Screening for asymptomatic carotid atherosclerosis

DOMINIKA HÖGBERG
Abstract


Ischemic stroke is the most common cause of handicap in adults and the third most common cause of death in Sweden. Internal carotid artery atherosclerosis is an important cause and accounts for 20% of ischemic strokes. Screening for carotid atherosclerosis has been debated over the past two decades.

The aims of this thesis were (I) to study the prevalence of and risk factors associated with carotid artery atherosclerosis among 65 year old men, (II) to evaluate a simplified ultrasound protocol (the grayscale/mosaic method) for the exclusion of significant carotid artery stenosis for screening purpose, (III) to evaluate the required effect of primary preventive therapy in reducing risk of stroke among patients with asymptomatic carotid disease in order for screening to be cost-effective and (IV) to study natural history of carotid atherosclerosis and outcome five years after screening in 65-year old men.

The prevalence of atherosclerotic plaques was high (25%), while the prevalence of >50% stenosis was relatively low (2.0%). Smoking, hypertension, diabetes mellitus and coronary artery disease were independent risk factors and individuals with several risk factors had a higher prevalence of stenosis. Most of those at risk were not on any preventive medication. A simplified grayscale/mosaic method was found to have a high negative predictive value for significant carotid stenosis. The minimum stroke risk reduction effect required for preventive intervention to be cost effective was 22%. Carotid atherosclerotic plaque and stenosis 50-79% has a relatively benign development during five years if treated with BMT and risk factor adjustment. Very few progressed to symptomatic disease. More severe stenosis (80-99%) had higher rate of neurological events, and may benefit from additional intervention.

In conclusion, prevalence of silent atherosclerotic disease in carotid arteries was common among 65-year-old men. Most of those at risk had no secondary prevention. There is a simple DUS method that could be used for screening purpose. Screening for carotid disease is only cost-effective if the preventive strategy lowers the risk of stroke by 22%. Men with plaques and moderate stenosis have a good prognosis, but among those with severe stenosis there is a need for further intervention.

Keywords: Carotid stenosis, carotid atherosclerosis, screening, cost-effectiveness, natural history, carotid ultrasound

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urn:nbn:se:uu:diva-328803 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-328803)
To my beloved boys

Urban, Oliver and Victor

We have not succeeded in answering all our problems. The answers we have found only serve to raise a whole set of new questions. In some ways, we feel that we are as confused as ever, but we believe we are confused on a higher level and about more important things.

Earl C. Kelley
List of Papers

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


_Eur J Vasc Endovasc Surg 2014;48(1):5-10_

II Högberg D, Dellagrammaticas D, Kragsterman B, Björck M, Wanhainen A. Simplified ultrasound protocol for the exclusion of clinically significant carotid artery stenosis.


Submitted manuscript


Submitted manuscript

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The cover picture is an ultrasound image of a carotid artery stenosis on color doppler. Picture kindly provided by Maimun Abdi Poljarevic from Vascular Laboratory at University Hospital in Uppsala.
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Abbreviations

AAA Abdominal aortic aneurysm
ACAS Asymptomatic Carotid Atherosclerosis Study
ACST Asymptomatic Carotid Surgery Trial
CAD Coronary artery disease
CEA Carotid endarterectomy
COPD Chronic obstructive pulmonary disease
CVD Cerebrovascular disease
DUS Duplex ultrasonography
ECST European Carotid Surgery Trial
ICA Internal carotid artery
IMT Intima-media thickness
NASCET North American Symptomatic Carotid Endarterectomy Trial
NPV Negative predictive value
PPV Positive predictive value
PSV Peak systolic velocity
TIA Transient ischemic attack
Introduction

In the following paragraphs of this introduction, key characteristics of the disease are described and general aspects of screening for carotid artery disease are discussed.

Carotid disease and symptoms

Various definitions of asymptomatic carotid artery disease exist. In the Asymptomatic Carotid Atherosclerosis Study (ACAS) an asymptomatic patient had no previous symptoms in either the ipsilateral cerebral hemisphere or the vertebrobasilar circulation (Executive Committee for ACAS 1995) while in the Asymptomatic Carotid Surgery Trial (ACST) patients were eligible for entry as long as the stenosis had not caused any stroke, transient cerebral ischemia or other relevant neurological symptoms in the past 6 months (Halliday 2004). Symptoms of carotid disease are more strictly defined as: amarosis fugax, transient ischemic attack (TIA) and minor or major stroke.

