup combinations, are presented in detail. Because my research is in the pre-operative evaluation setting, I focus on such issues, forgoing detailed descriptions of atherosclerosis morphology and surgical techniques. In addition, my emphasis is on the indication for carotid endarterectomy (CEA) and when appropriate, weighing this against the perioperative risk. Other factors that affect the clinical decision, including technical aspects of surgery, life expectancy, patient preference, and the meaningfulness of the procedure, are not presented in detail.

Elias Johansson,
September 27, 2011, Umeå, Sweden

Introduction

Stroke is a disease caused by disturbance in the blood flow to the brain leading to a sudden decrease in neurological function with symptoms lasting longer than 24 hours from onset [1]. A transient ischemic attack (TIA) is the same thing as a stroke, except that all neurological functions are restored within 24 hours [2]. For stroke, the disturbance in blood flow is either ischemic (85%) or haemorrhagic (15%) [3]. Ischemic stroke is sometimes caused by local thrombosis in the cerebral vessels [4], venous disease [5], or dissection [6], but more often by an embolus to the cerebral or precerebral arteries. In rare cases, monogenetic conditions (such as CADASIL) [7] or conditions entailing an unbalanced haemostasis [8] are the underlying cause. Emboli can originate from the heart [9] or from atherosclerotic plaques and stenoses in the precerebral vessels [10]. A carotid stenosis is a pronounced atherosclerotic lesion in the carotid arteries (see figure 1) [10]. The word “carotid” comes from the Greek word “Karos”, which means “deep sleep”, because the compression of these arteries induces deep sleep (i.e., fainting because of strangulation).

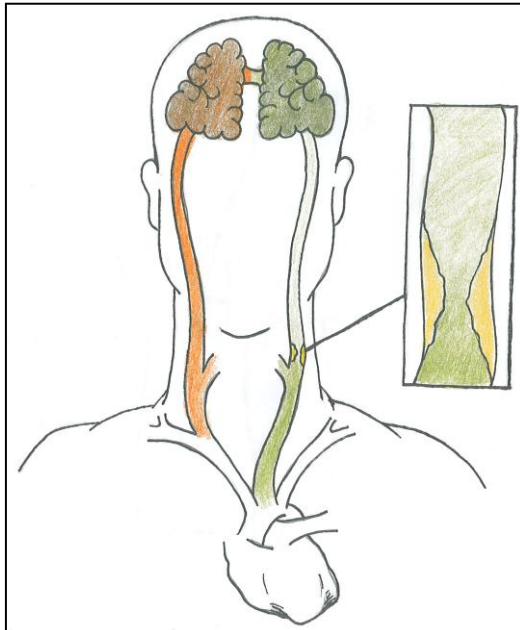
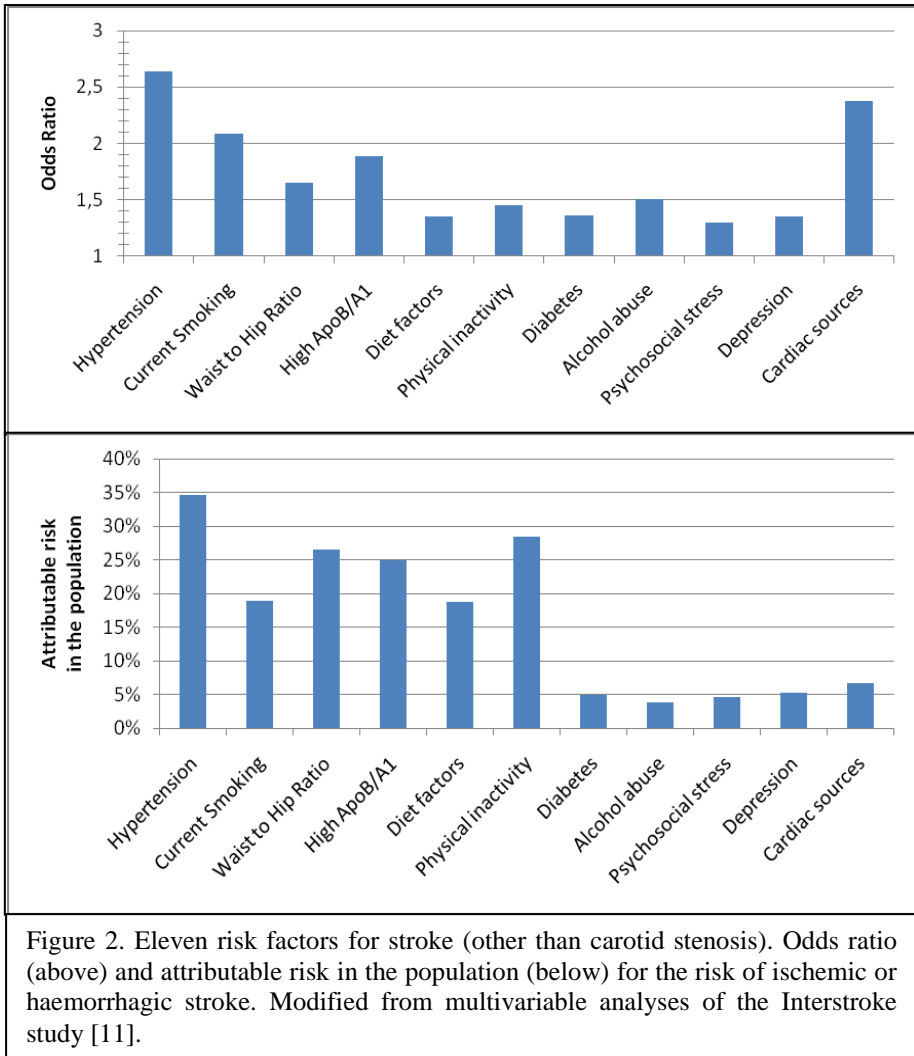


Figure 1. A carotid stenosis in the proximal left ICA. Note that the ipsilateral hemisphere is supplied by this artery (green) and not the contralateral artery (orange)

General risk factors and treatment for stroke

There are several risk factors for stroke [11]: hypertension, current smoking, high waist-to-hip ratio, high ApoB/ApoA1 ratio, dietary factors, physical inactivity, diabetes, alcohol abuse, stress, depression, atrial fibrillation or other cardiac sources, and carotid stenosis [10,11] (see figure 2). Some risk factors, such as physical inactivity, do not incur a very high odds ratio for the individual but account for a large proportion of the total number of strokes because of being quite prevalent (e.g., 92% in the case of physical inactivity). The opposite applies to cardiac stroke sources, which incur a high odds ratio for the individual patient but account for a minor proportion of the total number of strokes because of being rarer factor with a prevalence of 12% [11]. That the risk for the individual is high but the total numbers of attributable strokes is low has also been suggested for carotid stenoses [12].

In clinical practice, secondary prevention of stroke after a TIA or stroke includes lifestyle advice to promote increased physical activity, smoking cessation, and a fruit- and vegetable-rich diet. The standard medications are blood pressure-reducing, lipid-lowering, and platelet-aggregation inhibitors. In patients with atrial fibrillation, an anti-coagulant is often indicated instead of a platelet aggregation inhibitor. Carotid stenoses can be removed by endovascular surgery, CEA, or widened with carotid angioplasty.



The pathophysiology of carotid stenosis

Atherosclerosis

Carotid stenoses are caused by a process called atherosclerosis, which means “hard porridge” (in Swedish “hård gröt”) [13]. Atherosclerosis leads to an asymmetrical thickening of the artery wall resulting in formation of an atheroma (plaque) that narrows the lumen [14-16]. This atheroma can rupture, leading to a thrombus formation that might occlude the vessel locally and/or produce an artery-to-artery embolus that occludes a smaller, more distal vessel [14-16].

In more detail, atherosclerosis involves the parts of the vessel wall that is closest to the lumen (the intima and the media) [14-16]. First, lipids are deposited in the vessel wall [14-16]. Monocytes enter the vessel wall, evolve to macrophages, and take up these lipids [14-16]. Lipid-filled macrophages (foam cells) are a major component in the first stage of atherosclerosis, called the fatty streak [14-16]. With continued accumulation of lipids, through activation of immune cells (such as T-cells and mast cells), and the migration of smooth muscle cells from the media, an atheroma forms [14-16]. Atheroma formation is likely influenced by turbulence in the vessel lumen (such as the carotid bulb) because carotid stenoses are often only a few centimetres long and almost always situated in, or directly after, the carotid bulb. The atheroma consists of lipids, inflammatory cells, and often calcium crystals (calcifications). This “lipid core” is protected by a layer of smooth-muscle cells, the “fibrous cap” [14-16]. In some atheromas, this fibrous cap grows thick, reducing the risk of rupture, and thus is a stable atheroma (“stable plaque”) lesion [14-16]. In some atheromas, this fibrous cap ruptures (inflammatory activation and/or atheroma bleeding are believed to be culprits), exposing the lipid core to the bloodstream and leading to platelet activation and thrombus formation [14-16].

The clinical appearances of carotid stenosis

The most important clinical aspect of carotid stenosis is whether the stenosis is symptomatic or asymptomatic because the risk of stroke (recurrence) is much higher for patients with symptomatic carotid stenosis and management thus differs [10, 17]. A symptomatic carotid stenosis is one that has recently caused retinal emboli, TIA, or stroke whereas an asymptomatic stenosis has not [10, 17]. A carotid stenosis can be classified as symptomatic only if the symptoms conform to an embolus to the anterior circulation, i.e., the ipsilateral eye and most of the ipsilateral cerebral hemisphere [10]. For example, a patient with a recent stroke with symptoms conforming to the right cerebral hemisphere and a concurrent unilateral carotid stenosis on the left side has a left-sided asymptomatic carotid stenosis.

The definition of a symptomatic carotid stenosis is clinical, answering this question: “Is it possible that the stenosis has caused the symptoms?” Many patients who are screened for a symptomatic carotid stenosis turn out to have only a contralateral asymptomatic carotid stenosis. Thus, it is likely that some, perhaps most, patients with symptomatic carotid stenosis actually have an asymptomatic carotid stenosis ipsilateral to a cerebral ischemia caused by some other mechanism. The difference between a “truly symptomatic” and such a “falsely symptomatic” carotid stenosis cannot be made in the individual patient; thus, this line of reasoning is of no or very

limited use in the clinic. However, it does help to explain why groups differ regarding the risk of stroke recurrence and treatment effect.

Patients with recent symptoms conforming to a retinal or cerebral embolus in the anterior circulation are screened for the presence of symptomatic carotid stenosis. Depending on local practice, either all such patients are screened or only those who are also preliminarily eligible for a CEA are screened. An asymptomatic carotid stenosis can be detected *en passant* or by screening. *En passant* detection is common and most often occurs when an asymptomatic stenosis is detected on “the other side” during screening for symptomatic stenosis, and sometimes when thyroid ultrasound and time-of-flight sequences in a neck MRI are performed. Screening is described further in the panorama-to-ultrasound (PtU) study.

In the Asymptomatic Carotid Surgery Trial (ACST) study, patients with an asymptomatic carotid stenosis were as likely to suffer a non-stroke vascular death ($n=127$; $\approx 2.4\%$ /year) as any stroke ($n=120$; $\approx 2.3\%$ /year) [18]. With asymptomatic CEA, the risk of stroke was reduced, but the risk of non-stroke vascular death remained the same [18]. As a rough comparison, the heart protection study randomized 21,889 patients with a “high risk of cardiovascular events” (65% with previous cardiovascular disease) [19]. Non-stroke vascular death occurred in 685 ($\approx 1.3\%$ /year) and 818 ($\approx 1.5\%$ /year) of the patients randomized to receive simvastatin and placebo, respectively [19]. However, this rough comparison is confounded by the fact that in the ACST study, there were more people aged >75 years (21%) than in the heart protection study (6%) [18, 19]. In addition, a carotid plaque ($<50\%$ carotid stenosis) has been shown to independently increase the risk of cardiovascular events [20]. Thus, it is reasonable to regard an asymptomatic carotid stenosis as a risk marker for cardiovascular events as well as a risk factor for stroke.

Hemodynamic or embolic?

I have been told by several peers that carotid stenosis was thought to be a hemodynamic disease in the 1960s, 1970s, and 1980s but has been viewed as an embolic disease since the 1990s. With a limited number of review articles available [21, 22], it is hard to find references describing how doctors thought during those periods. However, the negative results of the hemodynamically driven EC-IC-bypass study in 1985 and the many studies on anti-platelet medication presented between 1982 and 1991 might have contributed to this suggested shift in perspective [23, 24]. Figure 3 shows a schematic image of a carotid embolus.

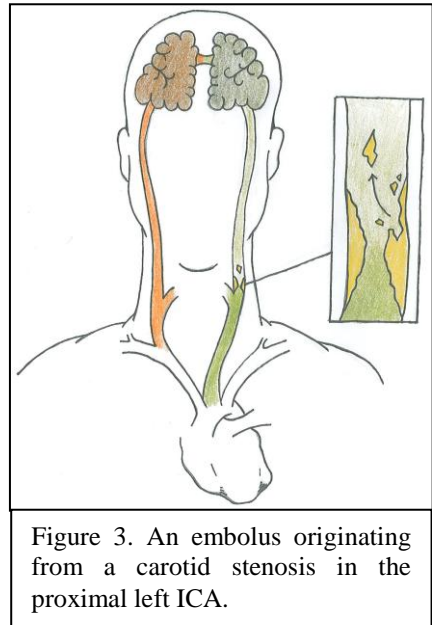
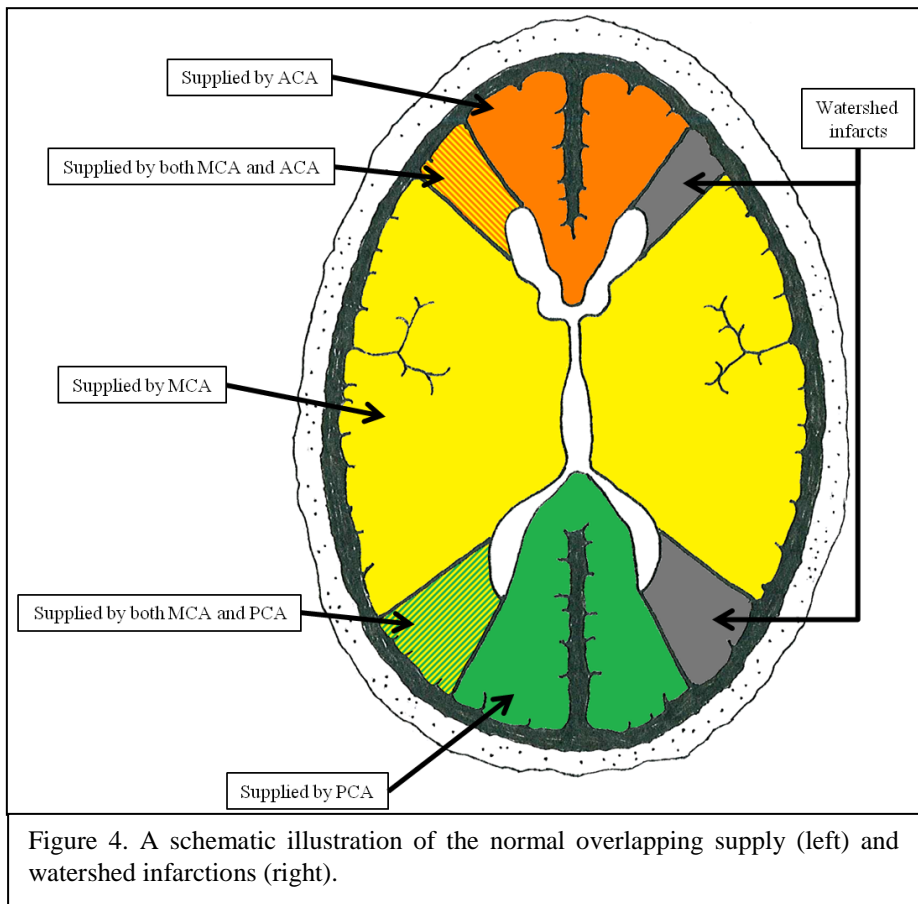


Figure 3. An embolus originating from a carotid stenosis in the proximal left ICA.

The hemodynamic effect of a carotid stenosis is complex and has a large inter-patient variation, mainly because of two factors [25]. First, in addition to the carotid artery in question, the contralateral carotid and both vertebral arteries also contribute to the circle of Willis, and there are ECA-ICA-anastomoses in the eye and in the leptomeningial vessel bed. The functional status of all of these vessels varies [25]. Second, cerebral autoregulation can dilate and constrict arterioles, closely regulated to respond to both blood pressure changes and metabolic changes [25]. Thus, from a hemodynamic standpoint, there is no degree of carotid stenosis that can be considered “significant” for all patients [21], although >50% is often regarded as significant clinically because CEA confers a treatment benefit for >50% of carotid stenoses [10]. The hemodynamic parameters of current collateral use, potential collateral use (collateral reserve), and the potential cerebral autoregulation use (cerebrovascular reserve) can all be evaluated with transcranial Doppler (TCD) combined with carotid compression and carbon dioxide stimuli [25].

Carotid stenosis is probably mostly an embolic disease because microemboli are both quite common and are reduced with increasing time since last event [26]; however, in some patients, a hemodynamic cause is apparent in the form of distinct



hemodynamic ischemia patterns on brain imaging, called watershed or border zone infarcts [27, 28] (see figure 4). These infarcts are situated in the parenchyma that is on the border between two artery supply areas; thus, when the blood flow is reduced in one or both of these arteries, this area is affected first [27, 28]. Hemodynamic stroke seems to be coupled more with the number of intracerebral collaterals than with the cerebrovascular reserve [27, 29]. Although watershed ischemia on brain imaging is compelling evidence of a hemodynamic mechanism, a similar process in a patient with a TIA might be missed. Hemodynamic symptoms, such as limb shaking and orthostatic symptom onset, are predictive of hemodynamic causes, but not all hemodynamic strokes have hemodynamic symptoms [28, 30].

Some patients have a symptomatic carotid stenosis with a definitive hemodynamic mechanism. Likewise, some patients are likely to have a definitive embolic mechanism regardless of hemodynamic factors. However, the combination of both factors might be common: It is possible that a patient with a carotid stenosis that entails a reduced cerebrovascular reserve is more susceptible to an embolus when it appears because of little or no reserve capacity for recruiting additional blood (as the arterioles are already dilated). This scenario might explain why patients with symptomatic or asymptomatic carotid stenosis and reduced cerebrovascular reserve have a higher risk for stroke than those with normal cerebrovascular reserve [31, 32]. Although the difference between a hemodynamic and embolic mechanism does not affect management of the individual patient with a symptomatic carotid stenosis (CEA regardless of mechanism), hemodynamic measurements with TCD might become useful for the selection of which patients with an asymptomatic carotid stenosis that should undergo CEA.

Crossover embolization

Given the structure of the circle of Willis (figure 5), it is possible that an embolus from a carotid artery can cross over and cause ischemia in the contralateral hemisphere (see figure 6). Two factors work against the occurrence of such crossover embolization. First, the median cerebral artery (MCA) is essentially the direct continuation of the internal carotid artery (ICA); whereas the anterior cerebral artery (ACA) and the posterior communicating artery (Pcom) are branches [33]. Thus, the most likely destination for an embolus coming from the ICA is the ipsilateral MCA, not the ipsilateral ACA (possibly on its way to the contralateral hemisphere). This notion is validated by a study showing that out of 891 patients with first ischemic strokes, 865 had a singular territory stroke; of these 865 patients, 67% had an infarct in the MCA territory and 2% in the ACA territory [34]. Second, a carotid stenosis often activates collaterals, including the anterior communication artery (Acom), shunting blood from the contralateral hemisphere [25]. Thus, for a patient with a unilateral stenosis, the embolus needs to make an unlikely trip against the blood flow to reach the contralateral hemisphere. However, a patient with bilateral carotid stenoses might shunt blood from the side of an embolus-producing carotid stenosis towards the contralateral hemisphere, especially in the case of symptomatic carotid stenosis with a contralateral occlusion.

The several case reports and small clinical studies on crossover embolization [35] are limited to basic descriptions; however, the risk of crossover embolization

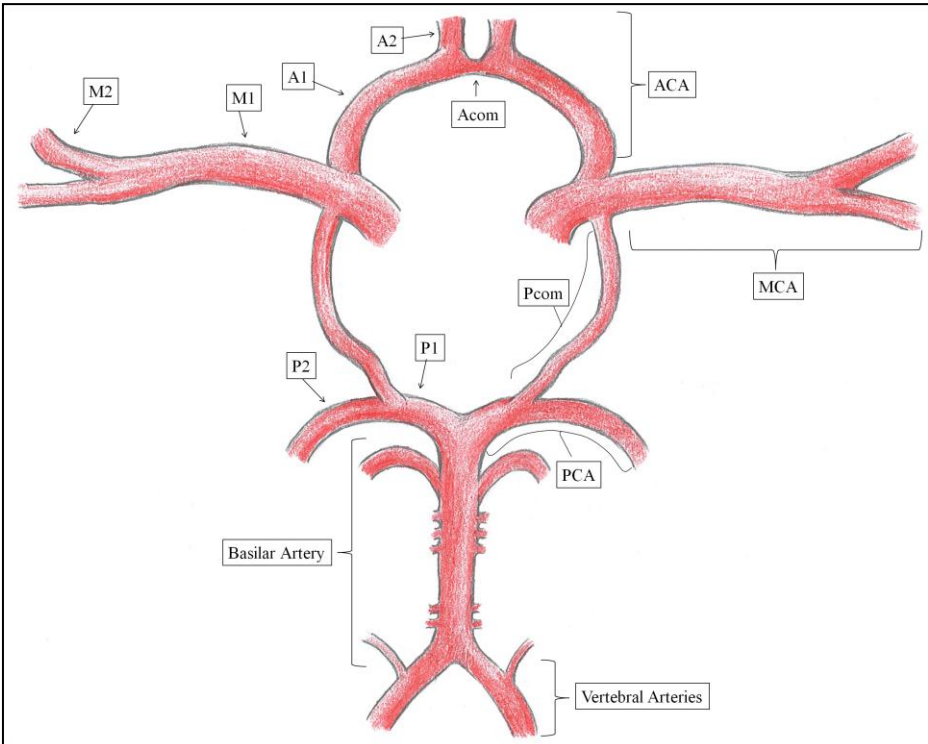


Figure 5. A schematic presentation of the circle of Willis and the major intracerebral arteries.

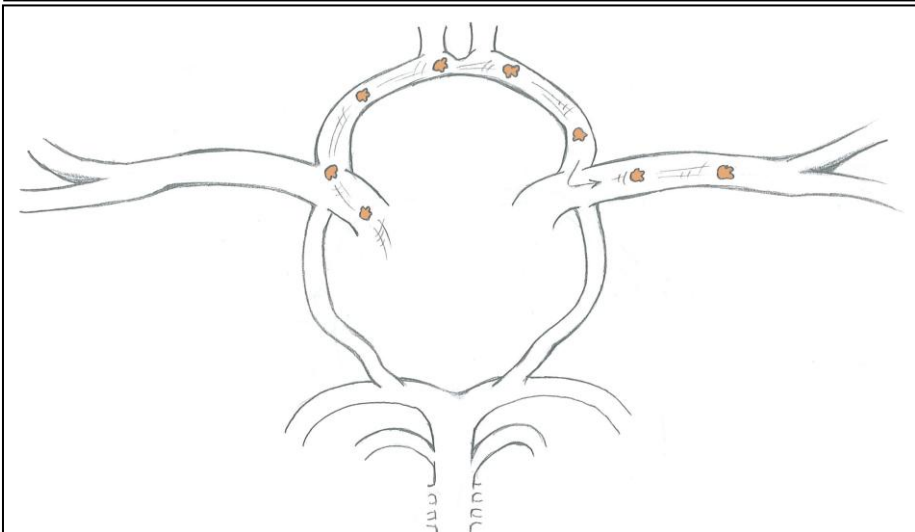
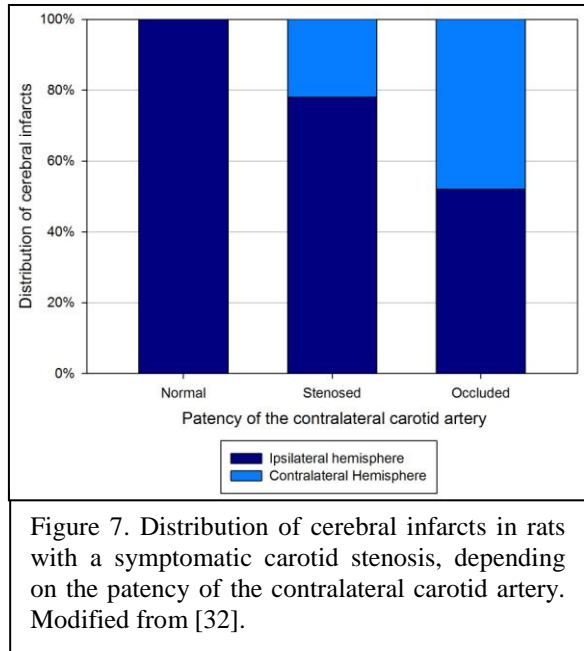


Figure 6. A schematic presentation of a crossover embolization from the left terminal ICA to the right MCA, via the left A1, Acom, and right A1.

depending on contralateral vessel status has been studied more extensively in rats [36]: All rats had a unilateral symptomatic carotid stenosis induced by laser irradiation. The contralateral carotid artery was either normal, stenosed (induced by external pressure from tying a narrow tube around the artery), or occluded (induced by ligature). The number of infarcts in each hemisphere was compared (see figure 7). These infarcts were shown to be foremost caused by embolic rather than by hemodynamic mechanisms [36]. However, these findings are confounded by the fact that in rats, the ACA (and not the MCA as in humans) is the continuous vessel of the terminal carotid artery [37].



For a patient with a unilateral carotid stenosis, crossover embolization is unlikely because blood is shunted towards rather than from the ipsilateral hemisphere. For a patient with bilateral carotid stenosis, however, crossover embolization is possible. In addition to the crossover pathway, several other embolus pathways have been proposed [35]. However, the crossover pathway is of particular interest because it has the potential to change the clinical picture of a carotid stenosis from asymptomatic to symptomatic. In the individual patient, though, crossover embolization is hard to distinguish from ipsilateral embolization or hemodynamic symptoms, but TCD can be of value in some cases. If the patient is microemboli positive, the origin of the microemboli (ipsilateral or contralateral) can be established in Power-M mode (although I am unaware of any specific case) whereas an exhausted cerebrovascular reactivity would support a hemodynamic cause.

The quality of the different arteries in the circle of Willis exhibits large inter-individual variations, with artery quality ranging from hypoplastic to very prominent [33]. Thus, for some patients, crossover embolization might be more likely than for others, possibly including the ICA-Pcom-PCA pathway, resulting in occipital ischemia.

Carotid occlusions

A carotid occlusion (figure 8) can cause cerebrovascular symptoms when it forms [38], but in clinical practice, the patient is usually seen after the carotid occlusion has occurred. In a 10-year follow-up study, the annual risk of stroke recurrence was

comparable to that of asymptomatic carotid stenoses at 2.4% [30]. Carotid occlusions are considered “safe” regarding embolization because there are no blood flows through a carotid occlusion; however, embolization from the top of the occlusion has been suggested [39].

Hedera and colleagues studied the number of recruited collaterals in patients with a unilateral occlusion. They found that 82% of the patients with a severe stroke had recruited only one collateral vessel, whereas 93% of patients who remained asymptomatic had recruited two or three collaterals ($p < 0.001$) [27].

The few patients with a carotid occlusion and an exhausted cerebrovascular reserve are at very high risk of hemodynamic stroke [40]. One suggested treatment for such patients is an EC-IC bypass surgery although such surgery did not reduce the risk of stroke in a large randomized study [23]. However, carotid occlusions made up only a small part of the study population, and no measurement of cerebrovascular reactivity was performed [23]. Nevertheless, a medium-sized randomized trial for EC-IC bypass that included patients with symptomatic carotid occlusion and an exhausted cerebrovascular reserve measured with positron emission tomography was recently stopped because of futility as there were too few strokes in the non-surgical arm (difference $p = 0.88$); the results have been presented but not published [41].

One clinical problem is that carotid occlusions sometimes are caused by a cardiac embolus lodged in the carotid arteries. Patients with such an occlusion should be managed differently from other cases, likely with anti-coagulation [9].

Carotid near-occlusions

Near-occlusion is a special type of carotid stenosis that does not fall into the normal percent system [42] (see figure 9). The carotid

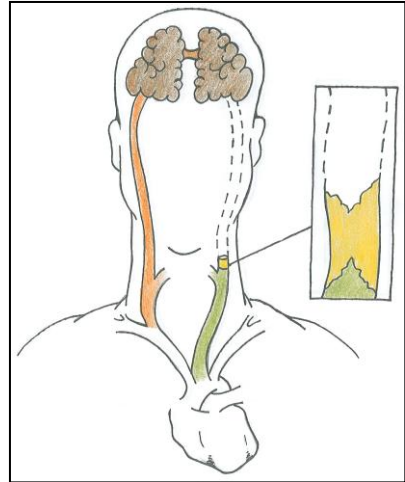


Figure 8. A carotid occlusion in the proximal left ICA. Note that the ipsilateral hemisphere is not supplied by this artery (green) but by the contralateral artery (orange).

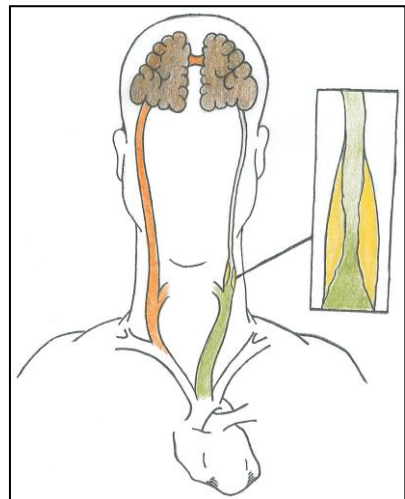


Figure 9. A carotid near-occlusion in the proximal left ICA. Note that although the ICA is patent, the ipsilateral hemisphere is not supplied by this artery (green) but by the contralateral artery (orange).

stenosis is so tight that the amount of blood flowing through the stenosis is reduced, leading to collapse of the distal artery [42]. The prevalence ratio of 70–99% carotid stenosis and near-occluded stenosis was roughly 4:1 in the NASCET (North American Symptomatic Carotid Endarterectomy Trial) + ECST (European Carotid Surgery Trial) trials [10]. Near-occlusions have been defined on conventional angiography [42]. Correlations for non-invasive modalities and the clinical implications of near-occluded stenosis are described further in the introduction to the studies.

Management of carotid stenosis

History

The first connection between carotid stenosis and stroke was shown in autopsy studies in 1906 [43]. In 1951, a case series (n=8) correlated carotid artery occlusions and cerebral infarction [44]. Subsequently, the first CEA was performed around 1953, although the exact date and surgeon are disputed [45]. Research collaborations have shown an 8% risk reduction for stroke with CEA [45]. CEA became more popular with 107,000 operations performed in 1985 in the USA [45]; however, criticism about current complication rates and the underlying studies arose [45]. The ECST study started to randomize patients in 1981, the NASCET study in 1987, the ACAS (Asymptomatic Carotid Atherosclerosis Study) study in 1987, and the ACST study in 1993 [18, 46-48]. These four studies form the foundation of our present knowledge on the management of carotid stenosis.

Carotid surgery and angioplasty

The risk of stroke is reduced with CEA in patients with symptomatic carotid stenosis [10, 47-50], but the CEA procedure itself entails a risk of stroke and death [10]. Two large trials have randomized patients between either best medical treatment and CEA or best medical treatment alone: NASCET and ECST [47, 47]. These studies were performed simultaneously and were roughly equal in size, including 5893 patients in total [10]. There were differences between the trials, but the ECST stenosis and outcome definitions have been “translated” into those used in the NASCET trial [51]. The studies have subsequently been pooled with data from individual patients [10, 49, 50]. The most important outcome was the net effect of CEA for ipsilateral ischemic stroke within 5 years, taking any stroke/death within 30 days of trial surgery into account: CEA reduced the net risk of stroke by 4.7% in patients with 50–69% carotid stenosis and 13.5% in patients with 70–99% carotid stenosis [49]. Patients with a <30% carotid stenosis had no benefit from CEA but suffered perioperative events; thus, the net effect was that CEA was harmful in these patients [10]. Patients with 30–49% or near-occluded carotid stenoses had a small benefit with CEA, equal to the number of perioperative events; thus, the net effect was that CEA was neither beneficial nor harmful for these patients [10]. In addition to degree of stenosis, the benefit of CEA was also influenced by age, sex, and timing of surgery [49]. Further description of these and other factors is presented in the “Patient Selection for Carotid Intervention” section.

Two large randomized trials have been performed with the same basic design as the NASCET and ECST studies, but including patients with asymptomatic 60–99% carotid stenosis: ACAS and ACST [18, 46]. The ACST study was larger (n=3120) than ACAS (n=1662) [18, 46]. In addition, in the ACAS study, the selection of surgeons was strict and centres were excluded from further inclusion after perioperative events had occurred [52]; thus, the ACAS study did not mirror the intended clinical practice. Subsequently, the ACAS results were debated, and the ACST study was undertaken [18, 53]. Both studies showed a benefit with asymptomatic CEA with the annual risk of stroke (excluding perioperative events) reduced from approximately 2% to 1% [17, 18, 46]. The perioperative risk for asymptomatic CEA is 2–3% [18, 54], so that the net benefit is small; thus, only

patients with a low perioperative risk (<3%) and a long life expectancy (>5 years) should be considered for asymptomatic CEA [17, 18, 55, 56]. Patients aged ≥ 75 years had no benefit from asymptomatic CEA because they suffered stroke more often than younger patients despite having undergone CEA [17]. A trend was detected in both studies for women's experiencing no benefit from CEA for asymptomatic carotid stenosis; however, this finding did not persist in the 10-year follow-up of the ACST study [17, 18, 46, 53]. There were no differences between degrees of stenosis, but few patients with stenosis <70% were included in these studies [17, 46].

Patients with both symptomatic and asymptomatic stenosis have been randomized between CEA and carotid angioplasty in several recent and ongoing trials [57]. The results thus far suggest that the periprocedural risk of stroke or death is comparable but slightly higher for patients who underwent carotid angioplasty [57]. The risk of myocardial infarction and peripheral nerve damage is higher with CEA than with carotid angioplasty [57]. During follow-up, the risk of stroke recurrence was comparable but tended to be lower for CEA [57]. Thus far, subgroup analyses have revealed that the periprocedural risk of stroke and death are similar for CEA and carotid angioplasty in younger patients, but that the periprocedural risk is higher for carotid angioplasty than for CEA in older patients [57]. Thus far, it seems that CEA is slightly superior to carotid angioplasty; further subgroup analyses and with longer follow-up are pending. Carotid angioplasty is preferable over CEA for patients with previous ipsilateral CEA and/or neck irradiation because these conditions involve soft tissue fibrosis, which increases the risk of damaging delicate structures during the operation [58].

Because carotid angioplasty is quite rare at the Umeå Stroke Centre, our knowledge of indications is mainly based on CEA, and to make this thesis more readable, I use the term CEA synonymous with carotid intervention (either CEA or carotid angioplasty), unless the context clearly shows otherwise.

Medical management of patients with carotid stenosis

To the best of my knowledge, no large randomized trial has compared different medical treatments specifically in patients with carotid stenosis. When patients with stroke were randomized in such trials, the presence or absence of carotid stenosis did not influence the treatment effect [59]. However, patients with carotid stenosis have often been excluded from trials studying anti-coagulation therapy [60-62]. Thus, the best evidence suggests that patients with symptomatic carotid stenosis should receive the same medical treatment as other patients with TIA or stroke [59]. Patients with asymptomatic carotid stenosis should be prescribed the same level of medical prevention as patients with symptomatic carotid stenosis because they are at high risk of suffering vascular events (see “The clinical appearances of carotid stenosis” section). Many patients with an asymptomatic carotid stenosis have suffered a cardiovascular event before their carotid stenosis is detected [18]; thus, in many cases, they have already been prescribed medical prevention at the appropriate level.

One study randomized 107 patients with symptomatic 50–99% carotid stenosis and microemboli (detected with TCD) to receive either aspirin and clopidogrel or aspirin alone. Compared to the patients with monotherapy, the patients receiving dual therapy had a larger reduction in the amount of microemboli at day 7 and a lower total number of microemboli at day 2 and at day 7. There was also a trend towards fewer TIA and strokes for patients receiving dual therapy [63]. A subsequent study randomized 60 similar patients to either aspirin and dipyridole or aspirin and clopidogrel. There were no differences in microemboli measurement and no recurrent strokes during the short follow-up [64]. Thus, dual therapy with aspirin and either dipyridole or clopidogrel might reduce the risk of stroke recurrence before CEA compared to aspirin alone. However, this reduction has been shown only with pseudo-outcomes. Our local surgeons advocate against the use of clopidogrel before CEA because it increases the risk of wound haematoma, a condition that in some cases can be serious.

Bilateral carotid stenosis of 70–100% should affect hypertension management [65]. One study compared 2×2 groups of patients, all with carotid stenosis on at least one side, either with or without bilateral 70–100% carotid stenosis and with a systolic blood pressure either higher or lower than 150 mmHg (measured over time). Patients without bilateral carotid stenoses of 70–100% and a systolic blood pressure of ≥ 150 mmHg have a higher risk of stroke than patients with the same degrees of carotid stenoses but with a systolic blood pressure of < 150 mmHg. Thus, for patients without bilateral 70–100% carotid stenoses, lowering the blood pressure to < 150 mmHg confers benefit. Patients with bilateral carotid stenoses of 70–100% and a systolic blood pressure of ≥ 150 mmHg have the same (high) risk of stroke as patients with the same blood pressure but without bilateral 70–100% carotid stenosis. However, patients with bilateral carotid stenoses of 70–100% and a systolic blood pressure of < 150 mmHg have a much higher risk of stroke than patients with the same degrees of carotid stenoses but with a systolic blood pressure of ≥ 150 mmHg. Although patients with bilateral 70–100% and a high systolic blood pressure have a high risk of stroke, lowering the blood pressure to < 150 mmHg entails harm. Therefore, for patients with bilateral carotid stenosis of 70–100%, systolic blood pressure should be maintained above 150 mmHg [65].

Carotid imaging

In summary:

- There are three methods for grading carotid stenosis: The NASCET method, ECST method, and CCA (common carotid artery) method. Evidence for treatment is mostly based on the NASCET method.
- Conventional angiography is the gold standard modality for carotid imaging. Because of the risk of stroke associated with this modality, it is seldom used.
- The diagnostic performance of carotid ultrasound depends on the method for translating the recorded flow velocities into diameter stenosis.
- Carotid ultrasound and CT angiography are both accurate and readily available methods. Either can be used for screening.
- CEMRA (contrast-enhanced magnetic resonance angiography) is slightly more accurate but less available than ultrasound and CT angiography.
- For patients with a high predicted gain with CEA, it is reasonable to abstain from confirmation of the degree of stenosis with an additional imaging modality; for patients with a low predicted gain, such confirmation could be considered.
- Sometimes carotid ultrasound and CT angiography do not concur, and the clinical decision is dependent on this difference. If the patient has a high predicted gain with CEA, it is reasonable to base the decision on the modality that shows the tightest stenosis. If the patient has a low predicted gain with CEA, it is reasonable to perform a third examination with CEMRA but to try to abstain from conventional angiography.
- For the final goal of reducing the risk of stroke, the imaging strategy is less important than achieving a short period to CEA and performing CEA on patients with 50–99% carotid stenoses (and not solely on 70–99% carotid stenoses).

Diagnostic tests in general

Diagnostic efficacy statistics relies on the assumption that something is true (the gold standard – sick or healthy) and that something may mimic this truth (the test – positive or negative). By analysing coupled observations, the test produces true-positive, false-positive, true-negative, and false-negative results.

Sensitivity is the proportion of true-positive findings among all sick individuals. Specificity is the proportion of true-negative findings among all healthy individuals. When a test is sensitive, a negative finding can be trusted because few individuals will be false negative. When a test is specific, a positive finding can be trusted because few individuals will be false positive.

Likelihood ratios combine sensitivity and specificity to a measurement of “what is the implication of a positive/negative finding”. The positive likelihood ratio is calculated by $\text{sensitivity}/(1-\text{specificity})$ and should be >10 [66]. The negative likelihood ratio is calculated by $(1-\text{sensitivity})/\text{specificity}$ and should be <0.1 [66].

Likelihood ratios are independent of prevalence and are most important when comparing different tests.

Predictive values are the most important in the clinical situation. The positive predictive value is the proportion of true positive findings among all positive findings; the negative predictive value is the proportion of true negative findings among all negative findings. Thus, when you have a positive finding, the positive predictive value tells you “what is the chance that this patient actually is sick?” and vice versa. The predictive values strongly depend on the prevalence. If one expresses prevalence and positive predictive values as odds, then the positive predictive value = prevalence * positive likelihood ratio, and essentially vice versa for the negative predictive value. Tests that are equally sensitive and specific will often produce higher negative predictive values than positive because the prevalence is low ($<<50\%$) in many clinical situations.

Receiver operator curves plot the sensitivity and specificity for different test values for a (preferably continuous) test variable, allowing for the detection of the most accurate threshold. In addition, the area under the curve represents the diagnostic ability of the test, expressed as a single measurement, and allows for comparisons between different tests.

More important than the efficacy measurements presented thus far is the effectiveness of a test, i.e., what the clinical implications will be. This is often, but not always, the predictive value in a specific clinical situation. An example is from a study based on the same ascertained population as in the HUS study [67]: Carotid bruits are 71% sensitive and 81% specific for identifying a 50–99% carotid stenosis, with ultrasound as the gold standard, with a positive likelihood ratio of 3.65 and negative likelihood ratio of 0.36. Thus, the efficacy is quite poor. One effectiveness scenario to consider is, “Should carotid screening in symptomatic patients be limited to those with a carotid bruit?” 36% of the patients with a symptomatic carotid stenosis in the study did not have a carotid bruit. Missing 36% of the patients with a symptomatic carotid stenosis is not acceptable. Thus, in this clinical situation, carotid bruits are not effective. Another effectiveness scenario to consider is, “If the goal is to find asymptomatic carotid stenoses, should carotid screening be performed in those with a carotid bruit found *en passant*?” The finding is that 31% (95%CI 22–40%) of patients with only a carotid bruit as an ultrasound indication had a carotid stenosis; the threshold for screening is $>5\%$ [68]. Thus, in this clinical situation, carotid bruits are effective.

Measurements of carotid stenosis

Carotid stenoses are measured as a percentage diameter reduction; calculated as $1 - (\text{the smallest lumen diameter in the stenosis} / \text{comparison})$. What the comparison is differs among the three different methods of calculating the diameter reduction (see figure 10):

- The NASCET method is named after the randomized trial that employed it. The comparison is the diameter of the unaffected internal carotid artery distal to the stenosis with an inter-observer kappa of 0.72 [69].

- The ECST method is named after the randomized trial that employed it. The comparison is the normal vessel diameter at the site of the stenosis, with an inter-observer kappa of 0.66 [69].
- The CCA method comparison is the diameter of the unaffected common carotid artery proximal to the stenosis, with an inter-observer kappa of 0.76 [69].

A rough translation among these degrees of stenosis is as follows:

- 50% NASCET stenosis = 70% ECST stenosis = 70% CCA stenosis [69].
- 70% NASCET stenosis = 80% ECST stenosis = 80% CCA stenosis [69].

The pooled data from the NASCET and ECST studies were subjected to the NASCET grading method [10]; thus, the best available evidence for symptomatic carotid stenosis is based on the NASCET method. The NASCET grading method includes near-occlusion as a separate category of degree of carotid stenosis [10]. The ECST method yields an estimation of the diameter of the carotid bulb; although this is intriguing because it measures the degree of stenosis in situ, it also entails a trend towards lower inter-observer reliability [69].

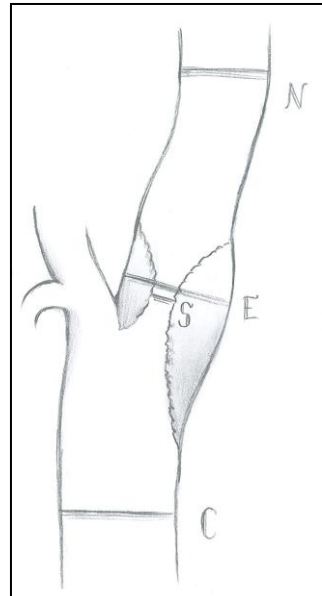


Figure 10. The diameter points used to calculate the degree of carotid stenosis. Comparisons: C: CCA-method. E: ECST-method. N: NASCET-method. S: Stenosis diameter

Throughout this thesis, the NASCET grading method is used.

Imaging modalities

Conventional (catheter) angiography: With an intra-arterial technique, a contrast medium is injected into the carotid arteries, and several projections are captured [70]. Diameter reductions are expressed as percent stenosis [69]. This modality was used in the randomized trials of symptomatic carotid stenosis [10] and has thus become the gold standard because clinical decisions are based on it [70, 71]. The pros are that it is the gold standard method and can be combined with carotid angioplasty, but the cons are that it is expensive and labour intensive and requires contrast and radiation, but above all, it incurs a 1.62% periprocedural risk of stroke or death [70, 72].

In contrast to conventional angiography, the remaining modalities are non-invasive or minimally invasive (only intravenous access). In this thesis, a “non-invasive” test/modality refers to ultrasound, CT angiography, MR angiography, or CEMRA.

Carotid ultrasound: With B-mode (grey-scale 2D picture), the vessel is imaged, and morphological details can be noted. With pulsed-wave Doppler mode, the blood-

flow velocities in the vessel are measured. The degree of carotid stenosis is determined by translating the measured blood flow velocities into percentage of diameter reduction; this translation is discussed further below. Because the diagnostic performance of carotid ultrasound depends on the choice of translation method, the mean values for the six articles discussed at the 2010 consensus conference (see below) are presented in table 1. Carotid ultrasound was widely used in the randomized trials of asymptomatic carotid stenosis [17, 46]. In these studies, blood flow velocities by themselves were not used as the measurement of stenosis but only as a way to reproduce the findings of conventional angiography. The pros are that it is non-invasive, cheapest, widely used and available, and makes detailed morphological evaluation possible. Cons are that it is operator dependent, that blood flow velocity translations are not standardized (see below), and that it is the only modality that does not depict the intracranial vessels [70].

The quality of a carotid ultrasound examination is dependant on the expertise of the sonographer. Throughout this thesis it is assumed that the carotid ultrasound is performed by an experienced sonographer. In clinical practice, this might require that patients examined with carotid ultrasound at small hospitals are re-examined at larger hospitals.

Table 1. Diagnostic performance of ultrasound, CT angiography, MR angiography, and CEMRA for 70-99% carotid stenosis. Conventional angiography is the gold standard.

	Sensitivity %	Specificity %	Likelihood ratio		Predictive value*	
			Positive	Negative	Positive %	Negative %
Ultrasound [73-79]	90	94	15.0	0.11	63	99
CT angiography [71]	77	95	15.4	0.24	63	97
MR angiography [71]	88	84	5.5	0.14	38	98
CEMRA [71]	94	93	13.4	0.06	60	99
*Assuming a prevalence of 10%, i.e. when performing screening on patients with recent symptoms						

CT angiography: Intravenous contrast is injected, and a CT examination is performed with a short delay, so that the contrast is in arterial phase [70]. Diameter reductions are expressed as percent stenosis [70]. For comparison with conventional angiography, see table 1. Pros are that it is minimally invasive and available for screening directly on admission. Cons are the radiation, contrast, and somewhat lower sensitivity [70].

MR angiography: Diameter reductions are expressed as percent stenosis [70]. CEMRA is the most accurate of the non-invasive modalities (see table 1). MR angiography (without contrast) has a poorer sensitivity and specificity than the other modalities (table 1) but can be used when the brain and neck are examined for other reasons. Techniques for morphological assessment are under evaluation. Pros are that CEMRA is highly accurate and minimally invasive and involves no radiation. Cons are that it is expensive and might not be readily available and that it involves contrast [70].

Translating flow velocities to percent diameter reduction

When the blood flows through a carotid stenosis, the blood flow velocity increases, which can be detected with ultrasound on a spectrogram [70]. The two most important measurements on the spectrogram are the peak systolic velocity (PSV) and the end diastolic velocity (EDV). PSV and EDV can be measured at the point of maximum stenosis, before the stenosis (in CCA), and/or distal to the stenosis. The most common measurement in different translation methods is the PSV in the stenosis; however, EDV in the stenosis and the quota between the PSV in the stenosis and the PSV in the CCA are sometimes used [73-79]. Of importance is also the Doppler angle; in some studies, the Doppler angle is kept constant while in others, different velocity criteria are used for different Doppler angles [73-82]. By comparing these velocity measurements with conventional angiography, velocity thresholds for different stenosis categories have been created in several studies, i.e., as ways to translate velocities into degree of carotid stenosis. Because several studies have been performed, there is a multitude of translation systems [73-93].

An inquiry among the different ultrasound examiners revealed that the hospitals referring patients to the Umeå Stroke Centre used six different translation systems. An analysis on parts of the ANSYSCAP study revealed that in 17% of the neck sides, the degree of stenosis category changed between the ultrasound examination at the referring hospital and the ultrasound examination at our hospital. If all providers had used the same translation system, this number would have been 6%. Thus, the difference in the translation system used resulted in clinical problems.

Choosing translation method – systematic review and consensus conference

A systematic review was conducted to find the best available translation system to recommend to all ultrasound examiners working in the referring hospitals. Four PubMed searches revealed 1642 potential articles. These were first title audited and then abstract audited by two observers (Elias Johansson and Per Wester); 231 articles remained relevant and were read. Additional articles were ascertained from reference lists or were known from previous searches. In total, 361 articles were audited. Articles selected compared carotid ultrasound to conventional angiography, involved ≥ 50 patients and velocity thresholds for 50% and 70% NASCET stenosis (or 70% and 80% ECST or CCA type stenoses), and presented sensitivity and specificity (or at least sufficient data to allow calculation of sensitivity and specificity). Nineteen articles fulfilled these criteria, evaluating 17 translation systems [74-79, 81-93].