Ischemic stroke is the most common cause of handicap in adults and the third most common cause of death in Sweden. There are around 30,000 strokes and 8-12,000 transient ischemic attacks annually (Riks-stroke). Approximately 15-34% of strokes are fatal and another 15% to 20% of stroke patients who recover will have a subsequent severe stroke in the future (Rosamund 2007, Kärlsjukdomar 2005). Mortality statistics alone underestimate the full impact of stroke on individuals and society. Only 50% to 70% of stroke survivors regain functional independence, 15% to 30% are permanently disabled, and 20% require institutional care 3 months after the onset of stroke (Rosamund 2007). It is the somatic disease that is responsible for most treatment days in our hospital today and the cost to society has been estimated to 18.3 billion a year (Riks-stroke).

Large-artery atherosclerotic disease accounts for 20% of ischemic stroke and is the most common cause in middle-aged patients (Grau 2001). Carotid atherosclerosis can proceed silently and the first manifestation can be a disabling or fatal stroke. About 10-15% of all first ever stroke patients will experience an unheralded stroke caused by thromboembolism from an previously untreated, asymptomatic carotid stenosis (Naylor 2015). Individuals with asymptomatic stenosis are at increased risk of ipsilateral carotid territory events with annual stroke risk between 2% and 5% before introduction of
modern medical treatment (Thompsson 1978, Chambers 1986, Hobson 1993) and lately with BMT estimated closer to 1-1.5% (Abbott 2009).

Epidemiology

Prevalence

The reported prevalence of ICA stenosis in the literature varies between 0-22%, with a pooled prevalence estimate of 4.2% (de Weerd 2009). Several factors contribute to this variation, such as non-population-based cohorts, different exclusion criteria (i.e. CVD, CAD or diabetes), wide age intervals, low participation rates and different definition of stenosis, making relevant comparisons difficult. Asymptomatic carotid stenosis affects approximately 7% of women and more than 12% of men over 70 years (de Weerd 2009). Most large cohort studies investigating prevalence are outdated and often exclude individuals with present CVD. There is therefore a need for contemporary studies of the general population. Prevalence studies of plaque and stenosis and their limitations are presented in Table 1-2.

Table 1. Overview of the prevalence studies of atherosclerotic carotid plaques

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Setting (population)</th>
<th>N</th>
<th>Age range (mean)</th>
<th>Men (%)</th>
<th>Plaque criteria</th>
<th>Prevalence (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prati (1992)</td>
<td>Italy (Pop. Sample)</td>
<td>1348</td>
<td>8-99 (ND)</td>
<td>47</td>
<td>IMT CCA &gt;1mm</td>
<td>25</td>
<td>Exclusion: CVD</td>
</tr>
<tr>
<td>O’Leary (1992)</td>
<td>USA (CHS)</td>
<td>5176</td>
<td>61-85 (ND)</td>
<td>43</td>
<td>IMT CCA and ICA algorithm</td>
<td>75</td>
<td>50% of eligible population</td>
</tr>
<tr>
<td>Hillen (2000)</td>
<td>Germany (BASE)</td>
<td>225</td>
<td>70-100 (80)</td>
<td>59</td>
<td>IMT CCA, bif, ICA &gt;2mm</td>
<td>66</td>
<td>only healthy subjects included</td>
</tr>
<tr>
<td>Hunt (2001)</td>
<td>USA (ARIC)</td>
<td>13123</td>
<td>53-57 (ND)</td>
<td>67</td>
<td>IMT limit ND</td>
<td>29</td>
<td>IMT limit not defined visual assessment</td>
</tr>
<tr>
<td>Scharett (2006)</td>
<td>USA (MESA)</td>
<td>6814</td>
<td>45-84 (63)</td>
<td>42</td>
<td>IMT &gt; 1.38mm</td>
<td>45</td>
<td>Exclusion: CVD and CAD</td>
</tr>
<tr>
<td>Rundek (2008)</td>
<td>USA (NOMAS)</td>
<td>2189</td>
<td>61% &gt;65 (68)</td>
<td>40</td>
<td>Wall thickening &gt;50% at 3 sites</td>
<td>58</td>
<td>Exclusion: CVD</td>
</tr>
<tr>
<td>Mathiesen (2011)</td>
<td>Norway (Pop. Sample)</td>
<td>6484</td>
<td>55-74 (ND)</td>
<td>50</td>
<td>IMT CCA, bif, ICA &gt;50%</td>
<td>53</td>
<td>Only right artery</td>
</tr>
<tr>
<td>Lim (2011)</td>
<td>Korea (KLoSHA)</td>
<td>1000</td>
<td>&gt;65 (ND)</td>
<td>44</td>
<td>IMT&gt;0.8</td>
<td>39</td>
<td>Exclusion: symptomatic chest pain</td>
</tr>
</tbody>
</table>