To judge the overall design of these 19 articles, a points system was created, based on the study design and the quality of the angiography. Important issues were given 2 points; less important issues were given 1 point:

- Consecutive patients (2p)
- >200 neck sides analysed (2p)
- Prospective design (1p)
- Validating an existing threshold system (1p)
- Blinded analysis (2p)
- Selective catheterization on angiography and at least two projections (1p)
- Two examiners on angiography (1p)

- Delay between ultrasound and angiography <1 month (2p) or <3 months (1p)

0–6 points was considered a poor study design, 7–10 points a good study design, and 11–12 points an excellent study design. Eleven articles had a poor design [81, 82, 85-93], and an additional two articles had a poor outcome (sensitivity or specificity <50%) [83, 84]. Six articles evaluating five translation systems had a good or excellent design and good outcome [74-79].

In February 2010, the Umeå Stroke Centre hosted a consensus conference for Northern Sweden at which these five translation systems were discussed. One translation system used three different velocity measurements, and depending on different physiological conditions, these should be combined in different ways [77, 78]. This translation was intriguing because it incorporated several physiological aspects; however, it was not chosen for use in the northern region of Sweden because it was too complex for use in the smaller hospitals. The four remaining systems were all considered feasible. The Leonardo system [75] was chosen because the study evaluating it had an excellent design and the outcome was very good: 95% sensitive and 94% specific for 70–99% carotid stenoses. The Leonardo system uses PSV and EDV in the stenosis, and if the contralateral artery has a $\geq 70\%$ stenosis, the thresholds are somewhat higher. The Leonardo system is currently under evaluation at the University Hospital of Northern Sweden, comparing it to the translation system already in use [74].

Are non-invasive modalities accurate enough for clinical decisions?

Usually quoted “rules of thumb” for when a diagnostic test is “good enough” are a positive likelihood ratio >10 and/or a negative likelihood ratio <0.1 [66]. However, whether a test is good enough depends on several factors; such as the inter-observer reliability of the gold standard method, the clinical implications of misdiagnosis, and the clinical implications of further testing.

For carotid stenoses, conventional angiography is the gold standard because it was used in the randomized trials of symptomatic carotid stenosis [10, 49, 50]. However, no evidence shows conventional angiography yields a better risk discrimination than the other modalities. There is reason to suspect that an area stenosis measurement or flow velocities are better at risk discrimination because these are more physiological measurements than the diameter stenosis measurement. To date, there are no hard data to support this hypothesis.

Rothwell and colleagues found that the inter-observer kappa for conventional angiography is 0.72 [69]. To facilitate a comparison of this kappa value to the parameters in table 1, the data presented in that article [69] were recalculated: One of the observers was set as the gold standard, and the diagnostic test efficacy of the other observer was calculated. This calculation was repeated after switching the observer roles. The total agreement was 91%. Depending on which observer was set as the gold standard, the positive likelihood ratios were 6.5 and 9.2, and the negative likelihood ratios were 0.07 and 0.10. These values are comparable to or worse than ultrasound, CT angiography, and CEMRA [71, 74-79]. Roughly, this implies that one is as likely (or more likely) to get an agreement between an examination with

any of these three modalities and one observer looking at a conventional angiogram compared to if another observer looked at the same angiogram. However, this conclusion is not completely accurate because most diagnostic studies employ a design of two angiogram observers with a consensus decision or a third observer in cases of disagreement.

Nevertheless, because the inter-observer agreement for angiography is 91%, any modality that has sensitivity and specificity around 91% is definitively accurate enough. This is true for carotid ultrasound and CEMRA but not for MR angiography. The somewhat lower sensitivity of CT angiography is acceptable because the high specificity results in a high positive likelihood ratio (table 1).

What modality should be used for screening?

Carotid ultrasound and CT angiography are both available methods. The diagnostic performance of these two modalities is similar. CEMRA is slightly superior but not readily available in many centres. MR angiography is not a good screening method because of its low diagnostic performance. To avoid any delay to CEA is more important than if ultrasound, CT angiography, or CEMRA is used for screening; the modality that provides results first should be used [94]. What modality that first provides results varies from hospital to hospital, but CT angiography in the same session as the standard CT brain might be considered if the kidney function allows for the use of intravenous contrast.

Is confirmation with conventional angiography required?

Both conventional angiography and CEA entail a risk of stroke and death [10, 72]. It is not reasonable to routinely perform conventional angiography if doing so means that the total periprocedural risk (risk with conventional angiography + risk with CEA) is increased. The total periprocedural risk depends on three factors: The risk with conventional angiography, the risk with CEA, and the prevalence of patients who actually will undergo CEA after the confirmation is made (i.e., the positive predictive value of the non-invasive imaging modalities used thus far). There are two management options: (1) Perform CEA without confirmation with conventional angiography, or (2) confirm with conventional angiography and only perform CEA on those for whom the indication remains. In the latter option, the total periprocedural risk is as follows:

$$CA-risk + Prev * CEA-risk$$

CA = Conventional Angiography; Prev = Prevalence of patients that will undergo CEA

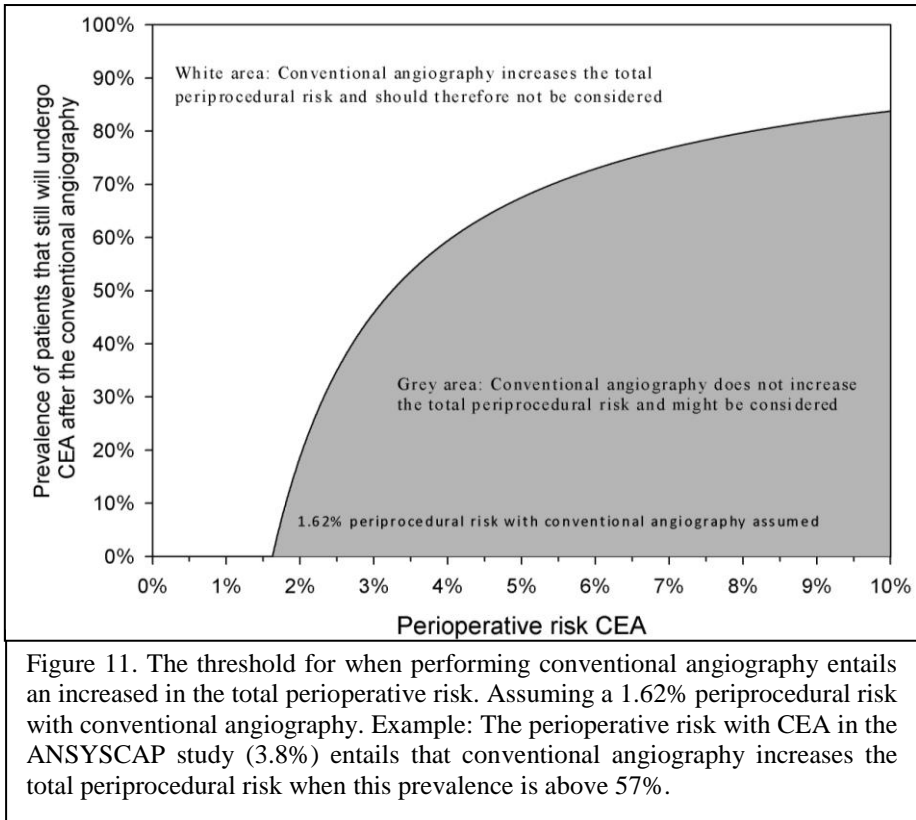
The threshold for when using conventional angiography increases the total periprocedural risk is as follows:

$$CEA-risk = CA-risk + Prev * CEA-risk$$

Simplified into: $Prev = 1 - (CA-risk / CEA-risk)$

Assuming a risk of conventional angiography of 1.62% [72], this threshold is presented in figure 11. With positive predictive values of around 60% (table 1), a CEA risk of <4.1% indicates that conventional angiography should not be

considered; this is roughly the expected perioperative risk [54, 57]. However, conventional angiography is not a perfect measurement (see the previous section); patients with a 30–49% symptomatic carotid stenosis who needlessly undergo CEA are actually not exposed to a net risk (see the “management of carotid stenosis” section), there is the additional cost of the examination, and it is likely that CEA will be delayed. Thus, it is not reasonable to routinely perform CEA without confirmation with conventional angiography [94].



Using multiple non-invasive modalities

In clinical practice, examinations with several non-invasive modalities are often performed on the same patient. The reasons include: (1) If the result of the first modality is of poor quality, an additional modality is often required. (2) The intervening physician often has the most experience with a particular modality and thus requests it; at the University Hospital of Northern Sweden, the vascular surgeons request an ultrasound (in part because only ultrasound has been validated against conventional angiography locally [74]), and the interventional radiologists request CT angiography. (3) There is the need to confirm that the degree of stenosis is tight enough for CEA to be performed.

At least in our clinical practice, ultrasound and CT angiography are the modalities that are most often combined. Often, these modalities have concurrent findings. Sometimes, one of the examinations is of poor quality, and then the other should be trusted. But what to do when ultrasound and CT angiography are in disagreement, both are of good quality, and the treatment decision depends on this difference? Two possible courses of action are as follows:

1. Base the decision on the modality that shows the tightest degree of stenosis (i.e., perform CEA). Both methods are more specific than they are sensitive; thus, a positive finding can be trusted, but a negative finding cannot be trusted as much. In this case, the disagreement is more likely caused by the fact that the modality showing the tightest degree of stenosis is correct (reflecting its high specificity) and that the other modality is false negative (reflecting its lower sensitivity). This scenario is even more likely when it is CT angiography that shows the less-tight degree of stenosis because its sensitivity is lower than that of ultrasound.
2. Perform a CEMRA examination. Because CEMRA is more sensitive than and as specific as ultrasound and CT angiography, there is reason to trust this modality more than the other modalities. This strategy applies only to a small subset of patients, so the lower availability of CEMRA is less of a problem. It is reasonable to consider conventional angiography in this situation if CEMRA cannot be performed, such as for patients with a pacemaker.

It is sound to pursue the first course of action for patients with a symptomatic carotid stenosis and a high predicted gain with CEA (such as all patients with <2 weeks delay to CEA). This course of action results in a clinical practice where it is more certain that CEA will be performed on the patients in need of it, but sometimes CEA will also be performed on patients who actually have a 30–49% carotid stenosis. Withholding CEA because of a misdiagnosis carries a high risk of stroke for these patients and must be avoided. In addition, performing CEA on patients with a true 30–49% stenosis is not that problematic because it does not incur an increased net risk of stroke (see the “management of carotid stenosis” section). Thus, for these patients, it is preferable to make sure that all patients in actual need of CEA undergo it, and it is acceptable that this means that some patients undergo CEA needlessly.

It is reasonable to pursue the second course of action for patients with a lower predicted gain from CEA, such as asymptomatic patients and symptomatic patients with long delay to CEA in combination with a 50–69% carotid stenosis and/or female gender. For these patients, the risk–benefit balance is narrower, and withholding CEA because of a misdiagnosis is not as precarious as for those with a high predicted gain. As mentioned above, performing CEA needlessly on symptomatic patients with a true 30–49% carotid stenosis is not problematic *per se*. It is unknown if CEA is of benefit or harm for patients with a <70% asymptomatic stenosis [17, 46]. In addition, the diagnostic accuracy of the non-invasive modalities is not as good in the 50–69% carotid stenosis category as it is in the 70–99% carotid stenosis category [71]. Thus, the target population has a small net benefit. To “mix” such a population with a population without net benefit or an unknown net benefit

will result in a “diluted” clinical practice with a very low (perhaps no) overall benefit. Thus, for these patients, it is preferable to be more certain of the indication for CEA.

Should confirmation with another non-invasive modality be routine?

The 2011 American Heart Association (AHA) guidelines suggest that carotid ultrasound is sufficient if the examination quality is high, so confirmation is not required [55]. It is reasonable that when deciding on whether or not a confirmation is required means first deciding if the predicted gain with CEA is high or low. If the predicted gain is high, the first course of action would apply in the case of disagreement, and CEA will be performed regardless of what the second imaging reveals; thus, a confirmation is not required. If the predicted gain is low, the second course of action would apply and, if needed, CEMRA would work as an arbitrator, and a confirmation test could be considered.

In the literature, the word “confirmation” has been used to describe a need to be reasonably sure that a patient has carotid stenosis before performing CEA [66, 70, 71, 94]. Although true, perhaps a confirmation is also needed that a carotid stenosis has not been missed when screening is undertaken to find symptomatic carotid stenoses. It may be that an additional carotid examination with a second modality is warranted when a reasonable suspicion remains, such as for those with a large carotid plaque on the first examination and/or a carotid bruit. In addition, in some instances, a patient with a 50–69% stenosis will not undergo CEA whereas if the stenosis were 70–99%, the patient would undergo CEA. In this circumstance, obtaining confirmation that the degree of stenosis is not actually 70–99% could be considered.

Patient Selection to Carotid Intervention

In summary:

- For patients with a symptomatic carotid stenosis, the treatment effect increases with male gender, older age, a tighter degree of carotid stenosis (except for near-occlusions), and a shorter delay to CEA.
- Speed is the key! If the delay to CEA is less than 2 weeks, the ARR with CEA is >10%, regardless of sex and the degree of carotid stenosis (except near-occlusions), and most likely also regardless of age.
- Worst symptom type (stroke > TIA > amaurosis fugax) and whether the symptomatic carotid stenosis is smooth or irregular affects the risk of stroke without CEA, but not treatment effect.
- The risk of stroke without CEA can be assessed using the carotid risk model. A >20% risk has been proposed as a threshold for when CEA should be performed. This model was created using standard statistical techniques and has been validated on separate material. However, in more than half of the possible combinations of different subgroups, whether CEA was to be performed was determined by worst symptom type even though worst symptom type does not affect the treatment effect.
- My main supervisor and I created the PARRCEA table for assessing the treatment effect, taking perioperative risk into account. Age, sex, degree of carotid stenosis, and delay to surgery were included, as were asymptomatic patients as an additional delay group. This model presents the treatment effect. However, the model is based on analysis of published data and has not been validated.
- For patients with an asymptomatic carotid stenosis, those aged ≥ 75 years should not undergo CEA. Statins were not widely used during the randomized trials because these trials were performed before statin treatment became extensively applied. The risk of stroke without CEA is lowered with statin treatment to such a degree that the meaningfulness of CEA under these conditions is now debated. However, an analysis of the largest randomized trial showed that CEA entailed a significant risk reduction despite statin treatment. A randomized trial with a “best medical treatment” group is ongoing. Risk discrimination techniques using carotid ultrasound and TCD are under development; the hope is that these techniques will allow for the selection of asymptomatic patients for CEA.

Subgroup interpretations in general

Subgroups must be interpreted with caution [95]. A *Lancet* educational series article [95] provided five brief advice points on subgroup interpretation and then explained them with examples. These pieces of advice are helpful when reading and interpreting articles and are rooted in basic science philosophy. In summary:

1. Creating subgroups requires dividing a study into smaller parts. Each part includes only a fraction of the patients and thus has only a fraction of the statistical power. If a study that shows a large benefit is divided into enough parts, no part will show benefit on its own. The focus must therefore be on whether there is a subgroup–treatment interaction, not on whether benefit is proven in a specific group.

2. Subgroup–treatment interactions should be expected from previous knowledge. A good trial designer should have pre-specified such subgroups in the trial protocol. However, in search of new knowledge, secondary (post hoc) analyses of trials are important. In these instances, it is not possible (as a reader) to accurately correct for multiple testing because there is no restriction in the number of possible post hoc analyses, and publication bias should at least be suspected.
3. Even pre-specification does not mean that a subgroup finding is valid because 5% of all findings are false positive.
4. Reproducibility between trials is a better marker of a valid finding than any p-value.
5. Most trials are powered to detect a treatment effect in the whole study group but not in subgroups. Thus, false-negative subgroup–treatment interactions are common.

Subgroup analyses and ensuing risk models allow a clinician to estimate the risk with and without treatment and also the treatment effect. The main purpose of a risk model is to provide the clinician with a tool to estimate when treatment is more beneficial than harmful. In contrast, some parameters affect the prognosis with and/or without treatment but not the treatment effect. Comparing different patients as “this patient has a higher risk and/or more benefit than that patient” is of no consequence if treatment is beneficial for both patients. However, some parameters may change during the course of an investigation, such as time since the last event. In these cases, comparing the current estimated treatment effect for a single patient with possible scenarios can be of value because alternative management strategies may emerge.

Subgroup differences for symptomatic carotid stenosis

There are several subgroups that affect the risk of stroke without CEA (medical risk), the risk of perioperative stroke, the risk of stroke despite CEA, and/or treatment effect [10, 49, 50]. Treatment effect is defined as the difference in risk of ipsilateral ischemic stroke within 5 years, taking all stroke and death within 30 days of CEA into account [10, 49, 50]. For treatment effect, the Cox model cannot be easily applied because the Kaplan–Meier survival curves cross each other, but it still has been used to some extent [10, 49, 50]. Several analyses of treatment effect in subgroup combinations have been published [10, 42, 49, 50]. The overall power ($n=5893$ and 795 outcome events) of the pooled NASCET + ECST studies is quite good [10]. Thus, it is reasonable to focus only on those parameters that have been presented as significant ($p<0.05$ for pre-specified and $p<0.01$ for post hoc [49], accepting the risk of a type 2 error).

A tight degree of carotid stenosis (excluding near-occlusions) has been shown to be a strong predictor of high medical risk and high treatment effect but does not affect the perioperative risk [10, 49]. The degree of carotid stenosis as well as source study was unevenly represented in the other subgroups; therefore, the remaining subgroup findings were presented after adjustment for the degree of stenosis and source study [49, 50]:

- Men had higher medical risk, lower perioperative risk, and higher treatment effect than women.
- Increasing age and short delay between the last symptom and randomization both entailed a higher medical risk and a higher treatment effect but did not affect the perioperative risk.
- Patients who had suffered a TIA or stroke (and not only ocular events), had diabetes, or had an irregular stenosis were found to have a higher medical risk and a higher perioperative risk, but these factors did not influence the treatment effect.

Four of these subgroups need further presentation:

- Age. Patients aged 65–74 years had a little higher treatment effect than those aged <65 years, but the main age effect was that patients aged ≥ 75 years had a much higher treatment effect than those aged <75 years. However, 90% of the included patients were <75 years [49].
- Delay between last symptom and randomization. This is the best available measurement for delay between symptom and CEA as there is no date that corresponds to “last symptom to CEA” for those who did not undergo CEA. The median delay between randomization and CEA was 6 days in the NASCET and ECST trials; thus, because the measurements are graded in several weeks, these numbers can with reasonable accuracy be used directly when discussing the delay between the last symptom and CEA. One theory is that the delay to CEA was significant because many stroke recurrences occur early; those who were randomized early suffered recurrent stroke after the randomization, whereas those patients who were randomized later suffered recurrent stroke before randomization (analysed as a baseline event, not as an outcome event) [49]. However, this theory does not explain why those randomized to the medical group within 2 weeks continued to suffer stroke recurrences at a high rate for 2.5 years before levelling off whereas those randomized after 2 weeks had a similar high rate for only 1–1.5 years before levelling off [50].
- Worst type of symptom. Worst type of symptom (stroke > TIA > ocular) affected the medical risk ($p=0.0067$) but not the treatment effect ($p=0.16$) [49]. This might be explained by the fact that although those with ocular events had a low medical risk, they also had a lower risk after CEA than those with TIA or stroke. Thus, regardless of symptom type, the patients benefited from CEA but from different baseline risks.
- Irregular stenosis. In the randomized trials, this was measured with conventional angiography [10, 49]. Subsequent morphological analysis has revealed that such a measurement with conventional angiography correlates well with lipid-rich atheromas [96]. For this reason, the creators of the carotid risk model argue that a similar finding on a non-invasive modality could be used inter-changeably with this finding on conventional angiography [97].

Assessing the medical risk: the carotid risk model

The carotid risk model was created by a multivariable analysis of the medical group in the ECST study and then validated on the medical group in the NASCET study

[97]. The model assesses the medical risk over 5 years. There are three ways to assess the risk:

- By multiplying specified values for different parameters, a risk point varying between 5 and 1394 can be calculated. This risk point can then be translated into risk using a nomogram [97]. Pros: The weight of different factors is visible, and it is possible to have the risk adjusted down with 20%, taking the increase in medical prevention into account. Cons: Hard to use.
- Using the previous model, but by an online questionnaire [98]. Pros: Easy to use. Cons: Requires Internet connection.
- By using a colour table; see figure 12 [97, 98]. Pros: Easy to use, and the table can be carried in your pocket. Cons: Only some of the variables in the model are used in the colour table, among other variables, near-occluded stenoses are excluded.

A comparison with the surgical group (in quintiles) revealed that there was no benefit with treatment for the three lowest risk quintiles, all with <20% medical risk; a moderate benefit (ARR 11%) in the fourth risk quintile, with an average ≈28% medical risk; and a clear benefit (ARR 32%) in the fifth quintile, with an average ≈42% medical risk [97]. Thus, a ≥20% medical risk can be used as way to select patients for CEA. Indeed, a <20% risk is the inclusion criterion in the ECST 2 study, randomizing patients between carotid intervention and best medical treatment [99]. That the three lowest risk quintiles were without benefit is not surprising because 54% of the patients included in the NASCET and ECST trials had a <50% carotid stenosis [10].

Assessment of treatment effect: the PARRCEA table

Four subgroups significantly altered the treatment effect: age, sex, degree of stenosis, and delay from last symptom to randomization. These subgroups have been combined in several articles; however, age has never been used in these combinations. The most comprehensive subgroup combination included degree of stenosis (excluding near-occlusions), sex, and delay from last symptom to randomization (see figure 13). This figure shows that if the delay to CEA is less than 2 weeks, all patients with 50–99% carotid stenosis (near-occlusions excluded) have a >10% ARR with CEA. Thus, speed is the key.

To make the information in figure 13 more accessible, my main supervisor and I created a colour table based on published data, designated as PARRCEA for “Predicted Absolute Risk Reduction with CEA” (In Swedish: KVIST “KärltiskirurgiVinst – Individuell StratifieringsTabell”). In the PARRCEA table, we assigned the table squares a colour based on the treatment effect with CEA, taking perioperative risk into account: ARR ≥ 20.0% was assigned a green square, ARR 10.0–19.9% was assigned a yellow square, ARR 3.0–9.9% was assigned an orange square, and ARR <3% or no available data was assigned a red square. In this table, we recommended that patients with an orange square might undergo CEA only if the perioperative risk is low. To make the PARRCEA table more useful in clinical practice, we also include patients with an asymptomatic carotid stenosis and/or with a near-occluded carotid stenosis. For asymptomatic patients, age is the

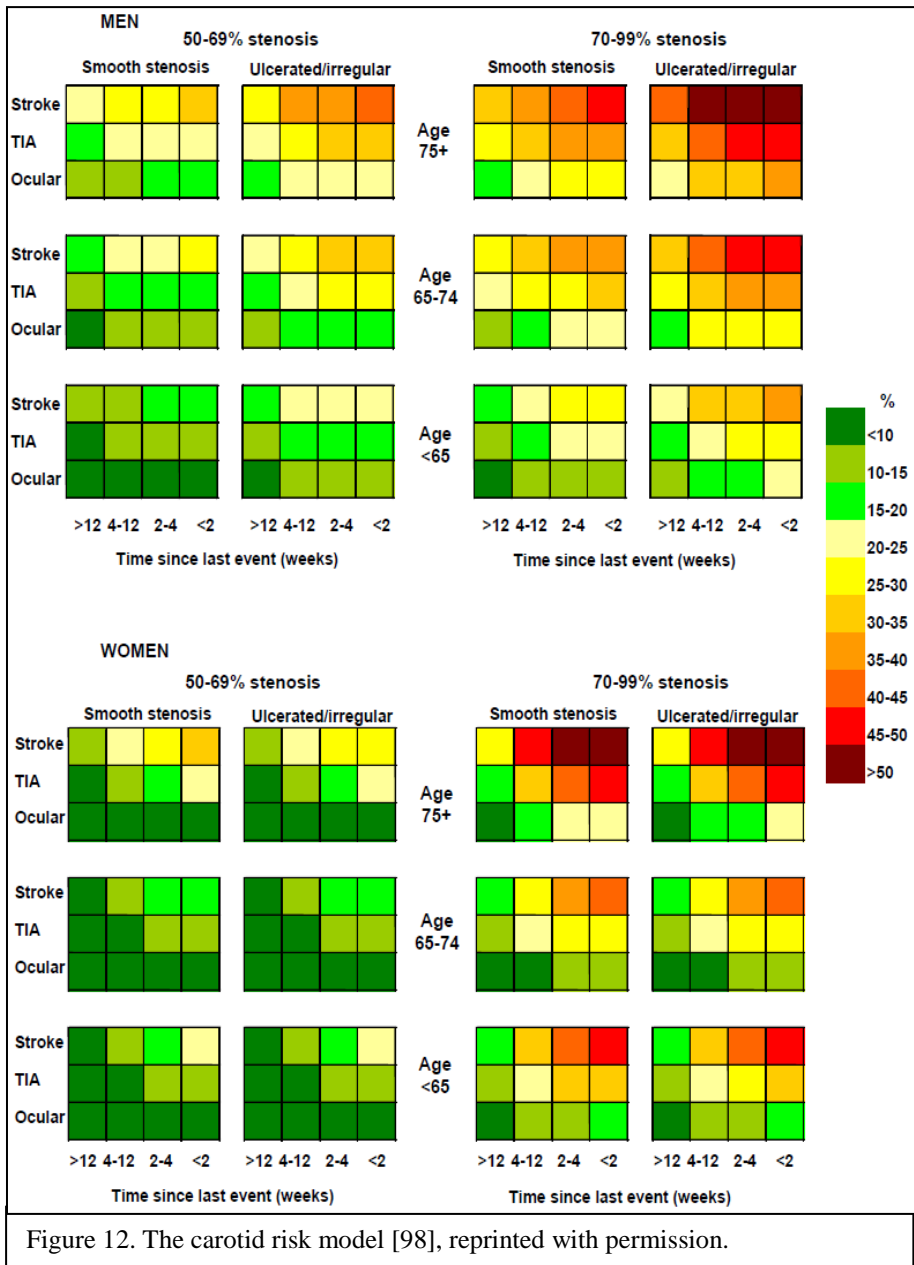


Figure 12. The carotid risk model [98], reprinted with permission.

only factor that significantly influences the treatment effect [17, 18]. Thus, age needed to be included in the table to make the table useful when assessing asymptomatic patients, even though age is difficult to interpret for symptomatic patients. To account for the fact that CEA was performed a few days after the randomization, the <2, 2-4, 4-12, and >12 week delay groups were modified into <0.5, 0.5-1, 1-3, and 3-6 month delay groups (after 6 months, patients were not eligible for the symptomatic trials [10]).