ND; not defined, CHS; Cardiovascular Health Study, BASE; Berlin Ageing study, ARIC; Atherosclerosis in community study, MESA; Multi-Ethnic Study of Atherosclerosis, NOMAS; Northern Manhattan Study, KLoSHA Corean; Longitudinal Study on Health and Aging.
Table 2. Overview of the prevalence studies of carotid artery stenosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting (population)</th>
<th>N</th>
<th>Age range (mean)</th>
<th>Men (%)</th>
<th>Stenosis criteria %</th>
<th>Moderate stenosis &gt;50%</th>
<th>Severe stenosis &gt;70%</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ljungquist (1991)</td>
<td>Sweden (Malmö birthcohort)</td>
<td>478</td>
<td>69 (69)</td>
<td>100</td>
<td>0-29, 30-50, &gt;60</td>
<td>-</td>
<td>3.1</td>
<td>Odd DUS criteria, selection criteria ND</td>
</tr>
<tr>
<td>Bots (1992)</td>
<td>Netherlands (Rotterdam study)</td>
<td>954</td>
<td>&gt;55 (ND)</td>
<td>69</td>
<td>0-15, 16-49, &gt;50</td>
<td>1.4</td>
<td>-</td>
<td>Sampling criteria ND, only right artery</td>
</tr>
<tr>
<td>Prati (1992)</td>
<td>Italy (pop sample)</td>
<td>1348</td>
<td>18-99 (ND)</td>
<td>45</td>
<td>&gt;40</td>
<td>2.7</td>
<td>-</td>
<td>Exclusion CVD</td>
</tr>
<tr>
<td>O’Leary (1992)</td>
<td>USA (Framingham study)</td>
<td>1189</td>
<td>66-93 (ND)</td>
<td>ND</td>
<td>0, 1-24, 25-49, 50-74, 75-100</td>
<td>5</td>
<td>2</td>
<td>Exclusion criteria ND</td>
</tr>
<tr>
<td>O’Leary (1992)</td>
<td>USA (CHS sub cohort)</td>
<td>5116</td>
<td>&gt;65 (ND)</td>
<td>43</td>
<td>0,1-24, 25-49, 50-74, 75-79, 80-100</td>
<td>6.2</td>
<td>1.6</td>
<td>57% of CHS cohort</td>
</tr>
<tr>
<td>Prati (1992)</td>
<td>Italy (pop sample)</td>
<td>457</td>
<td>18-97 (%)</td>
<td>50</td>
<td>&lt;25, 25-49, 50-75, 76-99, 100</td>
<td>3.9</td>
<td>0.9</td>
<td>Selection patients from general practitioner records</td>
</tr>
<tr>
<td>Mannami (1997)</td>
<td>Japan Suita (pop sample)</td>
<td>1145</td>
<td>50-79 (63)</td>
<td>50</td>
<td>&lt;25, 25-50, &gt;50</td>
<td>4.4</td>
<td>-</td>
<td>Exclusion CAD and CVD</td>
</tr>
<tr>
<td>Meissner (1999)</td>
<td>USA SPARK study sub-sample</td>
<td>567</td>
<td>&gt;45 (ND)</td>
<td>ND</td>
<td>&gt;49, 50-79, 80-99</td>
<td>8.1</td>
<td>0.4</td>
<td>Exclusion esophagus disease</td>
</tr>
<tr>
<td>Mannami (2000)</td>
<td>Japan Ikawa population sample</td>
<td>859</td>
<td>50-69 (60)</td>
<td>100</td>
<td>&lt;25, 25-49, &gt;50</td>
<td>9.6</td>
<td>-</td>
<td>Exclusion CAD and CVD</td>
</tr>
<tr>
<td>Hedblad (2000)</td>
<td>Sweden, Diet and cancer study</td>
<td>4816</td>
<td>46-68 (ND)</td>
<td>40</td>
<td>&gt;15</td>
<td>13-36</td>
<td>-</td>
<td>Exclusion CAD and diabetes, only right artery</td>
</tr>
<tr>
<td>Mathiesen (2001)</td>
<td>Norway population sample</td>
<td>6420</td>
<td>25-84 (ND)</td>
<td>50</td>
<td>&gt;35</td>
<td>3.4</td>
<td>0.9</td>
<td>Only right artery</td>
</tr>
<tr>
<td>Lernfelt (2002)</td>
<td>Sweden birthcohort</td>
<td>142</td>
<td>78 (78)</td>
<td>50</td>
<td>&lt;50, 50-75, &gt;75</td>
<td>22.5</td>
<td>4.9</td>
<td>25% of 70year old men and then a new selection</td>
</tr>
<tr>
<td>Rundek (2008)</td>
<td>USA NOMAS</td>
<td>2189</td>
<td>&gt;65 (68)</td>
<td>40</td>
<td>&gt;40</td>
<td>4.0</td>
<td>-</td>
<td>Exclusion CVD</td>
</tr>
<tr>
<td>Ratchford (2009)</td>
<td>USA NOMAS</td>
<td>686</td>
<td>40-96 (68)</td>
<td>40</td>
<td>&lt;60, &gt;60</td>
<td>2.2</td>
<td>-</td>
<td>Exclusion CVD</td>
</tr>
<tr>
<td>De Weerd (2010)</td>
<td>Netherlands 4 different cohorts</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt;50, &gt;70</td>
<td>0.2-7.5</td>
<td>0.1-3.1</td>
<td>Different exclusion criteria for the four studies</td>
</tr>
<tr>
<td>Roh (2011)</td>
<td>Korea population sample</td>
<td>20712</td>
<td>18-91 (55)</td>
<td>83</td>
<td>50-74, &gt;75</td>
<td>0.9</td>
<td>0.1</td>
<td>Neurologically asymptomatic</td>
</tr>
</tbody>
</table>