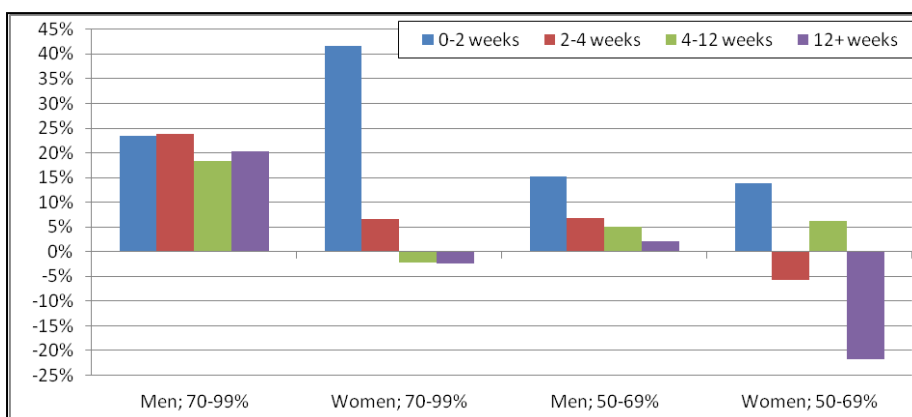


Figure 13. The absolute risk reduction of ipsilateral ischemic stroke within 5 years with CEA, taking perioperative stroke or death into account [50]. Reproduced with permission.

The perioperative risk in the NASCET + ECST studies was quite high (7.0%) [49, 50]. We thought that the 5.1% perioperative risk presented in a more recent systematic review [54] was more representative of our studies' findings and of the Swedvasc data [100]. Therefore, when we inserted the data from figure 13 into our table format, we also added 1.9% (7.0–5.1%) percentage points in each square (see figure 14). Adding a few percentage points seems to have been an appropriate measure: The perioperative risk with CEA was 4.6% in a recent systematic review of the trials randomizing patients between carotid angioplasty and CEA [57]. These trials were conducted after the NASCET and ECST trials; thus, it seems that the perioperative risk actually has dropped since the NASCET and ECST trials were conducted.

	Men				Women			
	Months between last symptom and CEA				Months between last symptom and CEA			
Stenosis	<0.5	0.5-1	1-3	3-6	<0.5	0.5-1	1-3	3-6
50-69%	17.1	8.7	6.9	8.2	15.7	-3.8	4.1	-19.8
70-99%	25.4	25.7	20.2	22.3	43.6	8.5	-0.3	-0.5

Figure 14. The numbers in figure 12 were converted into the PARRCEA format after 1.9% percentage points were added.

We assumed that the numbers in figure 13 are representative for patients aged <75 years because patients aged <75 years made up 90% of the studies [49]. We split the table into two age groups: those aged <65 years and those 65–74 years. The ARR was higher for those aged 65–74 years compared to <65 years; 4.1% higher for those with a 50–69% carotid stenosis; and 3.7% higher for those with a 70–99% carotid stenosis [49]. To calculate the ARR for those aged 65–74 years, we added the halves of these differences (2.0% for 50–69% stenosis and 1.8% for 70–99% stenosis) to

the numbers in figure 14; and in the same manner, to calculate the ARR for those aged <65 years, we subtracted these halves (see figure 15).

Men					Women				
Months between last symptom and CEA					Months between last symptom and CEA				
Stenosis	<0.5	0.5-1	1-3	3-6	<0.5	0.5-1	1-3	3-6	
<65 yr	50-69%	15.1	6.7	4.9	6.2	13.7	-5.8	2.1	-21.8
	70-99%	23.6	23.9	18.4	20.5	41.8	6.7	-2.1	-2.3
65-74 yr	50-69%	19.1	10.7	8.9	10.2	17.7	-1.8	6.1	-17.8
	70-99%	27.2	27.5	22.0	24.1	45.4	10.3	1.5	1.3

Figure 15. Based on figure 13, two age groups were created by adding or subtracting half of the difference in ARR between those aged <65 years and 65–74 years.

We made a conservative rounding of the figures in figure 15. In addition, to create the ≥75-year squares, we used the numbers for those aged 65–74 years in figure 15 and made a liberal rounding, attempting to take into account that the ARR was very high for those aged ≥75 years [49] (see figure 16). In the end, these rounding procedures affected the final table more than the age calculations did; thus, the differences in age groups in the PARRCEA table are mostly based on best judgement.

Men					Women				
Months between last symptom and CEA					Months between last symptom and CEA				
Stenosis	<0.5	0.5-1	1-3	3-6	<0.5	0.5-1	1-3	3-6	
<65 yr	50-69%								
	70-99%								
65-74 yr	50-69%								
	70-99%								
≥75 yr	50-69%								
	70-99%								

Figure 16. The numbers in figure 14 underwent a conservative rounding. In addition, the ≥75-year group was created by a liberal rounding of the 65–74-year group in figure 14.

We added near-occluded stenosis as a third stenosis category by interpreting the data on near-occluded carotid stenoses from the NASCET + ECST studies [10, 42, 49, 50]. Using best judgement, we assessed that the squares would be orange if CEA

were performed within 4 weeks and if the ARR in the age-sex corresponding 70–99% stenosis square were greater than 13.6% (see figure 17).

We added asymptomatic patients as an additional delay group (after 6 months). The subgroup differences for age, sex, and the degree of stenosis are presented in the “Asymptomatic carotid stenosis: the past, present and future” section below. Patients with a 50–69% carotid stenosis, near-occluded carotid stenosis, and/or ≥ 75 years old were assigned red squares [17, 18]. We used the ARR presented in the ACST study for those aged <65 years (7.8%) and aged 65–74 years (7.5%) and subtracted 2.8% to take perioperative risk into account [18]; the 2.8% number was derived from a systematic review [54] and is equal to the risk observed in those allocated to CEA in the ACST trial [18]. Based on these calculations, both age groups had an ARR of 3.0–10.0% and thus were assigned an orange square for both sexes. See figure 17 for the final PARRCEA table.

PARRCEA										
Predicted Absolute Risk Reduction with Carotid EndArterectomy										
Potential risk reduction to compare to perioperative risks										
Men						Women				
Months between last symptom and CEA						Months between last symptom and CEA				
Stenosis*	<0.5	0.5-1	1-3	3-6	Asym	<0.5	0.5-1	1-3	3-6	Asym
<65 yr	50-69%									
	70-99%									
	Near-occ									
65-74 yr	50-69%									
	70-99%									
	Near-occ									
≥ 75 yr	50-69%									
	70-99%									
	Near-occ									

	Very high risk reduction with CEA (ARR $\geq 20\%$), moderate perioperative risk is acceptable
	High risk reduction with CEA (ARR = 10-20%), moderate perioperative risk is acceptable
	Moderate risk reduction with CEA (ARR = 3-10%), only low perioperative risk is acceptable
	Not appropriate for CEA (ARR $\leq 3\%$ or no available data)

* NASCET-type degree of stenosis

Risk reduction for ipsilateral stroke and all perioperative stroke or death within 5 years for symptomatic patients.

Risk reduction for ipsi- and contralateral stroke and all perioperative stroke or death within 5 years for asymptomatic patients.

The risk reduction is adjusted for 5.1% perioperative risk for the symptomatic patients and 2.8% perioperative risk for the asymptomatic patients.

Figure 17. The PARRCEA table.

Comparison of the carotid risk model and the PARRCEA table

The reason that the PARRCEA table was created was that there were limitations in the clinical usefulness with the carotid risk model; however, the methodology is more solid for the carotid risk model than for PARRCEA (see table 2).

Table 2. Comparison between the carotid risk model and PARRCEA.

	Carotid risk model	PARRCEA
Creation	Calculated with patient data using appropriate statistical methods	Synthesis of published data using best judgement
Validity	Validated with patient data	Not validated
Included parameters	Includes parameters that do not influence treatment effect and/or are non-significant in multivariable analyses	Only includes the four parameters that affect treatment effect
Easy to use	In table format, yes. In the whole model, no. Excludes asymptomatic patients.	Yes
Useful for treatment decisions	Only a rudimentary analysis that those with >20% risk should undergo CEA. No group is specified for when CEA should be performed only if the perioperative risk is low.	Yes

The biggest disadvantage with the carotid risk model is that the worst symptom type is included in the model when it does not significantly influence the treatment effect ($p=0.16$) [49, 97]. If 20% medical risk is used as threshold for CEA, if the patient's worst symptom type is ocular or stroke affects treatment decision in 52% (50/96) of the possible scenarios [97]. Basing this magnitude of management decision on a p -value of 0.16 is questionable, even if the treatment effect analysis might be a case of a type 2 error. The biggest disadvantage with PARRCEA is the labile methodology: It is essentially a best-judgement rounding of the numbers in figure 13 with the effects of age in mind, and then addition of the squares for asymptomatic patients and for near-occlusion.

Although the idea of PARRCEA is appealing, the derivation methodology borders on what can be acceptable. In addition, the underlying dataset (NASCET + ECST) was collected without the widespread use of medical prevention [47, 48]. Some of these drawbacks could be circumvented if the PARRCEA table were derived from patient data. Thus, an effort by the Carotid Endarterectomy Trialist Collaborators to create a PARRCEA-like table is welcomed. It is reasonable that such a table is created by using only the parameters that influence treatment effect. One reasonable approach is to calculate the medical risk and then subtract the non-perioperative risk in the surgical group, thus creating a table showing the risk reduction with CEA to which the varying perioperative risk is to be compared. In an additional version, incorporating a reduced risk in both the medical and surgical groups, taking the more widespread use of medical prevention into account, might be considered.

CEA must be performed early after the presenting event and in patients with 50–99% carotid stenoses (not only 70–99% carotid stenosis) [49, 50, 94]. If using either of these models means that such a practice is achieved, that model should be used. Currently, PARRCEA is used in clinical practice at the University Hospital of

Northern Sweden. Any other clinic that wants to use it might do so, as long as they accept the methodological issues in its derivation.

Asymptomatic carotid stenosis: the past, present and future

In 2004, the ACST study confirmed the results of the ACAS study [18, 46]. As a result, the first asymptomatic CEA at the University Hospital of Northern Sweden was performed in November 2004. Subgroup analyses have been performed both on the 5-year follow-up data and on 10-year follow-up data [17, 18]:

- In both analyses, asymptomatic patients aged ≥ 75 years did not benefit from CEA. This difference was caused by the fact that the risk of a stroke despite CEA was higher for the patients aged ≥ 75 years compared to the patients aged < 75 years.
- In the 5-year analysis, there was a (much debated) trend towards women's having less benefit than men with CEA for asymptomatic stenosis; however, women were overrepresented in the > 75 -year group. In the 10-year analysis, the annual risk of stroke was reduced from 2.1% to 1.1% for men and from 1.8% to 1.0% for women with CEA. Thus, both the ARR (1.0% for men and 0.8% for women) and relative risk reduction (RRR) (48% for men and 44% for women) were similar. When only those aged < 75 years were considered, the ARR remained similar (1.1% for men and 1.0% for women), but the RRR tended to be higher for women (52% for men and 63% for women).
- No trend towards difference in risk or treatment effect was detected when different degrees of carotid stenosis were compared. Essentially, patients with 60–99% carotid stenosis were included. However, no lower limit was defined, and a multitude of ultrasound criteria were used; most reproduced NASCET-type stenoses. Thus, there is no treatment effect difference among different degrees of stenosis within the 60–99% carotid stenosis span. However, unlike the NASCET + ECST studies, CEA conferred a benefit in the lowest studied degree of carotid stenosis, and the lower threshold for when asymptomatic CEA might be performed is therefore unknown. In addition, near-occluded stenoses were not presented. There are at least three reasons why the 70–99% is a reasonable span of carotid stenoses for asymptomatic CEA in clinical practice: (1) The data for $< 70\%$ carotid stenoses are limited because only 10% of the patient years in the 10-year analysis were from patients with a $< 70\%$ carotid stenosis. (2) A diagnostic “safety margin” is appropriate because of the inaccuracy of the non-invasive imaging modalities in the 50–69% carotid stenosis span. (3) The clinical consequence of not performing asymptomatic CEA because of a diagnostic error is not severe; i.e., the risk of stroke without CEA is low, and only an opportunity to lower the risk further would be missed.

The results of the ACST trial have come into question because cardiovascular preventive medications, mostly statins, were not used as much in the beginning of the trial as the use of these medications evolved significantly during and after the study [17, 18, 101-104]. A systematic review of observational studies involving patients with asymptomatic carotid stenosis but in whom CEA was not performed revealed that the risk of stroke declined over time as statin use increased [104]. In

the 10-year report of the ACST study, 10-year risk of stroke was 7.6% in patients with CEA and statins, 13.4% with no CEA but with statins, 17.9% with CEA but with no statins, and 24.1% in patients with neither CEA nor statins [17]. Thus, giving statins to a patient with an asymptomatic carotid stenosis reduces the risk of stroke more than CEA. However, when a statin was given, there was still a significant ($p=0.002$) reduction in the risk of stroke with CEA [17]. This analysis is not perfect because it was a time-varying analysis, but it still is the largest available four-group analysis for the use/non-use of statins and CEA/no CEA [17].

The ongoing SPACE-2 study includes three arms, “CEA”, “carotid angioplasty”, and “Best medical treatment only”; thus, results from a randomized trial with all patients treated with statins will be presented within a few years [105]. In addition, stenosis morphology on ultrasound, CT angiography, and/or MR angiography and microemboli detection and cerebrovascular reactivity testing with TCD seem promising as tools for the future selection of which patients with asymptomatic carotid stenosis need CEA [32, 106-109]. Of these, microemboli detection with TCD has the best current documentation [109].

The view on the management of asymptomatic carotid stenosis has changed over the last few years and will continue to change in the future. In the recent past, CEA was performed in those under age 75 years and with a 70–99% carotid stenosis, and there was some uncertainty about how to treat women. In the uncertain present, the need for statins has been emphasized, with great benefit for the patients; however, now it is uncertain whether or not CEA should be performed at all, or perhaps only in those with microemboli. In the bright future, it will be known if the use of statins removes the need for CEA for most patients with asymptomatic carotid stenosis, and the hope is that CEA will be indicated only for the small share of patients who have an unstable stenosis seen with some imaging modality, microemboli, or an exhausted cerebrovascular reactivity.

Background of the studies in this thesis

This thesis is based on three studies:

1. The **HUS study** (HalsUltraljudsStudien, “Neck Ultrasound Study”): Including patients with carotid stenosis undergoing preoperative evaluation before CEA between January 1, 2004, and March 31, 2006. Paper I was derived from this population.
2. The **ANSYSCAP study** (Additional Neurological SYmptoms before Surgery of the Carotid Arteries – a Prospective study): Including patients with carotid stenosis undergoing the preoperative evaluation before CEA between August 1, 2007, and December 31, 2009. Papers II and III were derived from this population.
3. The **PtU study** (Panorama to Ultrasound): Including consecutive persons with calcifications in the carotid arteries seen on panoramic radiographs. Paper IV was derived from this population.

The ANSYSCAP study is the prospective version of the retrospective HUS study.

HUS study

Historically, to perform CEA early after a symptom was feared because doing so supposedly increased the perioperative risk [8]. The authors of the NASCET and ECST trials originally recommended CEA in the 4–6-week time window [49]. The predecessor to the carotid risk model determined that CEA should be performed within 2 months ($p=0.04$) [110]. This changed in 2004 with the pooled analysis of the NASCET and ECST studies: Instead of waiting 4–6 weeks, CEA was now recommended within 2 weeks of the last symptom because the net benefit increased, with no indication of an increased perioperative risk [10, 49, 50]. CEA as early as within 1 week did not increase the perioperative risk, but no analysis of benefit for time periods shorter than 2 weeks was performed; likely because of a low number of patients randomized within 1 week [50]. That the perioperative risk was not increased with early CEA was also seen in a systematic review published in 2003 [111]. With this change of suggested timing of CEA, it is likely that the delay between symptom and CEA was long in 2004 and has decreased since then.

ANSYSCAP study

In recent years, the high risk of stroke recurrence within a few days of a TIA or a minor stroke has become apparent [112-115]. This has been observed mostly in populations with mixed stroke aetiologies [112-115]. Of the different stroke aetiologies, large artery disease carries the highest risk of stroke recurrence [116, 117]. In addition, when taking other risk factors into consideration, an ipsilateral carotid stenosis is predictive of a higher risk for stroke recurrence after a TIA compared to other causes [118]. There is no doubt that CEA should be performed within 2 weeks of the last symptom [49, 50, 55, 56]; however, if the risk of ipsilateral ischemic stroke recurrence is high within the first few days, then perhaps an increased benefit can be achieved with even earlier CEA.

Several studies have described the risk of stroke recurrence within a few days in patients with a symptomatic carotid stenosis [31, 38, 119, 120]. Three of these studies were limited by the fact that they were performed before the current widespread use of medical prevention [119], lacked a clinically relevant design [119], excluded patients with a <80% carotid stenosis [31], and had main outcomes other than ipsilateral ischemic stroke [31, 120]. Ipsilateral ischemic stroke as an outcome is required for comparisons with the findings of the NASCET and ECST studies [49, 50]. The fourth study is relatively well designed but is limited by a small sample size [38].

Historically, carotid near-occlusion was believed to be an emergency requiring urgent CEA: “Immediate diagnostic clarification and emergency endarterectomy are mandatory” [121]. However, the evidence to support this notion was scarce by today’s standards [121]. The NASCET and ECST trials randomized 262 patients with a symptomatic near-occlusion [10, 42]. Unlike 70–99% stenoses and in contrast to previous belief, a near-occlusion entailed a low risk of stroke without CEA, and the benefit with CEA was marginal within 4 weeks and non-existent after 4 weeks after the last symptom [42, 50]. However, because only a few patients were randomized within the first few weeks [50], it is possible that an early high risk was missed.

There are only a few diagnostic studies that have correlated the finding of near-occlusion on conventional angiography with ultrasound or CT angiography [122–125]. Of these, only the study performed by Hetzel et al. (correlating to ultrasound) was of adequate design, including 43 near-occluded stenoses mixed with 31 occlusions and 327 carotid stenoses of other degrees [122]. The carotid ultrasound findings of a very high-grade stenosis with a low velocity and pseudo-venous flow profile had a sensitivity of 82% and a specificity of 98.9%. Most false-negative near-occlusions were misdiagnosed as tight carotid stenoses. Thus, when these findings are seen during a carotid ultrasound examination, it is almost definitely a near-occlusion, but some near-occlusions have a high flow velocity that is indistinguishable from a tight stenosis on carotid ultrasound [122]. In a study including only near-occlusions and occlusions (not carotid stenoses of other degrees), CT angiography and conventional angiography had a perfect correlation [124]. Only one study, including four patients with near-occlusion, has compared CT angiography to conventional angiography in a population with occlusion, near-occlusion, and other degrees of carotid stenosis [125]. Thus, the evidence for the diagnostic accuracy for near-occluded carotid stenosis is adequate for ultrasound but lacking for CT angiography, especially in comparison to the multitude of studies performed on 50–99% carotid stenosis [71, 73–79, 81–92].

PtU study

Ultrasound screening for asymptomatic carotid stenosis is indicated if the prevalence of carotid stenosis is $\geq 5\%$ in populations with an average low perioperative risk, and $\geq 20\%$ in populations with an average increased perioperative risk [68]. Screening is only reasonable if the aim is asymptomatic CEA; thus, only persons <75 years of age might undergo screening [17, 18].

A systematic review of population studies showed that asymptomatic carotid stenoses were more common among men and among the elderly (see figure 18) [126]. However, in this review, no analysis was done for the 75-year threshold [126]; thus, whether men 70–74 years old have a prevalence that is marginally over 5% is unknown. However, it appears that ultrasound screening is not indicated in the general population, although ultrasound screening of certain groups with a higher prevalence (directed screening) can be feasible.

Panoramic radiographs are widely used for examinations of teeth and jaws within dentistry. The Panoramic x-ray machine comprises a conventional x-ray tube and an opposing x-ray detector that rotates around the head during exposure. A single image is produced in which the teeth and jaw are lined up for interpretation. The x-ray beam is tilted upward, and the centre of the detector is placed above the x-ray source; this entails that captured images includes not only the teeth, but also the upper part of the neck, see figure 19.

A calcification in the area of the carotid arteries is sometimes (3.5–4.2%) seen on panoramic radiographs [127, 128]. An antero-posterior projection (APP) can be used to verify the location of these calcifications, see figure 19. The calcification might indicate that the person in question has a calcified carotid stenosis (although not all carotid stenoses are calcified). In two previous studies, such calcifications were followed up with carotid ultrasound in a total of 85 individuals [127, 128]. Among these, a 50–99% carotid stenosis was detected in 26% of the neck sides with a calcification [127, 128]. Two limitations to these studies are that persons who were ineligible for asymptomatic CEA were included, often those >75 years of age, and that men were overrepresented [127, 128]. These limitations are both likely to have led to a false high estimation of the prevalence of 50–99% carotid stenoses.

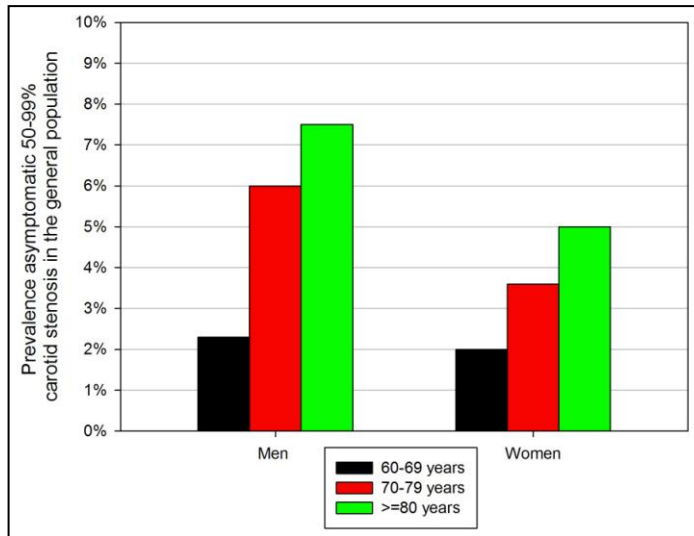


Figure 18. Prevalence of 50–99% asymptomatic carotid stenosis in the general population. Modified from [122].

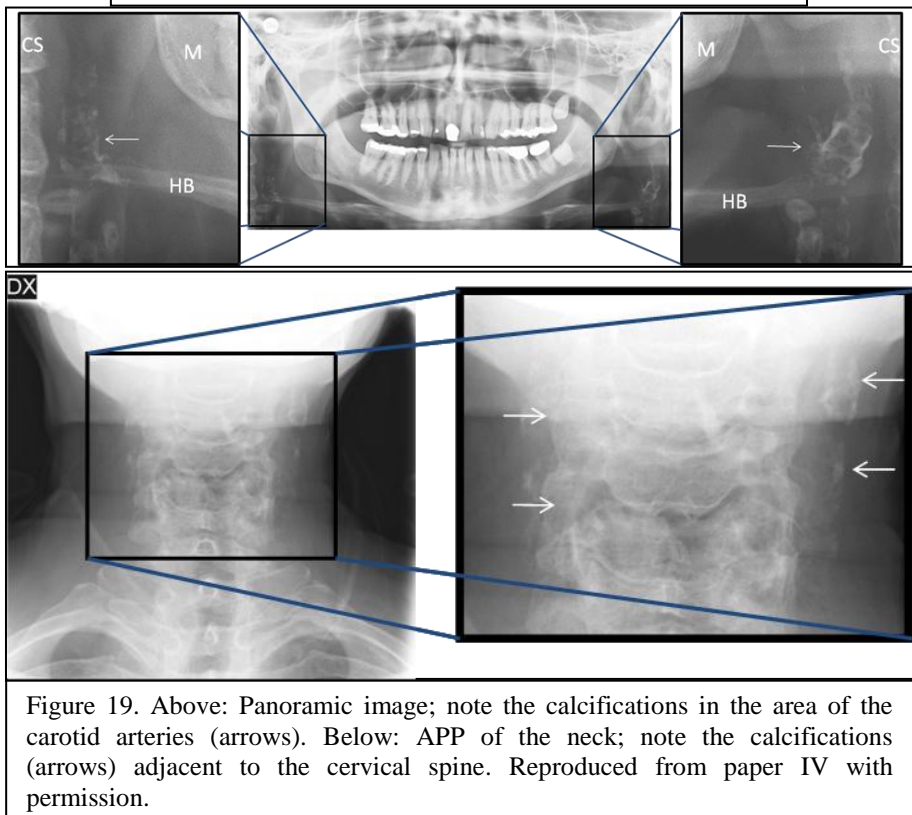


Figure 19. Above: Panoramic image; note the calcifications in the area of the carotid arteries (arrows). Below: APP of the neck; note the calcifications (arrows) adjacent to the cervical spine. Reproduced from paper IV with permission.

Aims

The aims of this thesis are as follows:

To describe the delay between the presenting symptom and CEA for patients with a symptomatic 50–99% carotid stenosis. How long is the delay? Has it changed since 2004? What part of the investigation prolongs the delay?

To determine the risk of ipsilateral stroke recurrence before CEA in patients with symptomatic 50–99% carotid stenosis. What basic clinical factors affect this risk? Is this risk high or low for patients with near-occlusion?

To determine if the incidental finding of a calcification in the area of the carotid arteries on a panoramic radiograph is a valid indication for ultrasound screening in persons eligible for asymptomatic CEA. A valid indication is defined as a prevalence of >5%.

Methods

The standardized preoperative evaluation before CEA at Umeå Stroke Centre

Both the HUS and ANSYSCAP studies were based on the standardized preoperative evaluations before CEA performed at Umeå Stroke Centre (In Swedish: “Karotisutredningar”). These studies have several important strengths and weaknesses resulting from this clinical practice.

Patients with a stroke, TIA, amaurosis fugax, or retinal artery occlusion with symptoms and signs conforming to an embolus to anterior cerebral circulation or the eye are screened to detect a possible symptomatic carotid stenosis. This screening is limited to the patients who are preliminarily eligible for a symptomatic CEA. When a 50–99% carotid stenosis is detected, the patient undergoes the preoperative evaluation at Umeå Stroke Centre. A majority of the patients who undergo this preoperative evaluation are referred from the other 11 hospitals in the Northern Region of Sweden (total population \approx 880 000). The Umeå Stroke Centre at the University Hospital of Northern Sweden is the only centre that performs these evaluations for the referring hospitals.

The preoperative evaluation includes several parts: As a clinical routine, a new carotid ultrasound is performed at the department of physiology at the University Hospital of Northern Sweden. The carotid ultrasound examinations are performed by experienced vascular sonographers. Published criteria are used for the translation of flow velocities to diameter stenosis [73]. These criteria have been validated locally [74]. At the discretion of the attending physician, a CT, MR, or conventional angiography is performed, either at the University Hospital of Northern Sweden or at the referring hospital. CT, MR, or conventional angiographies are reviewed by several experienced neuroradiologists. All carotid imaging is aimed at reproducing NASCET-type carotid stenoses [10, 69]. A cardio-echogram and a brain CT examination are always performed, either at the University Hospital of Northern Sweden or at the referring hospital.

A neurologist evaluates if the symptoms conform to the anterior circulation or the eye, and what the degree of carotid stenosis is on the corresponding side. An internal medicine specialist evaluates the perioperative risk and adjusts the medical treatment if warranted. At the time of the beginning of the HUS study, these two physicians met together with a vascular surgeon, a radiologist, and a vascular physiologist every Friday on a “Carotid round”. To reduce the delay to CEA, immediate discussion among the neurologist, internal medicine specialist, and vascular surgeon became more common during the course of the HUS and ANSYSCAP studies, with the carotid round preferably reserved for more challenging cases and for patients with asymptomatic carotid stenoses.

HUS Study

Population ascertainment

A search was made for patients who had been examined with carotid ultrasound at the department of physiology at the University Hospital of Northern Sweden between January 1, 2004, and March 31, 2006, in the administrative system of the physiology department. A total of 1555 examinations were found. All referrals and answers were reviewed; the indication of the examination and the degree of carotid stenosis on each neck side was noted. The medical records of all the patients with a 50–100% carotid stenosis were reviewed (n=362).

The initial search was validated by also searching for all CEA procedures performed in the medical records program BMS Cross. All but one patient who underwent CEA were already identified by the initial search; this additional case was not included because it was an endovascular procedure on the subclavian artery that extended into the proximal CCA.

Inclusion criteria

All patients with a symptomatic 50–100% carotid stenosis in whom the carotid ultrasound was performed as part of the preoperative evaluation or targeted such an evaluation were included (n=275). The patients for whom an alternative aim of the ultrasound examination was clear were excluded, such as when it was performed as a preoperative examination before cardiac surgery.

Registered parameters and analyses

By review of medical records, the dates of the presenting event for the different parts of the investigation and for the CEA were registered; the delay between presenting event and CEA and which part of the investigation prolonged the delay were calculated. Baseline features such as age, sex, blood pressure, lipid levels, and current medications were registered, as were the type of presenting event and additional symptoms. For the patients who underwent CEA, additional symptoms were registered until CEA, with perioperative events until 30 days after the CEA gathered from further review of medical records and from the Swedvasc registry. The patients who did not undergo CEA were followed for 4 months after the preoperative evaluation by further review of medical records and/or telephone interviews. Except for the perioperative risk, the symptom registration was of poor quality because the medical records were sometimes vague, additional records from the referring hospital were not zealously pursued, and further information could not be collected from the patients because of the retrospective design.

ANSYSCAP Study

Population ascertainment

Local patients were identified by continuous audit of all local admissions to the Umeå Stroke Centre. If a carotid screening was performed, if a carotid stenosis was detected and if a preoperative evaluation was initiated was noted. The distinction between whether a preoperative evaluation was initiated or not was straightforward: If it was initiated, then a cardio-echogram was performed (which it seldom is otherwise) and the specialist who was not primarily responsible for the patient also evaluated the patient.

The administrative staff at Umeå Stroke Centre helped in the ascertainment of the referred patients: This staff knew about all referred patients who arrived at Umeå Stroke Centre because they booked all patient stays and examinations. As a routine, the administrative staff entered the referred patients into the database when they booked the referred patients' preoperative evaluation. In addition, the administrative staff catalogued all incoming referrals. As a "cold pursuit", these referrals were reviewed and cross-referenced against already known patients. Some patients did not arrive at Umeå Stroke Centre; all of these patients were followed up to ascertain why they did not arrive. Patients with a carotid stenosis who did not arrive because of a major stroke as the presenting event or pre-existing co-morbidity were not entered into the database. Patients with a carotid stenosis who did not arrive because of a major stroke as a recurrent event were entered into the database.

Inclusion criteria

All patients with an asymptomatic or symptomatic 50–100% carotid stenosis were ascertained and data were gathered on all these patients. For the analyses, only the patients who reflected the clinical picture of symptomatic carotid stenosis were selected. Thus, the inclusion criteria were as follows:

- Symptomatic 50–99% carotid stenosis
 - Symptom conforming to the stenosis within the last 6 months was required; however, a vast majority of the patients had symptoms within the last few days/weeks.
- Underwent the preoperative evaluation (n=226)
 - Or would have done so before a major stroke recurrence rendered them ineligible for symptomatic CEA (n=4).

Registered parameters and analyses

All cerebrovascular symptoms were recorded, with notation of the date, type of symptom (for a possible ABCD2-classification [129]), duration of symptom, and vascular territory. The main source for the symptom data was patient medical records. This included entries from the referring hospital, the patient interview on admission to the pre-operative evaluation at Umeå Stroke Centre, the neurologist consultation, the internal medicine specialist consultation, and on admission to and discharge from the vascular surgery department. In addition, a simple questionnaire was collected in which the patients were asked to, in free text, described the recent symptoms and previous cardiovascular diseases. Patients were also followed up by mail after 45 days, 6 months, and 12 months; if no answer had arrived or if new

events were suspected from the mail reply, a telephone interview was conducted. Also, a pre-operative and post-operative neurological consult was always performed to assess eventual perioperative complications. The primary analysis of the symptom data was to calculate the risk of ipsilateral ischemic stroke recurrence after the patient sought health care but before CEA.

Dates for different parts of the investigation were recorded, and calculations similar to those in the HUS study were performed. Baseline features such as previous cardiovascular risk factors and current medications were recorded. The results of all carotid imaging at the referring hospital and at the University Hospital of Northern Sweden were recorded. For the primary analysis, the degree of carotid stenosis on the symptomatic side was dichotomized into 50–69% and 70–99%, with suspected near-occlusions included in the 70–99% carotid stenosis group. If the results of different imaging modalities were in disagreement, the stenosis category on which the attending clinician chose to base the clinical decision was used.

For the analysis of near-occlusion, one experienced neuroradiologist re-evaluated all CT angiography examinations performed at the University Hospital of Northern Sweden. As presented in the introduction, studies comparing CT angiography to conventional angiography for near-occluded stenoses are scarce and of poor design [124, 125]; thus, lacking a better alternative, the criteria proposed by Fox and colleagues were used because Fox is currently the authority on near-occluded stenosis [42, 130]. The carotid ultrasound examinations were analysed in accordance with the findings of Hetzel et al. [122]. The carotid ultrasound answers were re-reviewed to make sure that no near-occluded stenoses (with low flow velocities) had been graded as tight stenoses in the database. A total of 11% (9/83) of the CT angiographies and 9% (20/225) of the carotid ultrasound examinations were excluded because the examination quality was poor on the symptomatic side.

False-positive findings of near-occluded stenosis with CT angiography are to be expected because the difference between whether or not a distal artery is collapsed is often subtle. However, the exact effect of this on the specificity of CT angiography is unknown. False-negative findings of near-occlusion with ultrasound are to be expected because the sensitivity is 82% [122]. Thus, discrepancies with a positive CT angiography and negative carotid ultrasound examination were expected. Therefore, two categories of near-occlusion were pre-specified: Definite near-occlusion and possible near-occlusion. A carotid stenosis was categorized as a definite near-occlusion in three instances: (1) When conventional angiography was performed, that finding was used regardless of what CT angiography and ultrasound showed. (2) When carotid ultrasound and CT angiography concurred that it was a near-occlusion. (3) When only one non-invasive modality was performed with acceptable quality and found a near-occlusion. A stenosis was categorized as a possible near-occlusion when either ultrasound or CT angiography found a near-occlusion, but the other modality did not concur. No MR angiography or CEMRA examinations were performed.

To clarify the categories of carotid stenosis used in this thesis: The degree of carotid stenosis on the symptomatic side was categorized both pre hoc and post hoc. The

pre-specified division in the primary analysis was 50–69% and 70–99%. In the secondary analysis of near-occlusion, the categories of definite near-occlusion and possible near-occlusion were defined before the analysis was executed. These were compared to 50–99% carotid stenosis because no difference between 50–69% and 70–99% carotid stenosis was seen in the primary analysis. In addition, explorative (post hoc) analyses were also performed with a division of the degree of carotid stenosis into definite near-occlusion, possible near-occlusion, 70–99%, and 50–69%, but also for carotid ultrasound separately and CT angiography separately (with and without string sign).

PtU Study

Population ascertainment

The PtU population was prospectively ascertained from consecutive persons who underwent a panoramic examination at the department of Oral and Maxillofacial Radiology between August 1st 2007, and February 26, 2009. Only persons aged 18–74 years were eligible for the study: About half of the panoramic examinations performed at this department are performed on children (often for orthodontic procedures); thus, only persons aged >18 years were included in order to make the demographic representative of adults. Persons aged ≥ 75 years of age were excluded because they are not eligible for CEA if asymptomatic [17, 18]. People with a calcification in the area of the carotid arteries on a panoramic radiograph were also examined with an APP. If the calcification was confirmed, the person was asked to participate in the study.

Inclusion criteria

There were two inclusion criteria: A calcification in the area of the carotid arteries and being eligible for asymptomatic CEA.

The panoramic examination and APP for study participants were re-examined by two blinded expert observers. If a calcification was seen on a neck side on both the panoramic examination and the APP, this neck side was considered positive. At least one positive neck side was required for inclusion. The inter-observer kappa was 0.69, with 88% overall agreement. Consensus decisions were reached for the inclusion/exclusion for all persons.

Persons with cancer or other serious co-morbidities were excluded because they are not eligible for asymptomatic CEA because of a short life expectancy (<5 years) and/or increased perioperative risk. Those with a previous TIA or stroke were also excluded in order to create a truly asymptomatic population.

Registered parameters and analyses

For all persons aged 18–74 that underwent a panoramic examination during the study period, age, sex, and the indication for the examination were registered. The inclusion rate among these three parameters was compared. The indication was divided into three groups: (1) regular dental: indications that exist in all general practise with panoramic radiographs, such as for dental implants; (2) specialized dental: indications that exist in specialised dental clinics, such as orthodontics or fractures; (3) specialized medical: indications that exist in clinics in connection with a specialized medical centre, such as examinations before heart valve surgery or cancer treatments. The specialized dental and specialized medical groups were merged in some analyses because few of the included persons were in these groups.

The included persons were examined with carotid ultrasound. The findings on the panoramic radiographs, APP and carotid ultrasound were registered. These findings were compared and the prevalence of 50–99% carotid stenosis in persons with a calcification in the area of the carotid arteries was calculated.

In addition, through a review of patient records, previous cardiovascular events, current cardiovascular conditions, cardiovascular risk factors, and current cardiovascular medication were recorded. The prevalence of 50–99% carotid stenosis was compared between pre-specified subgroups.

Reference persons

A total of 198 age- and sex-matched reference individuals were randomly selected among the persons who had been examined with a panoramic radiograph but had no detectable calcification in the area of the carotid arteries. This selection was done to determine if the burden of cardiovascular diseases among the persons with calcifications in the area of the carotid arteries was comparable to persons without such calcifications. The reference persons' panoramic examinations were re-reviewed in a similar manner as that described above to make sure that they did not have a calcification in the area of the carotid arteries. A questionnaire was sent to these reference persons. If no answer arrived within a month, an effort to contact them by telephone was made. The questionnaire included questions about the same cardiovascular events, conditions, risk factors, and medications used for the included persons with calcifications in the area of the carotid arteries. To increase the validity of the comparison, reference persons were included on the principle that they would have been included in the study if they had had a calcification in the area of the carotid arteries: Of the 198 selected reference persons, 2 had died, 59 were not reached or declined participation, 10 were excluded because of cancer and 8 were excluded because of a previous stroke or TIA. Ultimately, 119 reference persons were included.

Imaging methods

The panoramic examinations were performed with an Orthopantomograph® OP100. The APP examinations were performed using a Cranex® Cephalostat. Images were stored and interpreted in a digital format.

General Methods

Definitions and outcomes

Stroke was defined in accordance with the World Health Organization definition [1]. TIA was defined as a stroke, but lasting less than 24 hours (regardless of imaging results). Retinal artery occlusion and amaurosis fugax were defined as monocular blindness lasting more or less than 24 hours, respectively, with no apparent cause other than vascular origin.

In the HUS and ANSYSCAP studies, the presenting event was defined as the last symptom of cerebrovascular disease before the patient sought health care.

In the HUS study, the main outcome was the median delay between the presenting event and CEA. This was also analysed in the ANSYSCAP study, but as a secondary outcome.

In the ANSYSCAP study, the main outcome was ipsilateral ischemic stroke recurrence after the presenting event; per definition, this stroke recurrence occurred after the patient had sought health care. Perioperative strokes were not included in the main outcome but are presented separately. Both stroke and retinal artery occlusion (“cerebral stroke” and “retinal stroke”) were included in the main outcome.

In the PtU study, the main outcome was a 50–99% carotid stenosis.

Statistical methods

Where appropriate, standard deviation and 95% confidence intervals were calculated. Fisher’s exact test or the chi-2-test was used when comparing two sets of binary or categorical values. When comparing mean values, the t-test was used if the data were normally distributed. When comparing delays between two dates, it is not reasonable to assume normal distribution; thus, the Kruskal-Wallis and/or Mann-Whitney test were/was used. A p-value of <0.05 was considered to indicate significance. SPSS 14.0 and 17.0 and PASW 18.0 statistics software were used.

In the ANSYSCAP study, the risk of stroke recurrence was calculated with Kaplan-Meier curves, with the log-rank test to test for differences between subgroups. The presenting event (the last event before the patient sought health care) was used as the index event. Patients were followed for 90 days but were censored at CEA. With the same index event, outcome and censoring, multivariable analyses were performed with Cox regression. Sometimes, the proportional hazard assumption was not reasonable: The survival curves for 50–69% and 70–99% carotid stenosis crossed; thus, carotid stenosis as a dichotomized variable was not evaluated in the Cox analysis. In addition, age was not analysed as a continuous variable but in categories because the increase in age was not proportional to the change in risk. Age, sex, 50–69% or 70–99% degree of carotid stenosis on the symptomatic side, and the type of presenting event were pre-specified as the main subgroup analyses.

In the PtU study, whether or not the prevalence of carotid stenosis was over the pre-specified threshold of 5% was determined using the one-sided nonparametric binomial test, with the exact calculation method. At the advice of a medical statistician, this method was chosen instead of the lower boundary of the 95% confidence interval because it has more statistical power and is an exact calculation for binary measurements; whereas 95% confidence intervals provide only an approximation for binary variables. The presented subgroups were all pre-specified.

Ethics

HUS study: In accordance with the then-current ethical legislation and practice, no approval from the local ethics committee was filed because it was an assurance of quality of health care study without any extra discomfort for the patients.

ANSYSCAP study: The study protocol was audited by the local research ethics committee, which found that the study did not require committee approval because it was strictly observational. Thus, informed consent was not obtained, in accordance with the current ethical practice. The study was registered at www.clinicaltrials.gov (NCT 00514592) before it was launched. The delay to CEA was not in any way prolonged for the purpose of the study.

PtU study: The Regional Ethical Review Board approved this study. All included and reference persons provided informed consent. The study was registered at <http://www.clinicaltrials.gov>, NCT00514644 before it was launched.

Results

HUS and ANSYSCAP: Population description

HUS Study

A total of 275 patients with a symptomatic 50–100% carotid stenosis were included; 33% were women and the mean age was 68.9 (SD 9.4; range 27–88) years. The presenting event was a stroke in 50% of the patients, a TIA in 34% of the patients, an amaurosis fugax in 14% of the patients, and a retinal artery occlusion in 2% of the patients.

A total of 127 patients underwent CEA and one underwent carotid angioplasty (and is included in the operative group in the remaining analyses). A total of 46% of the men and 48% of the women underwent CEA ($p=0.70$; chi-2-test). The mean age was 68.1 (SD 7.8; range 47–83) years among those who did undergo CEA and 69.6 (SD 10.5) years among those who did not undergo CEA ($p=0.18$; t-test). Of the patients who underwent CEA, 92% had a 70–99% carotid stenosis on at least one side. CEA was performed in 39% of the patients with stroke, 51% of the patients with TIA, 63% of the patients with amaurosis fugax, and 40% of the patients with retinal artery occlusion ($p=0.038$; chi-2-test).

A total of 147 patients did not undergo CEA: 60% were not considered to have an indication for CEA because of occlusion or a carotid stenosis that was too low grade; 15% had a major contraindication such as cognitive dysfunction, a major stroke, or other major co-morbidities; 5% of the patients refused CEA; and 20% had other reasons such as technical reasons or high perioperative risk.

ANSYSCAP study

Out of 2208 consecutive local admissions and 423 consecutive referred patients, 230 patients had a symptomatic 50–99% carotid stenosis and were included. Of these, 36% were women. The mean age was 71.0 (SD 7.7; range 48–86) years. A total of 77% had a 70–99% carotid stenosis on the symptomatic side. The presenting event was stroke in 42%, TIA in 30%, retinal artery occlusion in 5%, and amaurosis fugax in 23% of the patients. At the end of the pre-operative evaluation, 99.6% had any type of platelet inhibitor or anti-coagulation medication; 93% had any type of blood pressure-lowering medication, and 90% had any type of lipid-lowering medication.

A total of 181 patients underwent CEA and 2 underwent carotid angioplasty (and are included in the operative group in the remaining analyses). CEA was performed more often among the patients with male sex, younger age, and a tighter degree of carotid stenosis on the symptomatic side: 84% of the men and 71% of the women underwent CEA ($p=0.018$; chi-2-test). The mean age was 70.4 (SD 7.6; range 48–86) years among those who did undergo CEA and 73.5 (SD 7.7) years among those who did not ($p=0.013$; t-test). A total of 86% of the patients with 70–99% carotid stenosis and 59% of the patients with a 50–69% carotid stenosis underwent CEA ($p<0.0001$; chi-2-test). Also, there was a tendency for CEA to be performed more often with a less-severe presenting event ($p=0.055$). In the secondary analysis of

near-occlusion, patients with definite near-occlusion underwent CEA less often (30%) than patients with the other degrees of carotid stenosis ($p<0.001$; chi-2-test).

Forty-seven patients did not undergo CEA: In 36%, the potential benefit with CEA was considered too low. In 11%, the potential benefit with CEA was considered lower than the increased perioperative risk, and in 19%, the reason was patient refusal. In 15%, neither CEA nor carotid angioplasty was feasible for technical reasons while for 19%, CEA was considered not meaningful because of either cognitive decline ($n=1$) or a major stroke ($n=8$). In six of these eight cases with major stroke, this was a recurrent stroke. For the two other patients with major stroke, the major stroke was the presenting event; however, these two patients did undergo the preoperative evaluation and were thus included in the study (whereas most patients with major stroke and a symptomatic carotid stenosis did not undergo the preoperative evaluation).

HUS and ANSYSCAP: Delay to CEA

Presenting event – CEA in the HUS Study

Seven percent of the patients underwent CEA within 2 weeks, 11% between 2 and 4 weeks, 53% between 4 and 12 weeks, and 29% after more than 12 weeks after their presenting event. The overall median delay between presenting event and CEA was 8.8 (IQR 5.1–13.5) weeks. In the first half year of 2004, the median delay between presenting event and CEA was 11.7 (IQR 8.4–17.7) weeks; this dropped over time to 6.9 (IQR 4.2–9.4) weeks during the first quarter of 2006, i.e., between the first and last time periods of the study ($p=0.006$; Mann–Whitney test, see figure 20). Neither sex, age, nor the type of presenting event affected the delay between presenting event and CEA (see table 3).

Table 3. The delay between presenting event and CEA in the HUS study

		n	Median delay (IQR) Weeks	Significance
Sex	Men	88	8.6 (5.0–13.0)	$p=0.26^*$
	Women	44	9.4 (5.2–17.9)	
Age	<65 years	41	9.1 (5.6–13.7)	$p=0.84^\dagger$
	65–74 years	62	8.8 (5.1–13.9)	
	≥ 75 years	25	7.7 (4.9–13.4)	
Type of presenting event	Stroke	54	9.0 (5.1–13.3)	$p=0.73^\dagger$
	TIA	48	8.5 (5.0–12.9)	
	Amaurosis fugax	24	9.1 (5.1–19.0)	
	Retinal artery occlusion	2	7.9 ‡	
Total		128	8.8 (5.1–13.5)	-

*Mann–Whitney test. † Kruskal–Wallis test. ‡ IQR was not estimated because of too few cases.

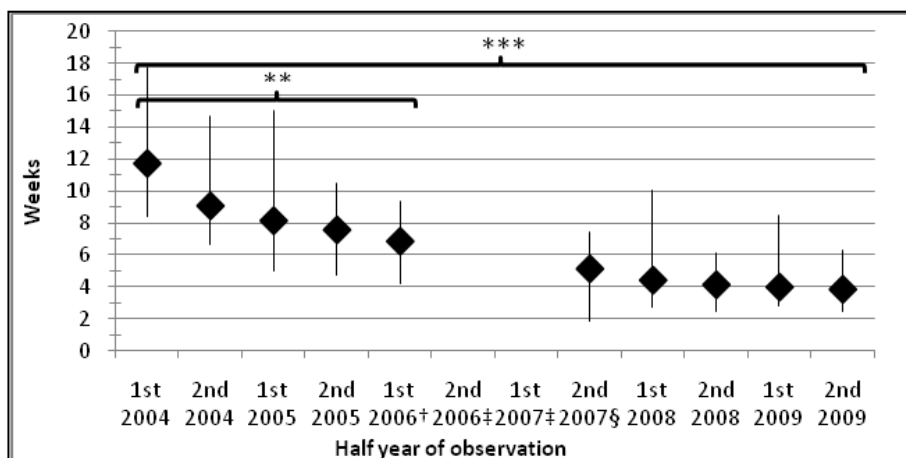


Figure 20. The delay between the presenting event and CEA in the HUS and ANSYSCAP studies, presented in quartiles.