ND; not defined, CHS; Cardiovascular Health Study, SPARK; Stroke Prevention Assessment of Risk in a Community, NOMAS; Northern Manhattan Study
Natural course
Carotid artery disease is defined by the narrowing or blockage of the internal carotid artery and bifurcation due to atherosclerotic plaque build-up and is an important cause of ischemic stroke. A stroke can occur if a piece of plaque or a blood clot breaks off from the wall of the carotid artery and travels to the smaller arteries of the brain. Another rarer mechanism is when the narrowing of the vessel becomes so severe that a blockage decreases blood flow to the brain which may cause a stroke.

The link between the degree of stenosis and ipsilateral stroke risk was described in the 1980s by Chambers and Norris (Chambers 1986). Patients with carotid bruits and varying degrees of carotid disease were followed with Doppler ultrasound. At 1-year TIA or stroke had occurred in 2.1% of patients with 0% to 29% stenosis, in 5.7% of patients with 30% to 74% stenosis, and 19.5% of patients with 75% to 100% stenosis. A linear relationship between the degree of carotid stenosis (calculated by the ECST method) and the neurologic event rate was demonstrated in ACSRS study (Nicolaides 2005).

Degree of stenosis and progression of atherosclerotic plaques are the two strongest correlates to stroke risk. Clinically important stenosis, at which point the risk of stroke is increased, is defined as stenosis greater than 50% or 60% according to the NASCET method (Wolff 2007). A significant number of neurological events happen, however, also in individuals with stenosis <50%. Therefore, there is an ongoing discussion whether total plaque area may be a better predictor of neurological events than the degree of stenosis (Spence 2002, Perez 2016, Spence 2016) and a recent meta-analysis showed that total plaque area is a stronger predictor of cardiovascular risk than the carotid intima-media thickness (Inaba 2012).

Approximately 20-61% of plaque progress to a more severe stenosis while around 4-50% show regression (Spence 2010, Kakkos 2013, Balotta 2007, Conrad 2013). Although the detection of progression of atherosclerosis can identify a subgroup with about twice the risk of stroke compared with those without progression, the majority of strokes occur in individuals with no changes in stenosis severity (Sabeti 2007). Annual stroke risk is also dependent on plaque texture features such as: large lipid-rich necrotic core (LNRC), a thin or ruptured fibrous cap (FC), the presence of inflammatory cells, ulcerations and intraplaque hemorrhage (IPH), (Takaya 2006, Altaf 2008, Kwee 2013). Depending on vulnerable plaque features stroke risk can differ from 1 to 10% (Nikolaides 2013).