Mann–Whitney test: ** $p<0.01$ *** $p<0.001$ † Only first 3 months available. ‡ No data available. § Only last 5 months available

Presenting event – CEA in the ANSYSCAP Study

Twenty percent of the patients underwent CEA within 2 weeks, 28% between 2 and 4 weeks, 37% between 4 and 12 weeks, and 15% after more than 12 weeks after their presenting event. The overall median delay between the presenting event and CEA was 4.1 (IQR 2.4–7.1) weeks. In the second half year of 2007, the median delay between the presenting event and CEA was 5.1 (IQR 1.9–7.5) weeks; this tended to drop over time and was 3.9 (IQR 2.5–6.3) weeks during the second half year of 2009, i.e., the last time period of the study ($p=0.38$; Mann–Whitney test, see figure 20). Analyzing both studies, the delay between the presenting event and CEA dropped significantly ($p<0.001$; Kruskal-Wallis test). This delay tended to drop between the end of the HUS study and the beginning of the ANSYSCAP ($p=0.16$; Mann–Whitney test); however, the drop from the beginning of the HUS study to the end of the ANSYSCAP study was statistically significant ($p<0.001$; Mann–Whitney test, see figure 20). The delay between presenting event and CEA in different subgroups is presented in table 4; this delay was shorter for those with TIA or stroke as the presenting event compared to those with an amaurosis fugax ($p=0.042$; post-hoc Mann–Whitney test).

Table 4. The delay between presenting event and CEA in the ANSYSCAP study

		n	Median delay (IQR) Weeks	Significance
Sex	Men	124	4.2 (2.5–6.6)	$p=1.00^*$
	Women	59	3.7 (2.1–8.7)	
Age	<65 years	48	4.1 (2.6–8.4)	$p=0.83^\dagger$
	65–74 years	81	4.1 (2.2–8.6)	
	≥ 75 years	54	4.2 (2.4–6.2)	
Degree of stenosis on the symptomatic side	50–69%	32	3.4 (1.7–4.9)	$p=0.062^*$
	70–99%	151	4.3 (2.7–7.1)	
Type of presenting event	Stroke	69	4.0 (2.5–5.6) \ddagger	$p=0.14^\dagger$
	Retinal artery occlusion	10	5.2 (3.8–9.4)	
	TIA	57	3.7 (1.9–7.1) \ddagger	
	Amaurosis fugax	47	5.6 (3.0–10.3) \ddagger	
Total		183	4.1 (2.4–7.1)	–
*Mann–Whitney test. † Kruskal–Wallis test. \ddagger Post-hoc comparison of stroke + TIA against amaurosis fugax: $p=0.042$ (Mann–Whitney test).				

Different parts of the management chain in both studies

Five stages of the management chain were analysed in both studies, as follows: (1) for referred patients, the delay between presenting event and the referral; (2) for the referred patients, the delay between referral and the preoperative evaluation; (3) for the local patients, the delay between presenting event and the preoperative evaluation; (4) for all patients, the delay between the preoperative evaluation and the management decision; and (5) for those who underwent CEA, the delay between management decision and CEA. In addition, patient delay, i.e., the delay between presenting event and seeking health care was analysed in the ANSYSCAP study.

In the HUS study, three stages prolonged the median delay to CEA: The delays between the presenting event and the referral, between referral and the preoperative

evaluation, and between the management decision and CEA (see table 5). In the ANSYSCAP study, the delay between the management decision and CEA was the longest part of the management chain (see table 5). Patient delay was a minor factor in the median delay to CEA in the ANSYSCAP study because most patients sought health care the same day as the presenting event (see figure 21). However, in the few cases when the patient delay was >1 day, the ensuing investigation, i.e., the delay between seeking health care and CEA, was longer than if the patient delay was zero or one day ($p=0.011$; Kruskal–Wallis test).

Table 5. The median delay in the different parts of the management chain during the entire HUS study and during the entire ANSYSCAP study.

	Median delay (IQR) weeks	
	HUS study	ANSYSCAP Study
Referred patients: Presenting event – Referral	1.7 (0.7–4.5)	1.0 (0.4–2.9)
Referred patients: Referral – Preoperative evaluation	2.4 (0.5–4.3)	0.7 (0.3–1.7)
Local patients: Presenting event – Preoperative evaluation	0.7 (0.3–1.1)	0.4 (0.1–1.0)
Preoperative evaluation – Decision	0.3 (0.1–1.1)	0.3 (0.1–0.6)
Decision – CEA	3.7 (2.4–4.9)	1.9 (0.9–2.6)

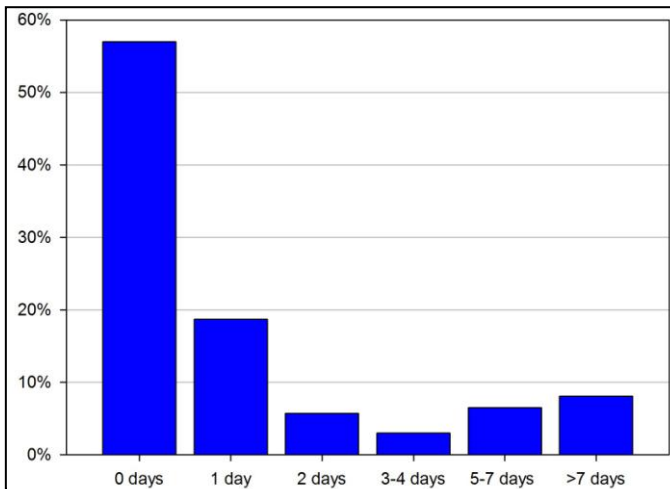
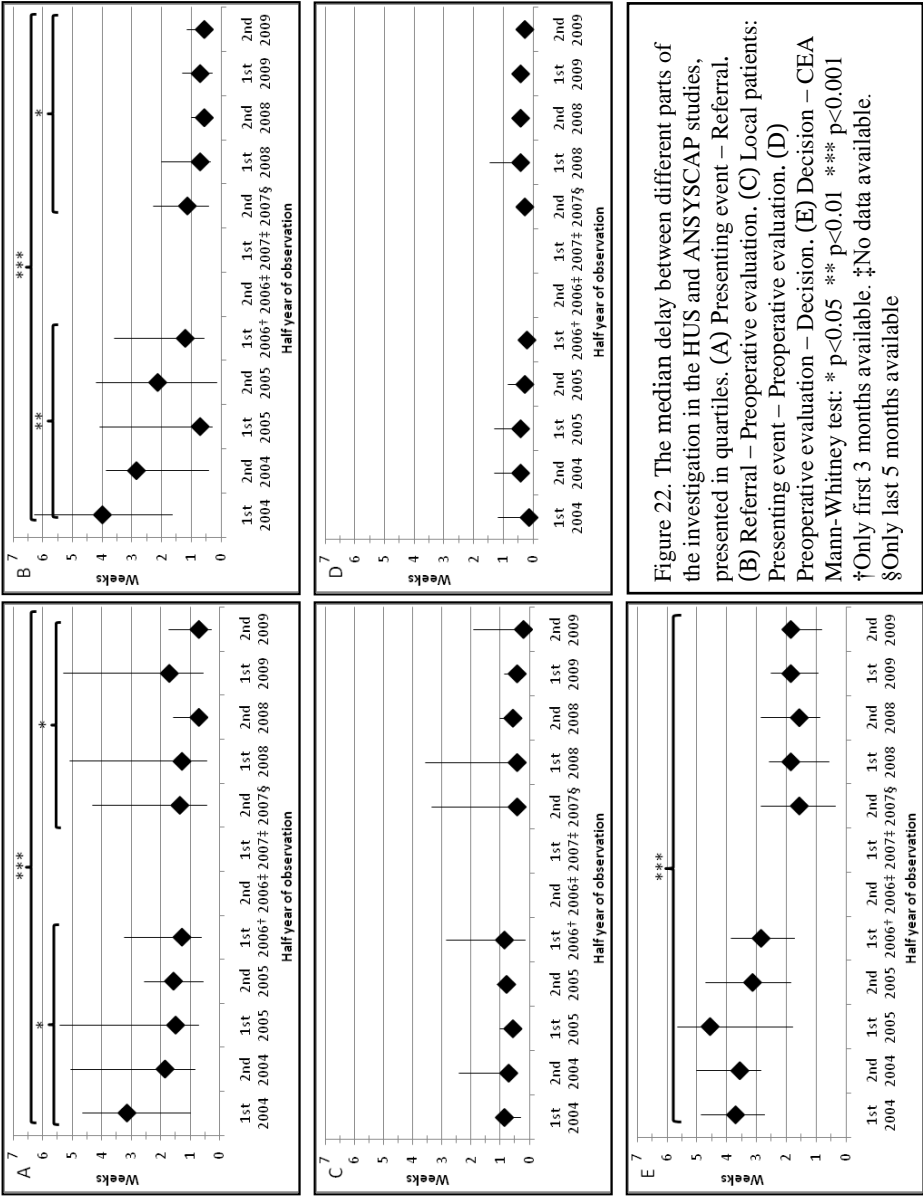


Figure 21. The patient delay in the ANSYSCAP study.

The different parts of the management chain during different time periods of the HUS and ANSYSCAP studies are presented in figure 22. The overall changes in the HUS and ANSYSCAP studies were analyzed with the Kruskal–Wallis test. The first and last time periods of the HUS and ANSYSCAP studies were compared with the Mann–Whitney test:

- Overall, the median delay between the presenting event and referral dropped significantly ($p=0.002$). The median delay between the presenting event and the referral dropped significantly from the beginning of the HUS study to the end of the ANSYSCAP study ($p<0.001$); this drop occurred during the HUS study ($p=0.049$) and during the ANSYSCAP study ($p=0.028$), but not between the studies ($p=0.81$).



- Overall, the median delay between the referral and the preoperative

evaluation dropped significantly ($p<0.001$). The median delay between the referral and the preoperative evaluation dropped significantly from the beginning of the HUS study to the end of the ANSYSCAP study ($p<0.001$); this drop occurred during the HUS study ($p=0.007$) and during the ANSYSCAP study ($p=0.026$), but not between the studies ($p=0.68$).

- Overall, the median delay between the presenting event and the preoperative evaluation for the local patients was unchanged ($p=0.65$).
- Overall, the median delay between the preoperative evaluation and management decision tended to be different between different half years of the study ($p=0.075$). But when comparing the beginning and end of the studies, no specific changes were detected ($p\geq 0.70$ in all instances).
- Overall, the median delay between the management decision and CEA dropped significantly ($p<0.001$). The median delay between the management decision and CEA dropped significantly from the beginning of the HUS study to the end of the ANSYSCAP study ($p<0.001$); this drop tended to occur during the HUS study ($p=0.11$) and between the HUS and ANSYSCAP studies ($p=0.069$) but was unchanged during the ANSYSCAP study ($p=0.82$).

HUS and ANSYSCAP: Additional symptoms

HUS Study

A total of 27% of the patients who underwent CEA had additional cerebrovascular events after the presenting event but before the CEA. In addition, two patients suffered a major stroke before the CEA that led to no CEA being performed. Although additional data on recurrent symptoms were collected in the HUS study, the quality of these data is quite poor. Thus, further symptom analyses are made solely in ANSYSCAP study.

ANSYSCAP Study

Thirty-three patients (14%) suffered an ipsilateral ischemic stroke recurrence within 90 days of the presenting event (excluding events that occurred after CEA). Of these 33 patients, five had at least one recurrent ipsilateral TIA or amaurosis fugax before their ipsilateral ischemic stroke recurrence; in the remaining 28 patients, the ipsilateral ischemic stroke recurrence was the first additional event after the presenting event. Of these 33 main outcomes, 30 were strokes and 3 were retinal artery occlusions. Three patients suffered other types of stroke recurrences: two contralateral ischemic strokes and one posterior circulation ischemic stroke (no haemorrhagic strokes); none of these three patients had a contralateral carotid stenosis of 50–100% or atrial fibrillation. Of the 197 patients who did not suffer an ipsilateral ischemic stroke recurrence, 58 suffered a recurrent ipsilateral ischemic TIA or amaurosis fugax. In total, 40% of the patients suffered an ipsilateral ischemic recurrence of any type.

ANSYSCAP study: Risk of ipsilateral ischemic stroke recurrence

The risk of ipsilateral ischemic stroke recurrence before CEA was 5.2% (95%CI 2.3–8.1%) at 2 days, 7.9% (95%CI 4.4–11.3%) at 1 week, 11.2% (95%CI 7.0–15.3%) at 2 weeks, and 18.6% (95%CI 12.2–25.0%) at 90 days after the presenting event (Kaplan–Meier analysis). The risk of ipsilateral ischemic stroke recurrence was higher if the presenting event was a stroke or a TIA compared to amaurosis fugax ($p=0.027$; log-rank test). The risk of ipsilateral ischemic stroke recurrence was very similar for the patients with a stroke or with a TIA as presenting event. For the patients with either stroke or TIA as the presenting event, the risk of ipsilateral ischemic stroke recurrence was 6.0% (95%CI 2.4–9.6%) at 2 days, 9.7% (95%CI 5.2–14.2%) at 7 days, 14.3% (95%CI 8.9–19.7%) at 2 weeks, and 24.7% (95%CI 16.1–33.2%) at 90 days after the presenting event. Neither sex ($p=0.29$; log-rank test) nor age ($p=0.21$; log-rank test) affected the risk of ipsilateral ischemic stroke recurrence. In the primary analysis, the degree of carotid stenosis on the symptomatic side was analysed as 50–69% and 70–99%; this division did not affect the risk of ipsilateral ischemic stroke recurrence ($p=0.66$; log-rank test). The risk of ipsilateral ischemic stroke recurrence in subgroups is presented in figure 23.

In a secondary analysis, the degree of carotid stenosis on the symptomatic side was divided into 50–99% ($n=201$), possible near-occlusion ($n=19$), and definite near-occlusion ($n=10$). The risk of ipsilateral ischemic stroke recurrence was higher for the patients with a definite near-occlusion compared to those with a possible near-occlusion or a 50–99% carotid stenosis ($p=0.007$; log-rank test). For the patients

with a definite near-occlusion, the risk of ipsilateral ischemic stroke recurrence was 20.0% (95%CI 0.0–44.8%) at 2 days, 30.0% (95%CI 1.6–58.4%) at 14 days, and 50.0% (95%CI 19.0–81.0%) at 28 days and at 90 days after the presenting event (Kaplan–Meier analysis). In an explorative analysis, this difference remained significant when the 50–99% category was divided into 50–69% and 70–99% (p=0.019; log-rank test). Both the type of presenting event and definite near-occlusion affected the risk of ipsilateral ischemic stroke recurrence independently of each other in a multivariable Cox regression analysis (see table 6).

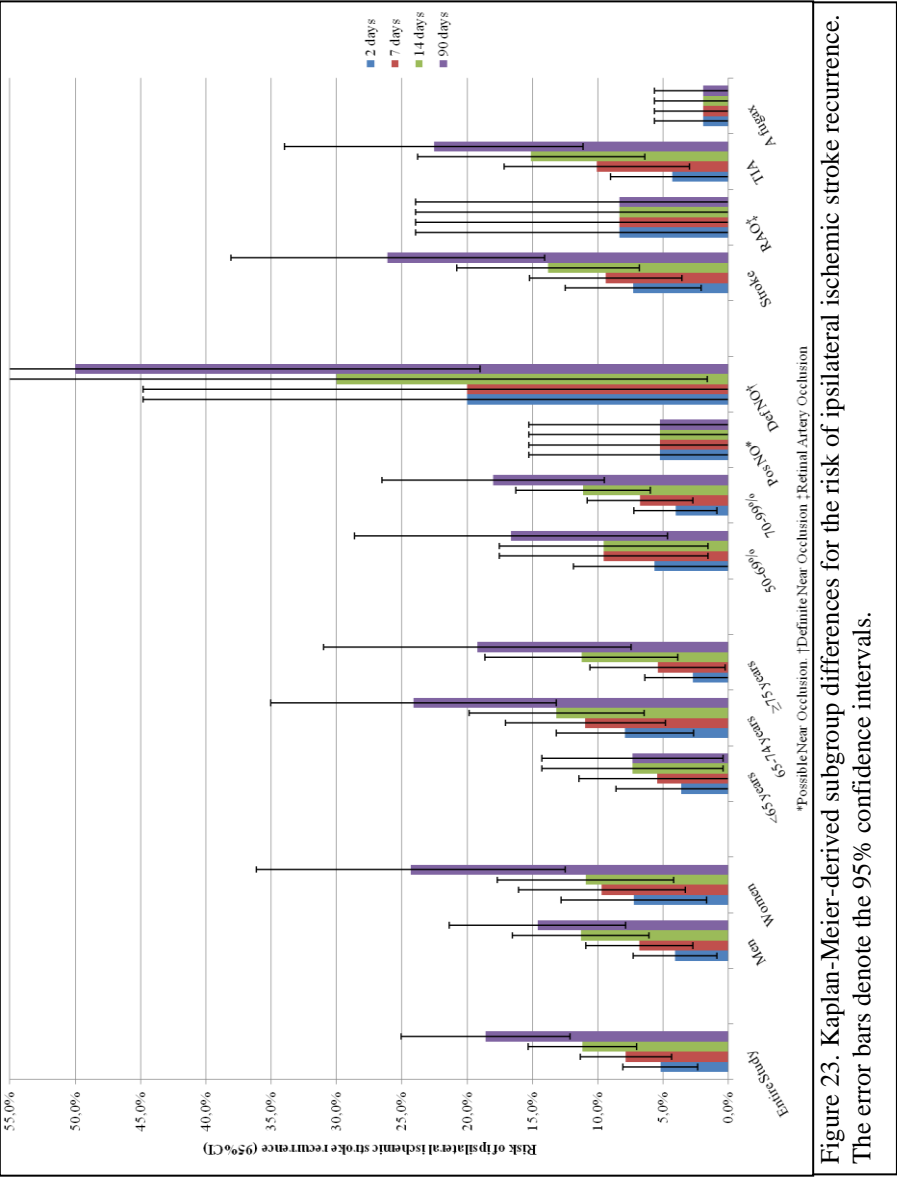


Figure 23. Kaplan–Meier-derived subgroup differences for the risk of ipsilateral ischemic stroke recurrence. The error bars denote the 95% confidence intervals.

Table 6 (reproduced from paper III). Univariable and two multivariable Cox regression models. Analysis of the risk of ipsilateral ischemic stroke recurrence within 90 days after the presenting event. Because CEA was used as a censor, perioperative strokes were excluded, and patients only contributed risk-time before their CEA.

		Univariable		Multivariable Model 1*		Multivariable Model 2†	
		HR	p-value	HR	p-value	HR	p-value
Sex	Women	1.0		1.0		–	–
	Men	0.70	0.299	0.68	0.276	–	–
Age group	<65 years	1.0		1.0		–	–
	65–74 years	2.6	0.090	2.7	0.074	–	–
	≥75 years	2.0	0.221	1.9	0.294	–	–
Type of presenting event	Stroke	10.6	0.021	14.4	0.010	12.3	0.015
	Retinal artery occlusion	4.7	0.277	7.6	0.157	5.7	0.223
	TIA	10.9	0.022	13.4	0.013	11.9	0.017
	Amaurosis fugax	1.0		1.0		1.0	
Degree of stenosis on the symptomatic side	50–99%	1.0				1.0	
	Possible near occlusion	0.42	0.398	0.41	0.385	0.38	0.338
	Definite near occlusion	3.7	0.007	4.4	0.003	4.4	0.002
* Model 1: Sex, age group, type of presenting event, and degree of stenosis on the symptomatic side							
† Model 2: After stepwise removal of sex and then age from multivariable model 1.							

Exploratory analyses were performed for the patients with near-occlusion: How the diagnosis of definite near-occlusion was reached (by conventional angiography, by multiple concurrent non-invasive imaging, or single non-invasive imaging) did not affect the risk of ipsilateral ischemic stroke recurrence because all were represented in stroke recurrence cases in similar quantity. Only 5 out of 205 cases had a near-occlusion on ultrasound; three (60%; 95%CI 17.1–100.0%) of these suffered an ipsilateral ischemic stroke recurrence within 90 days, a higher risk than for those without near-occlusion on carotid ultrasound ($p=0.003$; log-rank test). CT angiography was performed in 74 cases with 8 findings of near-occlusion with string sign and 18 findings of near-occlusion without string sign. Near-occlusion with or without string sign on CT angiography did not affect the risk of ipsilateral ischemic stroke recurrence ($p=0.76$; log-rank test), although patients with string sign tended to have a higher risk.

Among the patients with an ipsilateral ischemic stroke recurrence, the first examination of the carotid arteries after the presenting event was performed after the stroke recurrence in all five patients with definite near-occlusion, after the stroke recurrence in 52% of the patients with 50–99% carotid stenosis, and before the stroke recurrence in the single case of possible near-occlusion.

Among the patients with an ipsilateral ischemic stroke recurrence, the first examination of the carotid arteries after the presenting event was performed after the stroke recurrence in all five patients with definite near-occlusion, after the stroke recurrence in 52% of the patients with 50–99% carotid stenosis and before the stroke recurrence in the single case of possible near-occlusion. Although none of the patients with a definite near-occlusion suffered an ipsilateral ischemic stroke recurrence after the first examination of the carotid arteries, these patients did suffer

recurrent events after the first examination of the carotid arteries: 30% (3/10) of the patients with a definite near-occlusion suffered a recurrent ipsilateral ischemic stroke, TIA or amaurosis fugax after the first examination of the carotid arteries; as a comparison, 25% (56/220) of the patients in the rest of the study suffered a recurrent ipsilateral ischemic stroke, TIA or amaurosis fugax after the first examination of the carotid arteries, $p=1.0$ (chi-2-test).

Perioperative risk

In the HUS study, the risk of any stroke or death within 30 days of CEA was 6.3% (8/128), and in the ANSYSCAP study, the risk of any stroke or death within 30 days of CEA was 3.8% (7/183). No significant difference was detected that would suggest that the timing of CEA affected the perioperative risk in the ANSYSCAP study; however, the study included only 10 cases of CEA within 7 days. In addition, 3.8% of the patients suffered a post-operative TIA, and 3.2% suffered other types of severe complications in the ANSYSCAP study.

PtU study

A total of 1182 panoramic examinations were performed during the study. Of these, 47% were performed in women. The mean age was 51.5 (SD 18.0) years; 70% of those examined were 18–64 years old and 30% were 65–74 years old (persons ≥ 75 years were excluded). The indications were 57% regular dental, 24% specialized dental and 20% specialized medical.

Excluding duplicates, 200 persons had a calcification in the area of the carotid arteries. In 178 persons this calcification was verified on the APP. Thirty-two persons were excluded because they were not eligible for asymptomatic CEA due to cancer ($n=24$) or other serious co-morbidity ($n=8$). Fifteen persons were excluded because they had suffered a previous TIA or stroke. Seven persons failed to provide informed consent. One person was only visiting the area. Six persons met the inclusion criteria but were missed for various reasons. Ultimately, 117 persons were included.

Men and women were equally included in the study ($p=0.68$; chi-2-test). Five percent of the persons aged 18–74 years and 22% of those aged 65–74 years were included in the study ($p<0.001$; chi-2-test); the mean age of those in the study was 66.9 (SD 5.6) years compared to 49.8 (SD 18.1) years among those whom were not included ($p<0.001$; t-test). The inclusion rate for the different indications for the panoramic examination was 14% for regular dental, 2% for specialized dental and 7% for specialized medical ($p<0.001$; chi-2-test). Compared to the reference persons, the included persons with calcifications in the area of the carotid arteries had a statistically significantly higher prevalence of almost all measured cardiovascular events and cardiovascular risk factors (see table 7).

Table 7 (Reproduced from paper IV). Differences in the baseline features and in the burden of atherosclerotic diseases between the included persons (with calcifications in the area of the carotid arteries) and the reference group

	Included persons n (%)	Reference persons n (%)	Significance*
Women	53 (45)	56 (47)	$p=0.786$
65–74 years	77 (66)	79 (66)	$p=0.926$
Indication – Regular dental†	94 (80)	100 (84)	$p=0.458$
Myocardial infarction	24 (21)	7 (6)	$p<0.001$
Heart failure	6 (5)	3 (3)	$P=0.296$
Current angina	17 (15)	2 (2)	$p<0.001$
Symptomatic peripheral artery disease	4 (3)	1 (1)	$p=0.169$
Diabetes	32 (27)	10 (8)	$p<0.001$
Hypertension	88 (75)	54 (45)	$p<0.001$
Current smoking	21 (18)	8 (7)	$p=0.009$
Blood pressure medicine	85 (73)	56 (47)	$p<0.001$
Lipid-lowering medicine	61 (52)	27 (23)	$p<0.001$
Platelet-inhibiting or anti-coagulant medicine	53 (45)	34 (29)	$p=0.008$
Any cardiovascular event	44 (38)	12 (10)	$p<0.001$
Any cardiovascular risk factor	101 (86)	78 (66)	$p<0.001$
All	117	119	-

*Chi-2-test † Regular dental: Indications that exist in all practices with panoramic radiographs

Carotid ultrasound was performed in all included persons. The median delay between the panoramic examination and carotid ultrasound was 76 (IQR 51–91) days. Eight persons had a 50–99% carotid stenosis, seven had a unilateral stenosis and one had bilateral 50–99% carotid stenoses.