There are several natural history studies but most describe old cohorts while the risk factor profile and stroke incidence has changed in the last 20 years. Especially a significant decrease in smoking habits and the aging of the population influences both carotid plaque burden and incidence of cardiovascular events. Furthermore, the prescription of statins, antihypertensive drugs and antiplatelet inhibitors as prevention in patients with carotid stenosis has increased dramatically (Halliday 2010). Since there are no established screening programs for carotid artery atherosclerosis in most countries the outcome
for individuals participating in screening is not well studied. Contemporary studies are therefore needed to evaluate the natural course with current risk factor profile and medication and effect of screening in general population.

**Risk factors**

Well known risk factors for carotid atherosclerotic disease are smoking, older age, male sex, hypertension, hypercholesterolemia, coronary artery disease and diabetes (Fine-Edelstein 1994). Multiple risk factors increase the likelihood of carotid disease but the cumulative effect of multiple risk factors has been addressed only in a few small population studies (Jakobovitz 2003, Qureshi 2001).

**Duplex ultrasonography**

DUS is today the standard diagnostic method for carotid artery stenosis. This high resolution non-invasive technique is a very precise method for detection of both early stages and advanced carotid atherosclerosis (Grant 2003, AbuRahma 2011).

Carotid atherosclerosis is described either as plaque or stenosis. Both the definition of plaque and the definition and measurements of stenosis vary in the literature. Carotid artery plaque is in most trials described based on the intima-media thickness (IMT), the wall thickness between lumen-intima and media-adventitia interfaces. The measured segment and the specific IMT limits differ, however, between studies. There is a European consensus document, Mannheim Carotid Intima-Media Thickness Consensus (Touboul 2006) describing three definitions of plaque utilizing IMT:

1) a focal structure encroaching into the arterial lumen of at least 0.5 mm
2) a structure that is protruding >50% of the surrounding IMT value
3) a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.

Another way of measuring carotid arteriosclerosis is total plaque area (TPA). There are several studies evaluating total plaque burden where individuals in the highest risk group having a total plaque area >1.19 cm² (Spence 2002).

There are two major methods for measurements of the degree of carotid stenosis, the NASCET and the ECST method. The criteria for surgical intervention defined by CEA trials are based on percent stenosis as defined by angiography. In the NASCET and ACAS trials (Executive Committee for ACAS 1995, Inzitari 2000), stenosis was determined by comparing the residual lumen of the artery (measurement of the diameter of the artery at its narrowest point) with the reference diameter (the diameter of the ICA at the first location
distal to the bulb where the walls become parallel. In the ECST trial (European Carotid Surgery Trialists’ Collaborative Group 1998) the estimated normal lumen diameter at the site of the lesion, based on a visual impression of where the normal arterial wall was before development of the stenosis, was compared to the residual lumen, Figure 1.

Figure 1. Measurement of carotid stenosis. ECST=\(\frac{C-A}{C} \times 100\), NASCET= \(\frac{B-A}{B} \times 100\).

Both trials used cut-off point of 70% stenosis but the two methods differ in terms of plaque size or residual lumen. The NASCET method underestimates the severity of stenosis compared with the ECST method. A 55% stenosis according to ECST is a 20% stenosis measured with the NASCET method and an 80% stenosis is 70% stenosis respectively (Nikolaides 2005). However, with increasing degree of stenosis the value of the two methods converge and the discrepancy decreases.

Duplex ultrasound criteria are based on velocity measurements and are compared to these two methods. There are many different protocols for grading carotid stenosis through velocity measurements. Some use ICA PSV alone while other use ICA PSV; CCA PSV and ECA PSV measurements. Equalis consensus criteria for grading carotid stenosis that are used for the accreditation of vascular laboratories in Sweden are based on a method developed by Jogestrand et al (Jogestrand 2002, Nowak 2007), table 3.

Carotid ultrasound is an exact diagnostic tool. A meta-analysis of 47 reports examining the use of DUS for the assessment of carotid stenosis according to the NASCET criteria showed a sensitivity of 98% and a specificity of 88% for the detection of >50% ICA stenosis, while for the detection of >70% stenosis these figures were 90% and 94% respectively (Jahromi 2005).
Table 3. *Velocity criteria for grading carotid stenosis*

<table>
<thead>
<tr>
<th>Systolic maximal velocity with angle &lt;45°</th>
<th>Systolic maximal velocity with angle 55-60°</th>
<th>Degree of stenosis</th>
<th>Degree of stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.1 m/s</td>
<td>&lt;1.3 m/s</td>
<td>&lt;50%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>1.1-1.6 m/s</td>
<td>1.3-2.2 m/s</td>
<td>50-69%</td>
<td>20-49%</td>
</tr>
<tr>
<td>1.7-2.0 m/s</td>
<td>2.3-3.1 m/s</td>
<td>70-79%</td>
<td>50-69%</td>
</tr>
<tr>
<td>≥2.1 m/s</td>
<td>≥3.2 m/s</td>
<td>80-99%</td>
<td>70-99%</td>
</tr>
<tr>
<td>No signal</td>
<td>No signal</td>
<td>Occlusion</td>
<td>Occlusion</td>
</tr>
</tbody>
</table>

Carotid DUS includes three modalities: 1) B-mode (grayscale), 2) color Doppler evaluation, and 3) velocity measurements. B-mode allows measurements of IMT and characterization of atherosclerotic plaque morphology, figure 2. Color Doppler allows for visualization of flow abnormalities such as turbulent flow related to the presence of stenosis; which gives rise to a characteristic “mosaic” pattern, Figure 2.

*Figure 2.* Carotid stenosis: On the left B-mode greyscale image, on the right mosaic pattern on colour Doppler.
It is, however, spectral analysis of the Doppler waveform together with measurement of blood flow velocity that is the main parameter used for grading the severity of carotid stenosis, and this has been validated by correlation to measurements obtained from conventional angiography (Sabeti 2004, Clevert 2007), Figure 3. A full carotid duplex ultrasound protocol is operator dependent and time consuming since the velocity needs to be measured with the right insonation angle and in the right place in the vessel. Therefore, a simplified screening protocol could be of benefit for fast selection of high risk patients with significant disease.

![Figure 3. Spectral analysis and PSV measurements.](image)

**Treatment**

Therapeutic options for patients with asymptomatic carotid stenosis include carotid endarterectomy (CEA) plus medical treatment, carotid artery stenting (CAS) plus medical treatment or medical treatment alone.

**Surgical treatment**

The first carotid endarterectomy was performed by Eastcott, Pickering and Rob, who in 1954 documented the first successful reconstruction of the carotid artery to treat symptomatic carotid occlusive disease in a woman with recurrent TIA's (Eastcott 1954). Today, after the results from two large multicenter RCT (NASCET 1991, ECST 1998), CEA is a well-established treatment for
symptomatic patents and there are two large RCT that demonstrate a benefit even for asymptomatic patients.

The Asymptomatic Carotid Atherosclerosis study (ACAS) included 1662 patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter. Patients were randomized to either daily aspirin administration with risk factor management alone or combined with CEA. The aggregate 5 years risk for ipsilateral stroke or any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically, a risk reduction of 53%, (95% CI 2.2-7.2) (ACAS 1994).

The European asymptomatic carotid stenosis trial (ACST), completed in 2004, randomized 3120 patients with greater than 60% stenosis without recent neurological symptoms to immediate CEA or indefinite deferral of any CEA. The 30-days stroke risk after CEA was 3.1%, while the annual stroke risk for patients managed with medical therapy alone was approximately 2%. The 5-years stroke risk was 6.4% for immediate CEA vs 11.8% for deferred patients, gain 5.4% CI 3.0-7.8; P < 0.001. Men had greater 5-years risk reduction than women with gain 6.5% and 2.5% respectively. The 10-year stroke risk in patients who underwent CEA was 10.8% compared with 16.9% in those treated with medical therapy alone, gain 6.1%, (95% CI 2.7-9.4). This suggests that it is difficult to eliminate the risk of stroke with medical therapy alone and that if CEA is done safely (i.e. low perioperative stroke risk, <3%) it could be indicated in a carefully selected group (ACST 2004, Halliday 2010).

Carotid artery angioplasty and stenting (CAS) is a less invasive endovascular procedure that was first performed by Charles Kerber in 1980. CAS is mainly recommended to patients with high-risk for open endarterectomy based on data from large multicenter randomized studies: CAVATAS, SAPHIRE, EVA-3S, SPACE, CREST, ACT-1 (CAVATAS investigators 2001, Yardav 2004, Mas 2006, Ringleb 2006, Brott 2010, Rosenfield 2016).

Medical treatment
Although CEA in asymptomatic individuals has been proven to be an effective treatment in ischemic stroke prevention, the majority of these studies were conducted before the routine use of statins and newer antiplatelet drugs. Medical therapy has evolved significantly during the last decade and recent best medical treatment studies show an annual stroke incidence of only 1% (Constantinou 2013). The current recommended best medical management for carotid artery stenosis is a combination of smoke cessation and therapy with antiplatelet, antihypertensive, antidiabetic agents and treatment of hypercholesterolemia with statins (Constantinou 2013).