The prevalence of 50–99% carotid stenosis was 6.8% (8/117; 95%CI 2.2–11.5%) which was not significantly over the pre-specified 5% threshold ($p=0.23$; binomial test). There was a statistically significant sex difference because all of the carotid stenoses were detected in men ($p=0.008$; chi-2-test). The prevalence of 50–99% carotid stenosis was 12.5% (8/64; 95%CI 4.2–20.8%) which was statistically significantly over the pre-specified 5% threshold ($p=0.014$; binomial test). In addition, there were several other subgroup differences for the prevalence of carotid stenosis (see figure 24). The subgroups in which a statistically significant prevalence difference was detected were analysed further: In the group with the higher prevalence (such as having a history of myocardial infarction), the prevalence was statistically significantly over the pre-specified 5% threshold in all instances; $p<0.05$ in all instances (binomial test).

Of the 117 included persons, 40 had a unilateral calcification and 77 had bilateral calcifications. All nine carotid stenoses had a side-corresponding calcification in the area of the carotid arteries on their panoramic radiograph. In 99% of the 109 persons without a carotid stenosis, a calcified atherosclerotic lesion was detected. These were most often situated in the carotid bulb, proximal ICA, or proximal external carotid artery (ECA).

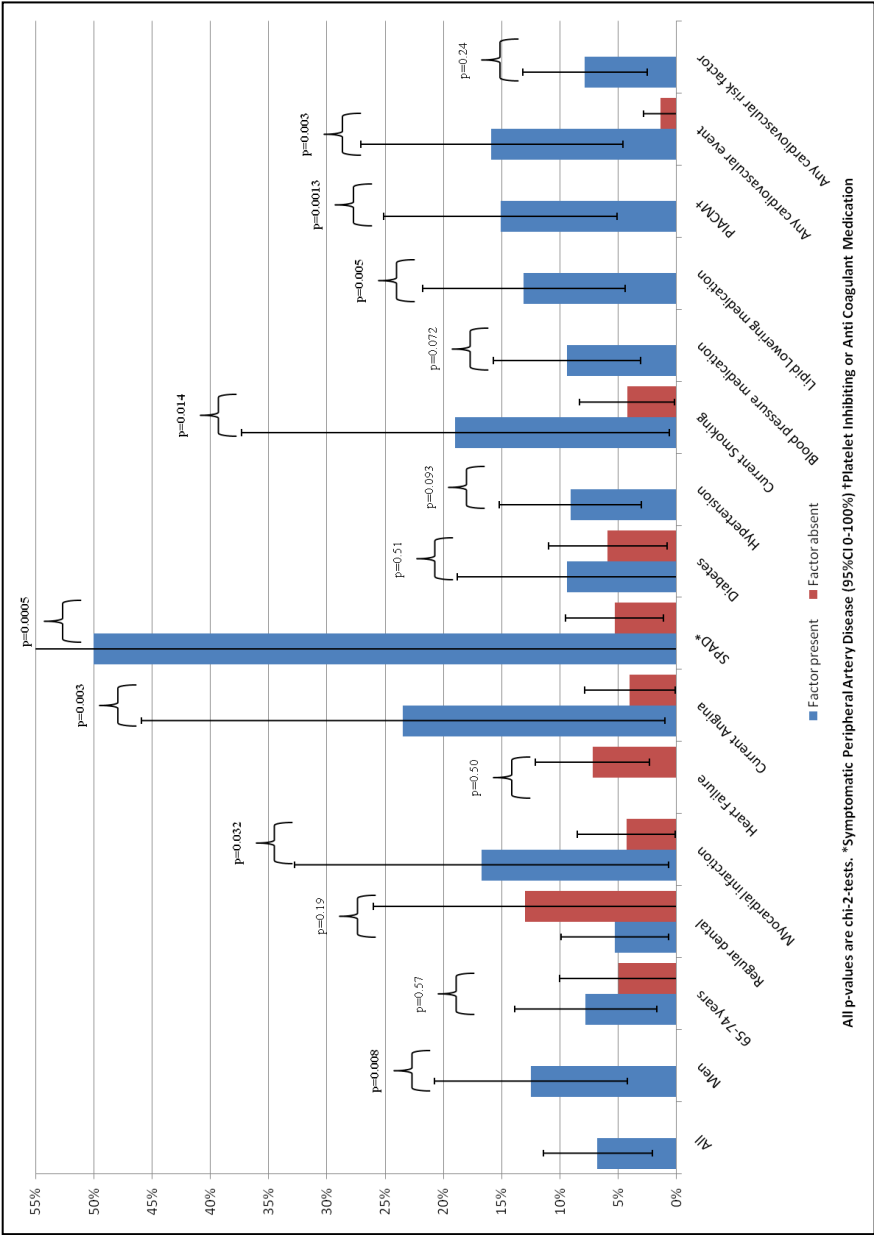


Figure 24. The prevalence of 50–99% carotid stenosis in the entire study and in all the pre-specified subgroups. The error bars denote the 95% confidence intervals.

Discussion

HUS study

Main findings

The main finding in the HUS study was that the delay between the presenting event to the CEA was much longer than 2 weeks. This was the first study that analysed the change in the delay between the presenting event and CEA after the publications showing that CEA should be performed within 2 weeks (and not after 4–6 weeks as previously believed) [49].

The delay to CEA – including the data from the ANSYSCAP study

The delay between the presenting event and CEA was foremost prolonged by the time to referral, the time between referral and the preoperative evaluation, and the time between the decision to perform CEA and the operation. All of these delay points were statistically significantly reduced from the beginning of the HUS study to the end of the ANSYSCAP study. However, the delay between decision and CEA remained quite long at 1.9 weeks at the end of 2009. As a result, the median delay between the presenting event and CEA was still 3.9 weeks at the end of 2009. During 2010, performing CEA directly after the preoperative evaluation became much more common at the University Hospital of Northern Sweden; as a result, the median time from the presenting event to CEA was lower than 2 weeks, according to the Swedvasc registry [100].

No statistically significant differences were detected when comparing the end of the HUS study and the beginning of the ANSYSCAP study. This comparison had lower statistical power because these time periods included only 3 and 5 months whereas all other time periods included 6 months.

Limitations

In some cases, because of the retrospective design, it was difficult to determine if the patients actually underwent the preoperative evaluation. Therefore, some patients who did not undergo the preoperative evaluation (and therefore did not have CEA) were included. Thus, some baseline analyses and the analyses of the management chain might be biased. However, patients who did not undergo CEA were per definition excluded from the main delay analysis. Also, the search for all CEA procedures performed during the study period did not reveal any missed cases of interest. Thus, the analysis of the delay between the presenting event and CEA was not biased as a result of the study design.

Some data on recurrent events were presented in the publication of the HUS study (paper I), but the quality of the symptom data was poor because of the retrospective design. As the quality of the symptom data is much better in the ANSYSCAP study, symptom data from the HUS study are scarcely presented in this thesis. The main implication of this limitation is that interesting analyses of the risk of recurrent stroke before CEA cannot be performed; however, analyses including the type of

presenting event might be biased. Also, the laterality of the symptoms was not registered; thus, the degree of carotid stenosis on the symptomatic side was not analysable.

Summary

The HUS study was a retrospective study. The strength of the study was that it was the first study to present the decrease in delay between the presenting event and CEA after the change in available evidence. Because of the retrospective design, a few cases were probably included despite the patients' not having undergone the preoperative evaluation and that the symptom data were of poor quality. These limitations could mean that some descriptive analyses might have been biased in unknown directions, and many analyses of interest could not be performed. The HUS study served as an excellent pilot study for the ANSYSCAP study.

ANSYSCAP study

Main findings

The main findings of the ANSYSCAP study were the high risk of early ipsilateral ischemic stroke recurrence: 4.8% at 2 days, 7.9% at 1 week, and 11.2% at 2 weeks; that this high risk was observed despite the fact that $\geq 90\%$ of the patients were prescribed medical therapy (in contrast to previous studies); and that this risk was higher if the presenting event was a TIA or stroke compared to amaurosis fugax and/or if a definite near-occlusion was detected compared to a 50–99% carotid stenosis.

Design

The strengths of the ANSYSCAP study are that $\geq 90\%$ of the patients were prescribed medical therapy and that the study was set in the pre-operative setting. The latter made it possible to include patients who did not undergo CEA; this is especially important when CEA was not performed because of a major ipsilateral ischemic stroke recurrence. The ANSYSCAP study had a good external validity because patients were clinically selected and patients with multiple simultaneous aetiologies were not excluded.

Comparison to previous similar studies

The ANSYSCAP study is not the first study in the field of the risk of recurrent stroke before CEA; four similar studies have previously been conducted, as described below:

- The medical arm of the NASCET study was analysed. Patients with retinal events were excluded [119, 131]. The number of included patients strengthens this analysis (n=1029), but there were two important limitations: First, the first-ever event and not the presenting event was used as the index event. Thus, if a patient suffered a TIA, then a stroke, and then sought health care, this patient was categorized as “TIA as index event and recurrent stroke”. In the ANSYSCAP study, such a patient would have been categorized as “Stroke as index event, with a pre-existing TIA”. Second, this study was performed before the widespread use of medical prevention [47, 119].
- The study conducted by Blaser and colleagues revealed the very interesting finding that the risk of stroke recurrence is associated with an exhausted cerebrovascular reserve [31]. A total of 143 patients were included. The limitations were that patients with $<80\%$ stenosis were excluded (not reporting if this was NASCET-type or ECST-type stenoses), the index event was not specified, and only disabling ipsilateral stroke was used in the main analyses. My inquiries on these topics have gone unanswered by the authors.
- The study presented by Ois and colleagues is of a similar design to the ANSYSCAP study with the presenting event as the index event [120]. Also, no CEA procedures were performed within the first 2 weeks, which is better from a study design point of view than the variable time to CEA in the ANSYSCAP study. A total of 163 patients were included. The study was limited by the fact that the main outcome was “Neurological

recurrence”, which includes ipsilateral and non-ipsilateral stroke and TIA. However, ipsilateral and non-ipsilateral stroke were briefly presented.

- The study presented by Fairhead and colleagues [38] is a well-cited study with 80 citations during the first 5 years after publication (according to the Web of Science database). Like the ANSYSCAP study, the presenting event was the index event, and ipsilateral ischemic stroke recurrence before CEA was the outcome. This study was limited by being a retrospective secondary analysis of two well-described population cohorts and having a small sample size (n=32).

The clinical problem addressed in the ANSYSCAP study is, “Is additional benefit to be expected if CEA is performed earlier than within 2 weeks”. Addressing this question required that data presented with the presenting event (and not the first-recorded event) are used as index events and that the same outcome measure as in the NASCET and ECST studies (ipsilateral ischemic stroke) is used [49]. Only the Fairhead study and the ANSYSCAP study fulfil these criteria [38].

The ANSYSCAP study had similar findings as the Fairhead study [38]: that it is likely that the benefit with CEA increases if CEA is performed within a few days rather than within 2 weeks of the presenting event. These findings were expected because there is an early high risk of stroke recurrence for patients with mixed aetiologies [112-115], and carotid stenosis is a particularly malignant aetiology [116, 117]. These results are nevertheless important: Although CEA within 48 hours was proposed in the 2007 UK Department of Health recommendation (without any reference to why this time window was proposed) [132], when the delay to CEA was discussed in the 2011 American Heart Association Guidelines, that CEA should be performed within 2 weeks (and not after 4–6 weeks) was the sole topic [55].

The NASCET and ECST studies might be considered arcane because only 21% were on lipid-lowering medication and 47% were on blood pressure-reducing medication [49]. The medical prevention was not presented in the Fairhead study, but it was conducted at the same time and at the same site as the first phase of the Express study, the phase with a less-than-zealous medical management of patients with TIA and stroke [38, 114]. Even though medical prevention was used in $\geq 90\%$ of the patients in the ANSYSCAP study, the findings are similar to both the analysis of the medical arm of the NASCET study and to the Fairhead study [38, 119]. However, this comparison is limited by being a historical control and by the fact that the medical prevention in the ANSYSCAP study was recorded at the time of the pre-operative evaluation (not at the time of the presenting event).

Subgroup findings

The detected low risk of stroke recurrence for patients with amaurosis fugax implies that such patients might undergo CEA at a somewhat slower pace than patients with TIA and stroke. Although similar findings have been observed in several previous studies [49, 97, 131], this particular clinical implication was not assessable in these studies because of differences in study design. Thus, further studies are needed to confirm it.

Another possible explanation is analogous to occlusions: a stroke can occur when a carotid stenosis becomes near-occluded, but when detected, the near-occlusion does not confer an increased risk for further events. This possibility could not be ruled out in the ANSYSCAP study because all stroke recurrences in the definite near-occlusion group occurred before the first carotid imaging. However, an argument against this possibility is that the number of patients that suffered a recurrent ipsilateral ischemic event of any type after the first carotid imaging was similar for the patients with and without a definite near-occlusion.

There were 19 cases of possible near-occlusion. All of these had the expected combination with CT angiography showing a near-occlusion while the ultrasound did not. Ultrasound alone detected five cases of near-occlusion. Given the moderate sensitivity and next-to-perfect specificity of ultrasound, only one or two false-negative near-occlusions are to be expected [122]. Thus, most of the possible near-occlusions were likely false-positive findings on CT angiography. This might explain why patients with a possible near-occlusion had a risk comparable to those with 50–99% carotid stenosis.

It seemed that ultrasound might be a better risk discriminator than CT angiography for near-occlusions. However, this particular comparison is severely biased by the fact that CT angiography was used at the attending clinician's discretion, and in most cases only slices 2 mm thick were available for the re-examination of the CT angiography images.

Power calculation

Age, sex, and whether the degree of carotid stenosis is 50–69% or 70–99% are known to affect the medical risk for patients with symptomatic carotid stenosis, but these variables did not affect the risk of ipsilateral stroke recurrence in the ANSYSCAP study. These can be false-negative findings, however, so a post-hoc power analysis was performed. The power model used survival methodology with the observed day-to-day hazard rates and drop-out rates (i.e., when patients underwent CEA), and 80% power and $p < 0.05$ as thresholds were used. Sample power 3 was used as the software. The actual study sample size ($n=230$) was kept constant, and the prevalence of the studied group varied; so when the prevalence of the studied group was set at 40% ($n=92$), the baseline group contained 60% ($n=138$). Because of limitations in the calculation program, this model was somewhat conservative as the tested group's hazard ratio was compared to the entire study's hazard rate. Thus, the risk in a group was compared to the mean risk in the entire study; whereas in real life, a group with a high risk is always compared to a group with a low risk.

The threshold for which the hazard ratio was detectable with 80% power depended on the prevalence of the studied group (see figure 25). In groups with a prevalence of 10–80%, the possibility of a missed hazard ratio of >3 can be excluded. In groups with a prevalence of 40–85%, a missed hazard ratio of <0.2 can be excluded. To be more precise, there is a $\geq 80\%$ chance that a study with the same sample size, baseline hazard, and dropout rate would have detected a significant ($p < 0.05$)

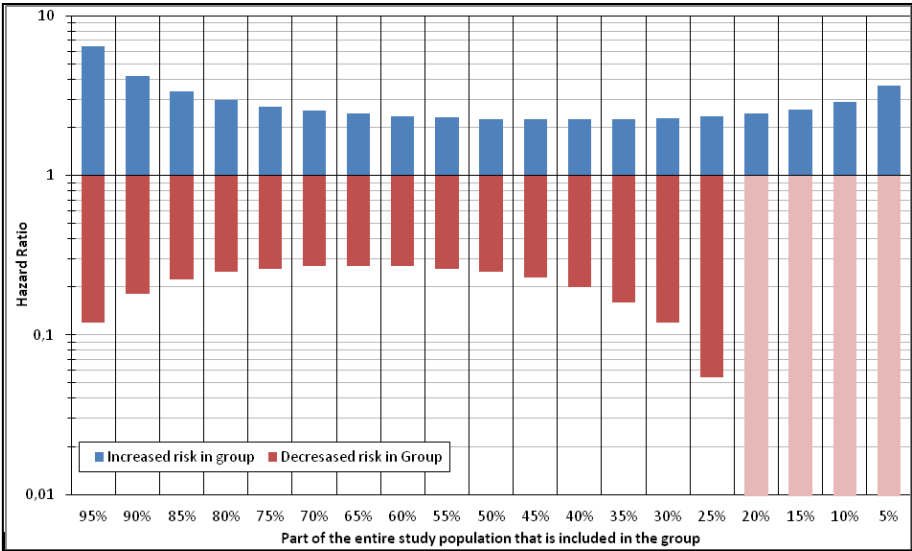


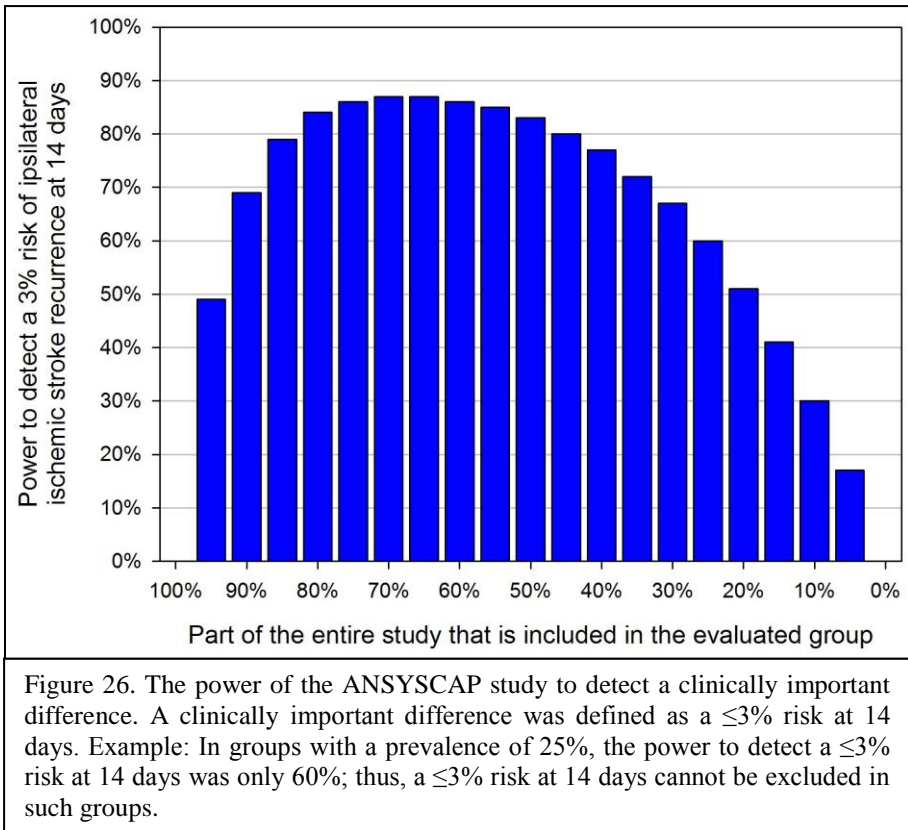
Figure 25. The hazard ratios that could be detected in the ANSYSCAP study at 80% power, depending on the size of the evaluated group. The light red bars all denote a hazard ratio of <0.01 . Example: In groups with a prevalence of 80%, a hazard ratio of 3 was detectable; thus a hazard ratio of >3 can be excluded in such a group, but not a hazard Ratio of <3 .

difference for hazard ratios >3 and/or <0.2 in these groups. Table 8 provides a translation between hazard ratio and a certain risk at 14 days.

The overall finding of this study was that the risk of stroke recurrence was high, suggesting that CEA might be of more benefit if it is performed within a few days. A group with an even higher risk is not clinically relevant (unless the finding is somewhat unexpected, such as for near-occlusions); thus, a clinically relevant subgroup finding is if the risk of stroke recurrence is low at 14 days because this would entail that CEA could safely be performed at a slower pace. A 3% risk at 14 days was defined as such a low risk; the 3% number was used because it is comparable to the perioperative risk observed in the ANSYSCAP study and can thus be viewed as a reasonable comparison. The power to detect a 3% risk at 14 days depending on the prevalence of the studied group is presented in figure 26. In the groups with a prevalence of 45–80%, a risk of $\leq 3\%$ at 14 days can be excluded with 80% power. Only men and the 70–99% carotid stenosis group had 45–80%

Table 8. The corresponding hazard ratio required for a certain risk at 14 days

Risk at 14 days (%)	Hazard ratio
1	0.084
2	0.169
3	0.225
4	0.341
5	0.429
6	0.517
8	0.695
10	0.878
11.2	1.00
12	1.06
15	1.35
20	1.85
25	2.37
30	2.93
40	4.16
50	5.58



Limitations

The biggest limitation was that no intervention group that underwent CEA within 24 hours was included. This does not bias the results, but it does limit the conclusion.

The study was based on the clinical practice that carotid screening was most often restricted to the patients who are preliminarily eligible for CEA. This limitation did not affect the study findings because only patients who were preliminarily eligible for CEA were included, an inclusion criterion that is appropriate when studying the “clinical” perspective of the disease. However, this limitation meant that patients with a symptomatic 50–99% carotid stenosis and a disabling stroke as the presenting event were not ascertained. Thus, it would be inappropriate to perform secondary analyses of the “biological” perspective of the disease, i.e., to widen the endpoint definition to include stroke as the presenting event when this stroke was preceded by a TIA.

If a patient suffered a disabling ipsilateral ischemic stroke recurrence before a referral was sent, it is likely that this referral was cancelled. Such patients should have been included in the study and would have reached the primary endpoint. This is likely to have happened in a few cases: six patients did not undergo CEA because of a major ipsilateral ischemic stroke recurrence; this occurred in 6.8% (3/44) of the

local patients and 1.6% (3/186) of the referred patients ($p=0.086$; chi-2-test). The upshot is that the observed risk is somewhat underestimated. However, because the conclusion of the study is the contention that the risk of ipsilateral stroke recurrence was unacceptably high, this bias only strengthens the conclusion.

Less than 1% (1/230) of the patients had undergone CEA at day 2, 4% (10/230) at day 7, 16% (36/230) at day 14, and 70% (162/230) at day 90. To withhold CEA for 90 days would have improved the validity of the study because more risk-time would have been observed, but it would have been grossly unethical (although such a withholding of treatment has been performed recently [133]). In addition, the delay to CEA varied from patient to patient. The survival analysis assumes that there is no association between the drop-out rate (i.e., the delay to CEA) and the studied risk. If patients with a high risk underwent CEA earlier than others, the observed risk is an underestimation and vice versa. Such an underestimation might have occurred because patients with stroke or TIA as the presenting event both had an increased risk of ipsilateral ischemic stroke recurrence and a shorter delay to CEA compared to patients with amaurosis fugax (see table 4 and figure 23). However, only a few patients had undergone CEA at 14 days, limiting the bias of the observed 14 day risk. It is possible that other hard-to-measure variables (such as the perceived vitality of the patient) might also influence both risk and the attending physicians' timing; thus, additional bias in an unknown direction might also exist.

For the analysis of near-occlusion, the degree of carotid stenosis was divided into definite near-occlusion, possible near-occlusion, and 50–99% carotid stenosis. This division was pre-specified and based on the best available evidence for the diagnostic accuracy of ultrasound and CT angiography for near-occlusions. However, few studies have compared ultrasound and/or CT angiography with conventional angiography for near-occlusion relative to the number of studies for 50–99% carotid stenosis [71, 73-79, 81-92, 122-125]. In light of this limitation, the study findings would have been more solid if conventional angiography had been performed more often. However, this does not mean that conventional angiography is required in the clinic because these findings should be regarded only as hypothesis generating. It is reasonable that future studies on symptomatic near-occlusion use conventional angiography, on the condition that the aims of these studies are to both establish the prognosis and to compare the findings on conventional angiography with several non-invasive modalities so that these non-invasive modalities can be used in the clinic. Perhaps either of the non-invasive modalities has a superior risk discriminatory ability, as is suggested for ultrasound in the ANSYSCAP study.

Interpretation

It is well established that CEA should be performed within 2 weeks of the last symptom [49, 50]. The ANSYSCAP study showed that many stroke recurrences had already occurred at day 2, suggesting that additional benefit can be gained by performing CEA as early as within 24 hours. However, whether CEA within 24 hours is beneficial for the patient compared to later CEA depends on whether it confers an increased perioperative risk compared to later CEA.

The perioperative risk with CEA within 24 hours of the relevant symptom is not well studied. According to a systematic review, only three studies have been published [54]. The perioperative risk was 4.2% (13/313) within 24 hours compared to 1.9% (57/2975) after 24 hours in these three studies [54]. The study by Goodney and colleagues accounted for 94% of the patients in this analysis [54, 134], used the presenting event as the index event, and also reported that the perioperative risk was 13.0% with CEA within 6 hours compared to 1.7% after 6 hours ($p < 0.001$) [134]. Thus, there is evidence that the perioperative risk is dependant on timing. Also, patients with unstable symptoms have a high (>10%) perioperative risk [54]. Uncontrolled observation studies of the perioperative risk might be biased because unstable patients might undergo CEA early more often. Instability in symptoms was not presented in the Goodney study [134]. Given that the perioperative risk is time-dependant (at least within 6 hours) and the number of studies on the risk with CEA within 24 or 48 hours is limited, perhaps CEA within 48 hours should be avoided in the clinic setting until further data are published.