Marquard et al performed a population-based cohort study between 2002 and 2009 in Oxford and showed low stroke rates in patients with asymptomatic >50% carotid stenosis on best medical treatment and with risk factor adjustment. A total of 101 patients were selected from a group of individuals sent for investigations for TIA or minor ischemic stroke in another territory.
During a mean follow-up of 3 years there were only 6 ischemic events. The annual stroke rate was thus lower than in patients undergoing CEA (Marquard 2010). Spence et al investigated carotid plaque progression and incidence of microemboli in 468 asymptomatic patients with carotid stenosis. In patients on BMT without evidence of microemboli disease (90% of patients) the annual risk of stroke was 1%, 95% CI 1.01-1.36 (Spence 2010).

A review of studies investigating stroke risk among individuals with medical treatment show a decrease in annual stroke risk since mid-1980s with recent estimates below 1.5% (Abbott 2009). This fact has been attributed to introduction of more extensive medical treatment. A recent study investigating the role of BMT in preventing carotid disease progression and development of neurological symptoms showed that a significant number of patients (45%) progressed from moderate to severe stenosis and experienced neurological events despite modern medical treatment during 5 years follow-up (Conrad 2013).

A new RCT comparing CEA or CAS plus best medical treatment with best medical treatment alone is necessary to define the role for surgery today. Regardless of the degree of stenosis or whether the lesion is symptomatic best medical therapy together with lifestyle modification is today recommended for all patients with carotid artery stenosis.

Screening for carotid artery stenosis

Although vascular guidelines do not recommend screening in the unselected general population (Goldstein 2006, Ricotta 2011, US Preventive Service Tasc Force 2007), there are recommendation for screening high risk adults with cardiovascular risk factors (Qureshi 2007, SVS 2011). Screening for carotid artery stenosis has been highly debated during the last decades and lot of effort has been made to identify adults at risk (Ricotta 2011).

Modern therapeutic options for asymptomatic carotid stenosis include medical therapy alone, carotid endarterectomy (CEA) and medical therapy or carotid angioplasty and stenting and medical therapy. The main obstacle to screening has been to identify a high-risk population that would benefit from surgical intervention. However, as more studies point to an improved benefit from risk factor adjustment, such as cessation of smoking, and medical treatment, screening might be indicated in a larger group.

While the optimal therapeutic management strategy is unclear the main motive for screening should be to identify individuals at risk for cardiovascular events and initiate appropriate preemptive treatment. Screening has different impact on a population than intervention in cohorts with already manifest disease. There is a lack of studies investigating outcome of screening programs which is important to evaluate before a screening strategy could be recommended.
Health economics

Economic evaluation provides decision makers with solid information on how to reach an efficient use of the available resources in order to maximize the health of the population. It is therefore important in preparation of screening programs to evaluate cost-effectiveness in order to maximize the benefit of the screening per Euro spent (Wanhainen 2005).

Cost-effectiveness analysis aim to determine cost and health outcomes of different treatment strategies for a defined patient population. There are four main outcomes and these can be illustrated in a cost-effectiveness plane, Figure 4, (Drumond 2015). The more costly/less effective and less costly/more effective strategies are easy to understand while the two other strategies need further evaluation. To be able to conclude which strategy is the most cost-effective an incremental cost-effectiveness ratio (ICER) has to be calculated. It is a ratio of the difference in costs of interventions to the difference in outcomes. The ICER indicates the costs of achieving one extra unit of health benefit when switching from one alternative to another (HTA 2011). Whether an intervention is cost effective depends on its relation to the maximum willingness to pay threshold. If the ICER of an intervention is lower than the threshold the intervention is regarded as cost effective. The ICER does not describe the effect of the intervention being considered and should therefore always be presented along with other outputs of the economic analysis such as absolute health benefits, number of patients etc (Drumond 2015).

Costs of a treatment strategy can be divided into direct and indirect costs. Direct costs are all costs directly related to detection, prevention, and treatment or care of the patient (eg cost of BMT, cost of CEA, cost of stroke care).
Indirect costs are related to consequences of an illness (cost of sick leave, reduced working capacity due to neurological events and disablement, lost production due to early death).