Based on the best available evidence, CEA at 2 to 5 days after the presenting event thus seems to be the optimal timing. However, further (perhaps randomized) studies on the optimal timing of CEA are warranted, especially to establish the risk of early CEA. If CEA within 24 hours turns out to be safe, then CEA should be performed within 24 hours. Thus, this proposed time window, although based on the best available evidence, should be regarded as preliminary until more studies have been performed.

Speculations on the possible impact

There were 33 ipsilateral stroke recurrences and 3 non-ipsilateral stroke recurrences in the ANSYSCAP study. The three non-ipsilateral recurrences were likely the result of causes other than the carotid stenosis. Thus, it is reasonable to assume that 3 of the 33 ipsilateral stroke recurrences were also the result of other causes but happened to occur in the same territory as the presenting event. Therefore, 91% (30/33) of the stroke recurrences were likely caused by the carotid stenosis and would have been prevented with earlier CEA.

A calculation of the potential increase in annual benefit of earlier CEA in Sweden was performed. In this calculation, it was assumed that all of the additional risk attributable to the carotid stenosis after day 2 would have been averted with CEA at day 2 and that the perioperative risk was not increased with CEA at day 2. To compare CEA at day 2 to the current practice, data from the Swedvasc registry were used (courtesy of Strömberg [135]). This data set included the time between the presenting event and CEA, and the type of presenting event was included for all registered operations between May 2008 and May 2011 (3 years). The additional benefit was calculated to arise by two separate mechanisms: first, by changing the timing of CEA procedures that were performed after day 2 to day 2; and second, by performing CEA at day 2 in the patients who suffered a disabling stroke recurrence after day 2.

The additional benefit of changing the timing of the CEA procedures that were performed after day 2 to day 2 was calculated by multiplying three factors: (1) The

risk at a specific days subtracted from the risk at day 2 (as observed in the ANSYSCAP study). (2) The number of patients that underwent CEA at the specific day (as observed in the Swedvasc material). (3) The risk attributable to the carotid stenosis (91%), which is then assumed to be removed by the operation. This calculation was made separately for every day between 2-90 days for each type of presenting event separately. The data on the number of patients that underwent CEA was provided in spans of several days; thus, for this calculation, it was assumed that the patients in the Swedvasc material underwent CEA at the same rate as in the ANSYSCAP study within each specified time span. Example: Between days 3–7, nine patients underwent CEA in the ANSYSCAP study 11% of these at day 3, 11% at day 4, 11% at day 5, 22% at day 6, and 44% at day 7. Thus, 44% of the patients who underwent CEA between days 3–7 in the Swedvasc data were assumed to have undergone the procedure at day 7, and so on.

- For the 924 patients with stroke as presenting event that underwent CEA after day 2, 54.0 strokes were calculated to be preventable with CEA at day 2.
- For the 975 patients with TIA as presenting event that underwent CEA after day 2, 81.3 strokes were calculated to be preventable with CEA at day 2.
- For the 466 patients with either retinal artery occlusion or amaurosis fugax as presenting event that underwent CEA after day 2, no strokes were calculated to be preventable with CEA at day 2 since none of the patient with these presenting events suffered a stroke recurrence after day 2 in the ANSYSCAP study.
- In total 135.3 (54.0+81.3+0) stroke were calculated to be preventable with CEA at day 2 over three years.
- Thus, the annual additional benefit with CEA in Sweden is calculated to be $135.3/3 = 45.1$ by this mechanism.

With 135.3 stroke prevented over three years by changing the timing of 1899 (924+975) operations, the average absolute risk reduction with this change can be estimated to be 7.1% ($135.3/1899$). The increase in benefit is dependant of what the delay to CEA is to begin with; if the delay to CEA had been shorter to begin with, this absolute risk reduction would be smaller.

To calculate the additional benefit of performing CEA at day 2 in patients who suffered a disabling stroke recurrence after day 2, the first step was to determined the ratio between (1) how often a CEA was not performed because of a disabling stroke recurrence compared to (2) how often CEA was performed. In the ANSYSCAP study, cases of disabling stroke recurrence were sometimes missed among the referred patients; thus, only the data on the local patients were used. Three local patients suffered a disabling ipsilateral ischemic stroke recurrence before CEA that precluded performing CEA. All three patients had TIA or stroke as the presenting event. One of these stroke recurrences occurred after day 2. A total of 22 of the local patients with stroke or TIA as the presenting event underwent CEA after day 2. Thus, if CEA was always performed at day 2 instead of after day 2, for every 22 patients with TIA or stroke as the presenting event who undergoes CEA after day 2, one additional CEA is to be expected. Because this calculation means that additional CEA procedures are performed, a perioperative risk of 5.1% [54] was accounted for:

- In the Swedvasc material, 1899 CEA procedures were performed at day 2 or after on patients with TIA or stroke as the presenting event.
- An additional 86.3 (1899/22) CEA procedures would have been performed during the 3-year time period. Thus, the annual increase to be expected in Sweden is $86.3/3 = 28.8$.
- $1.5 (28.8 \cdot 0.051)$ of these patients would have suffered a perioperative stroke.
- In 9% (100%-91%), the disabling stroke was not preventable, $28.8 \cdot 0.09 = 2.6$.
- Thus, $24.7 (28.8 - (1.5 + 2.6))$ strokes would have been prevented annually in Sweden by this mechanism.

However, the 24.7 disabling strokes prevented might be an underestimation because only 33% (1/3) of the disabling stroke recurrences occurred after day 2 in the ANSYSCAP study, whereas 77% of the non-disabling stroke recurrences occurred after day 2. Thus, even more additional CEA procedures than these 24.7, most preventing a stroke, are likely to be achieved annually in Sweden with CEA at day 2 as the standard.

In total, $45.1 + 24.7 = 69.8 \approx 70$ additional strokes can be avoided annually in Sweden if CEA is performed at day 2 instead of when it actually is performed.

These calculations have a wide margin of error and are based on several assumptions. However, it is an estimation of the magnitude of strokes that can be prevented just by changing the timing of something we would otherwise do anyway.

Summary

The ANSYSCAP study was a prospective study with good internal validity and good external validity. The limitations meant that some possible analyses were inappropriate and thus were not performed. Furthermore, some biases are known and involved an underestimation in the observer risk, strengthening the contention of the conclusion. The main limitation is the lack of an intervention group, and the conclusion incorporates this accordingly. Although the results are for the most part expected, the ANSYSCAP study is an important step on the path to determining the optimal timing of CEA. In addition, the finding that a definite near-occlusion entails a high risk of stroke recurrence is interesting; although the limitations of that particular analysis mean that the study should not affect clinical practice, the need for further studies is clear.

PtU study

Main findings

The main finding of the PtU study was that the prevalence of 50–99% carotid stenosis in men with a calcification in the area of the carotid arteries was statistically significant over 5%; thus, directed screening is indicated.

Design

The internal validity was also good with a high inclusion rate and good inter-observer kappa. The study was designed and conducted to have a good external validity because only persons eligible for asymptomatic CEA were included in the study. Also, the findings are likely to be valid for all clinics using panoramic radiographic examinations because common dental indications were well represented and no significant difference in the prevalence of carotid stenosis was detected when comparing the different indications for the panoramic examination.

Comparison to previous similar studies

A lower prevalence of calcifications (fewer underwent ultrasound screening) and higher prevalence of carotid stenosis (better outcome) were detected in the two previous similar studies compared to the PtU study [127, 128]. The main difference between those studies and the PtU study is the design: In the PtU study, only those who were eligible for asymptomatic CEA were examined with ultrasound [127, 128].

A higher prevalence of calcifications in the area of the carotid arteries was detected compared to previous studies [127, 128]. This outcome has several possible explanations: The persons with calcification in the area of the carotid arteries had an increased burden of atherosclerotic disease compared to the reference population. Thus, the prevalence of calcifications in the area of the carotid arteries likely depends on the burden of atherosclerotic disease in the examined population, and the burden of atherosclerotic disease in the examined population can vary from population to population. In addition, depending on how the panorama image and/or APP are captured, the chance of detecting a calcification can vary.

A lower prevalence of 50–99% carotid stenosis among persons with calcifications in the area of the carotid arteries was detected compared to previous studies [127, 128]. It is well established that male sex and increasing age increase the prevalence of asymptomatic carotid stenosis [126]. In previous studies, participants aged >75 years were included, and in one study, 94% of the included persons were men [127, 128]. In addition, the velocity threshold criteria on ultrasound for the definition of a $\geq 50\%$ carotid stenosis were lower in the largest of the previous studies [127, 136] compared to the velocity criteria used in the PtU study [73, 74]. In a student project performed near the end of the inclusion period, the velocity findings on carotid ultrasound were analyzed according to several translation criteria [137]. A total of 115 of the persons examined with carotid ultrasound in the PtU study were analysed. Eight persons with a 50–99% carotid stenoses were detected with the translation system used in the PtU study [73, 74] while 18 persons with a 50–99% carotid

stenoses were detected with the velocity threshold used in the largest of the two previous studies [127, 136].

Subgroup findings

Heterogeneity for the prevalence of 50–99% carotid stenosis was detected in several of the pre-specified subgroups. These findings were expected because they are markers for generalized atherosclerotic disease. No multivariable analysis was performed as a result of a low number of detected 50–99% carotid stenoses. However, these findings are most likely not independent of each other because patients with cardiovascular events are prescribed the medications that were analyzed. Until a multivariable analysis has been performed, only one subgroup should be used in clinical practice. In the choice of subgroup, sex is preferable as it is one of the few parameters known in the dental clinic and includes all cases of carotid stenosis when positive. As an example, symptomatic peripheral vascular disease is a less preferable choice because it is seldom known to dentists and included only two of the eight cases with detected carotid stenosis.

Limitations

The main finding is based on a subgroup finding, weakening the validity [95]; however, similar studies have shown similar results and the differences have a plausible explanation [127, 128]. There were too few cases with a 50–99% carotid stenosis to allow for a multivariable analysis. The appearance of the calcification (size, shape, and/or intensity) was not analysed. The high prevalence of other atherosclerotic co-morbidities confounds the finding of a high prevalence of carotid stenosis: It is uncertain to what extent the high prevalence of carotid stenosis was attributable to a local atherosclerotic process or to a selection of persons with generalized atherosclerotic disease; however, the underlying mechanism does not affect the validity of the pragmatic conclusion.

As described in detail in the introduction to this thesis, the management of asymptomatic carotid stenosis is and will continue to change in the future. When a new management practice has been established, the threshold for the prevalence of carotid stenosis that is required for directed screening to be of value must be re-calculated. The PtU study findings should then be compared to that new threshold and the conclusion revised, if necessary.

Interpretation

Previously, the only indications for directed ultrasound screening were carotid bruits and symptomatic peripheral artery disease, although there are several additional candidates [67, 68]. Carotid bruits are straightforward for use in clinical practice, preferably in the general practitioner's setting. However, many of the patients with symptomatic peripheral artery disease are either >75 years and/or have such serious cardiovascular co-morbidities that asymptomatic CEA is not beneficial because of the increased perioperative risk. An incidental finding of calcifications in the area of the carotid arteries in panoramic examinations is now the third indication for directed screening, although only among men. It is hoped that further studies might enable an even better selection process for those with a calcification in the area of carotid arteries who might undergo ultrasound screening; thus, fewer patients would

need to be screened with ultrasound, with a minimal number of carotid stenoses missed.

In addition to the few persons with asymptomatic carotid stenosis, many of the persons examined with ultrasound in the PtU study had pronounced atherosclerotic plaques. Plaques in the carotid arteries are an independent risk marker for cardiovascular events [20]. Although the plaque size can be reduced with aggressive medical therapy [138], whether carotid plaques should be regarded as an indication aggressive medical therapy in patients without previous vascular events remains unknown [139]. If future studies show that carotid plaques are an indication for aggressive medical therapy, ultrasound screening of persons presenting with calcifications on panoramic examinations can be a way of detecting such plaques. If so, ultrasound screening is likely to be indicated for both men and women, regardless of age.

A woman with a carotid stenosis can definitely present with a calcification in the area of the carotid arteries on panoramic radiographs [140]. The PtU study showed that women with a calcification in the area of the carotid arteries have a statistically significantly lower prevalence of carotid stenosis than similar men. Although lower than the prevalence among men, however, the prevalence among women is possibly >5%. Further studies are needed to more precisely identify the prevalence of carotid stenosis among these women for determining if ultrasound screening should or should not be performed.

Experiences from clinical implementation

After the study stop date, examinations have been continued on a clinical basis with three important modifications in the protocol: (1) The APP is no longer required. Although the APP was helpful for the initial experience for the oral and maxillofacial radiologists in the beginning of the PtU study, they now have determined that the APP is no longer required for their assessment. Also, the APP is troublesome to acquire if the calcification on the panoramic image is noticed after the examined person has left the radiology department. However, no definite evidence that the APP should or should not be used exists, but the question could be studied. (2) Based on the findings in the PtU study, only men are examined. (3) Previous stroke or TIA is no longer exclusion criteria, and case-by-case assessment has been implemented instead. Between February 2009 and February 2011, an additional 65 men have been examined with carotid ultrasound. Six of these had a 50-99% carotid stenosis and one had a carotid occlusion. Thus, further study shows that 10.9% (14/129; 95%CI 5.4–16.3%) of men with a calcification in the area of the carotid arteries have a 50–99% carotid stenosis, statistically significantly more than the pre-specified 5% threshold ($p=0.005$; binomial test); In addition, the prevalence of 50–100% carotid stenosis was 11.6% (15/129; 95%CI 6.0–17.2%).

Speculations on the possible impact

The precise number of clinics with panoramic equipment is unknown as well as the number of persons aged 18–74 that are examined with panoramic radiographs annually. This makes it difficult to assess the number of annually detectable carotid stenoses per capita in Sweden. The number of annual examinations per 100,000 was calculated by dividing the number of annual examination in the PtU study with the

size of the local population ($n=144,000$). However, in the local Umeå region there is at least one additional clinic that uses panorama. On the other hand, some of the persons examined at the department of oral and maxillofacial radiology come from outside the local area. It is reasonable to use the PtU population because these two biases will more or less cancel each other out.

During the 575 days long PtU study, eight persons with carotid stenosis were detected. Thus, the annual number of detected carotid stenosis was $8/((575/365)*1.44) \approx 3.53$ per 100,000. Out of these eight persons, three were offered CEA (one underwent it, one refused, and one died before the operation), and five are followed with repeated examinations. For a general calculation, it is reasonable to assume that not one person but 2–3 persons out of 8 will undergo CEA because the refusal rate is not 33% in clinical practice and at least some of those followed might undergo CEA in the future. Thus, a CEA rate of $2.5/8 = 31.25\%$ can be expected, and the annual increase in asymptomatic CEA procedures performed would be $3.53*31.25\% \approx 1.10$ per 100,000.

Assuming all Swedish clinics start the suggested ultrasound screening procedure, for a population of 9 million, this change would entail an annual increase of $1.10*90 \approx 99$ asymptomatic CEA procedures. In 2009 and 2010, the average number of annual CEA procedures on asymptomatic carotid stenoses was 214 [100]; thus, a 46% increase is possible.

This calculation is representative for men <75 years old. For men <75 years old, asymptomatic CEA entails a $10.1\% - 2.8\% = 7.3\%$ 10-year absolute risk reduction for stroke (after a 2.8% perioperative risk is taken into account) [17, 54]. Thus, an annual increase of 99 asymptomatic CEA procedures in men <75 years old would mean that $99*7.3\% \approx 7$ strokes that would be avoided each year if a nationwide screening is implemented.

These calculations have a wide margin of error because of uncertain assumptions and small sample sizes. Although a 46% increase in the number of asymptomatic CEA procedures performed, with the ensuing reduction of 7 strokes per year, is mathematically possible, the real life implementation is likely to be more modest because it is probable that some health care practitioners will not be zealous in the implementation of the findings of the PtU study.

Summary

The PtU study was a prospective diagnostic effectiveness study. Both the internal and external validity were good. The limitations mean that further studies are needed but do not affect the conclusion. The study identified a new indication for directed ultrasound screening for asymptomatic carotid stenosis to be added to the two previously known indications.

General Discussion

Possible alternative data sources

All data in this thesis were gathered independently of other research sources, with only one exception: Data on the 30-day perioperative risk were gathered from the Swedvasc registry for some of the patients in the HUS study. Less effort would have been necessary if the studies data were gathered from registries, such the Swedvasc registry [100]. However, the date of the presenting event was included in the Swedvasc registry in May 2008, i.e., after the HUS study and halfway through the ANSYSCAP study [100]. Also, Swedvasc registry data are insufficient for detailed analyses on the risk of stroke recurrence before the operations [100]. There are plans to attempt to validate the data on the delay to CEA registered in the Swedvasc registry with data from the ANSYSCAP study, strengthening the validity of this new feature of the Swedvasc registry. If valid, future studies on the delay to CEA could definitely use Swedvasc as a data source.

Statistics

The choice of statistical tests was straightforward in most instances. CEA served as a censor in the survival analyses of the ANSYSCAP study because this entailed that patients were followed only until their CEA. The possible bias resulting from non-random censoring is discussed. The rationale behind the use of the binomial test in the PtU study is described in the methods section.

There are 113 p-value calculations in this thesis: 51 were non-significant ($p > 0.05$) and 62 were significant ($p < 0.05$). Of the 62 significant findings, in 22, the p-value was < 0.001 ; in 18, the p-value was between 0.001–0.009; and in 22, the p-value was between 0.01–0.049. Because of multiple testing, there is a risk for false-positive findings, especially among the 22 calculations that revealed a p-value between 0.01–0.049. However, most calculations are only descriptive whereas others are more important. The 22 most important calculations in this thesis were as follows:

- The delay between the presenting event and CEA from the beginning of the HUS study to the end of the ANSYSCAP study.
- Four pre-specified and one secondary subgroup analyses on the risk of ipsilateral ischemic stroke recurrence in the ANSYSCAP study: age, sex, type of presenting event, degree of carotid stenosis as 50–69% or 70–99% and degree of carotid stenosis as definite near-occlusion, possible near-occlusion, or 50–99% carotid stenosis.
- The binomial test for the prevalence of carotid stenosis in the entire PtU study.
- 15 pre-specified subgroup analyses on heterogeneity for the prevalence of carotid stenosis in the PtU-study.

Of these 22 calculations, 11 were significant ($p < 0.05$), and 8 of these had a p-value < 0.01 . Thus, around 0–1 false-positive findings can be expected for the most important calculations. However, given the moderate sample size in the studies, ranging from 117 to 275 patients, false-negative comparisons are likely.

Ethics

Both the HUS study and the ANSYSCAP study were strictly observational. The HUS study was classified as an assurance of quality of health care study. In accordance with the then-current ethical legislation and practice, no ethical approval was sought. The ANSYSCAP study was audited by the local research ethics committee, which found that the study did not need ethics approval. In accordance with the then-current ethical practice, informed consent was not obtained, but good clinical practice for research was upheld. Since that time, the ethical legislation has changed [141], and informed consent is now also required for observational studies. To abstain from collecting informed consent might be questionable, at least in the light of this new legislation. However, the studies were conducted so that the anonymity of the patients was assured, with no discomfort and no risks to the patients.

Ethics approval and informed consent were secured in the PtU study. Anxiety while waiting for the examination has been raised as an issue. To date, more than 240 persons have been informed about the finding of a calcification in the area of the carotid arteries and three persons expressed anxiety before the examination (incurring a more urgent examination). A few more persons expressed minor anxiety during this waiting period when I talked to them after the examination. However, it is my experience that a majority of the persons are spontaneously grateful that they were informed about the calcification and that the ultrasound examination was performed.

For the clinician who manages patients with stroke

- Make sure that all patients with ischemic stroke/TIA receive appropriate medical prevention initiated within 24 hours. Platelet inhibition and lipid lowering should be initiated the same day; blood pressure should not be left unchecked, but it seems that aggressive early blood pressure treatment is harmful [142].
- Screen patients with stroke, TIA, amaurosis fugax, and retinal artery occlusion with symptoms conforming to the anterior circulation with ultrasound, CT angiography, or CEMRA. Whichever gives the earliest answer should be used because time to CEA is more important than modality.
- If you are at a referring hospital, you should discuss and/or refer the patient directly when you have detected a symptomatic carotid stenosis; do not wait for the regular discharge day. Also, keep in mind to plan for follow-up visits and rehabilitation because patients will often be referred before you are “done”.
- For the indication for CEA: Speed is the key! With the time from presenting event to CEA of less than 2 weeks, the NNT with CEA will be <10 regardless of sex, age, or a degree of carotid stenosis of 50–69% or 70–99%. However, with CEA at 2–5 days, this benefit is even larger because the risk of stroke recurrence is very high early after the presenting event, especially for patients with TIA or minor stroke as the presenting event.
- For the contraindications for CEA: A moderate perioperative risk (4–8%) should affect only your decision to perform CEA if the delay to CEA is >2

weeks and occurs in combination with an unfavourable mix of sex, age and degree of carotid stenosis; otherwise, CEA will still be beneficial because the “NNT<10” number already includes a perioperative risk of 5.1%. If technical aspects make CEA unfeasible, consider angioplasty. Also, use your common sense regarding the meaningfulness of the procedure.

Personal views

There are several possible improvements for the management of the carotid stenosis. A more individual assessment with microemboli detection, cerebrovascular reactivity testing, and characterization of stenosis morphology will improve the physician’s understanding of the individual patient. Also, although more research is needed, these parameters might affect treatment decisions in the quite near future:

- More urgent CEA (or CEA at all) for patients with the supposedly asymptomatic (but actually symptomatic) carotid stenosis with crossover embolism to the contralateral hemisphere [35];
- Patients with asymptomatic carotid stenosis who will need aggressive medical prevention, but only those with microemboli, exhausted cerebrovascular reactivity, or unfavourable stenosis morphology characteristics will also need CEA [32, 105-109].

Aggressive medical primary prevention in the large population of patients with carotid plaques but without any previous vascular events will, it is hoped, lead to fewer cardiovascular events in the future [20, 138, 139]. If so, detection and ultrasound screening of persons with calcifications in the area of the carotid arteries on panoramic examinations will have an even larger role to fill.

In the last decade, several studies on CEA versus angioplasty and one study of anaesthetic technique have been performed [57, 143]. These studies were all relevant because they answered many important questions. However, as it turned out, the results were always similar or differed within just a few percentage points compared to established practice [57, 143]. Thus, these studies have not significantly improved the situation for the patients because the risk of stroke recurrence and periprocedural risk have not been significantly improved. The ANSYSCAP study points to the great potential of increased benefit with CEA at 2 to 5 days after the presenting event. If only one of these large multicentre studies had studied timing instead of technique, our patients would have been much better off. Thus, as a scientific community, it is time to spend less of our effort trying to determine *how* to treat a symptomatic carotid stenosis and instead focus our attention on *when* to treat a symptomatic carotid stenosis. CEA at 2-5 days is definitely achievable, although efforts will often be needed to make sure that patients are screened, referred, evaluated, and operated in time. This coordination is troublesome because the necessary improvements in the logistics will require both training and ambition for all involved parties. But the reward is an increased benefit with CEA, likely with an additional 5–10% absolute risk reduction, perhaps more.

Conclusions

For patients with symptomatic 50–99% carotid stenosis, the median delay from the presenting event to CEA was 11.7 weeks in the first half year of 2004, dropped to 6.9 weeks in the first quarter year of 2006, and dropped further to 3.6 weeks in the second half year of 2009. Initially, this delay was caused by long periods between the presenting event and referral, between the referral and the preoperative evaluation, and between the decision to perform CEA and the operation. All of these delays were shortened from 2004 to 2009, but the period between the decision and the operation was still 1.9 weeks in the end 2009.

The risk of ipsilateral ischemic stroke recurrence before CEA in patients with a 50–99% carotid stenosis was 4.8% at 2 days, 7.9% at 1 week, 11.2% at 2 weeks, and 18.6% at 90 days after the presenting event. About 90% of these stroke recurrences were likely caused by the carotid stenosis and could have been prevented with CEA. An additional benefit is likely to be gained by performing CEA within a few days of the presenting event instead of at 2 weeks. Because other studies suggest that the perioperative risk might be increased during the first day, the optimal timing seems to be 2–5 days after the presenting event. The risk of ipsilateral stroke recurrence was independently increased for patients with stroke or TIA as the presenting event compared to patients with amaurosis fugax as the presenting event, and for the patients with a near-occluded carotid stenosis compared to the patients with a 50–99% carotid stenosis. Age, sex, or if the degree of carotid stenosis was 50–69% or 70–99% did not affect the risk of ipsilateral ischemic stroke recurrence. The finding that patients with an amaurosis fugax as the presenting event had a low risk of stroke recurrence might suggest that patients with amaurosis fugax may undergo the preoperative evaluation and CEA at a slower pace than other patients. The finding that near-occlusion entails an early high risk of stroke recurrence stands in sharp contrast to previous studies. One possible explanation is that this high-risk period missed in previous studies.

The incidental finding of calcification in the area of the carotid arteries on a panoramic radiograph is a valid indication for carotid ultrasound screening in men who are otherwise eligible for asymptomatic CEA.

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