Health effect of a treatment strategy is measured in utility produced by the treatment. Utility can be measured as life year gained or if the intervention affects both the length and the quality of life, a composite outcome measure, such as Quality Adjusted Life Years (QALYs) could be used (Folland 2007). Each year lived in perfect health is assigned the utility value of 1.0 QALY, down to the value of 0.0 for death. There are several instruments for estimation of utility weights of QALYs. One of the most widely used is the EuroQol groups EQ-5D instrument that renders a single index value for health status. The utility values for the Swedish population in different age groups have been established by means of EQ-5D, Table 4 (Burstrom 2011).

Table 4. *Health utility index in different age groups*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Utility index Male</th>
<th>Utility index Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-69</td>
<td>0.83</td>
<td>0.78</td>
</tr>
<tr>
<td>70-79</td>
<td>0.81</td>
<td>0.78</td>
</tr>
<tr>
<td>80-88</td>
<td>0.74</td>
<td>0.74</td>
</tr>
</tbody>
</table>

There are different methods for modeling an economic evaluation. Two of the most common are decision-trees and state-transition models. A decision-tree is used to compare different strategies based on a number of possible outcomes and their expected probabilities and consequences while a state-transition model should be used if a process occurs at a certain risk or with a changing probability over time e.g. development of carotid stenosis with a risk of neurological events (Sonnenberg 1993). A Markov model is a cycle-based model where hypothetical individuals are in one of a finite number of exclusive health states and were all events are represented as transitions from one state to another, Figure 5. Each health state is associated with a cost and health outcome. The model may be evaluated as a cohort simulation (Markov cohort) or as a Monte-Carlo simulation (microsimulation).
In a cohort simulation, a hypothetical cohort of patients with a certain distribution between states at the beginning of the process is modeled to go through the state-transition diagram over a set of cycles. This simulation has an underlying assumption that transition probabilities do not depend on history neither on past states nor the time spent in the current state. This assumption is called the Markov property and can be very limiting for clinical applications. The Monte Carlo simulation is a method that is not restricted by the Markov Property since it simulates one individual at a time with retained memory of previous events or allowing uncertain parameters to vary over a given range with a given distribution (Briggs 1998). Parameters influencing cost-effectiveness can be analyzed with sensitivity analysis that answers which factors have most effect. If the exact value of a parameter is unknown the parameter can be range tested to evaluate its influence on cost-effectiveness.
Aims of the thesis

The overall aim of this thesis was to study aspects of screening for carotid artery disease.

The specific aims were:

1) To study the prevalence of carotid artery disease in a general population of 65-year old Swedish men (Study I)

2) To study risk factors associated with carotid atherosclerosis in a general population of 65-year-old Swedish men (Study I)

3) To examine whether a simplified DUS protocol consisting of assessment for presence of stenosis on B-mode and/or mosaic patterns on colour Doppler (the grayscale/mosaic method) could be used as a rapid and reliable screening method for the exclusion of clinically significant carotid stenosis (Study II)

4) To evaluate the required effect of primary preventive therapy (medical and/or surgical) in reducing risk of stroke among patients with asymptomatic carotid disease in order for screening to be cost-effective (Study III)

5) To determine the fate of 65-year old men five years following an ultrasound examination of both carotid arteries (Study IV)

6) To study the natural course and risk factors for 1) progression of carotid atherosclerosis, 2) ipsilateral neurological events, and 3) death after five years (Study IV)
Material and Methods

Subjects and methodology

Study I

In 2006 a general AAA screening program was launched in the County of Uppsala in middle Sweden, where all 65-year old men, consecutively identified through the National Population Registry, were invited to a one-time ultrasound examination of the abdominal aorta. Between 2007 and 2009 all men attending the AAA-screening program were offered an additional duplex ultrasound examination of the ICA free of charge.

Both carotid arteries were examined and presence of larger plaque and stenosis were recorded. All invited individuals who had been operated on with CEA during the 10 years prior to this investigation were identified in the Swedish Vascular registry (Swedvasc) and were included in the stenosis group, irrespective of the results from the present ultrasound screening.

All participants were asked to complete a health questionnaire on smoking habits and medical history. Coronary artery disease (CAD) was defined as a history of angina pectoris or myocardial infarction, cerebrovascular disease (CVD) as a history of stroke or TIA, hypertension as history of hypertension or current antihypertensive medication, diabetes mellitus as a history of dietary- or medically treated diabetes, Chronic obstructive pulmonary disease (COPD) as history of diagnosed COPD, and claudication as history of symptoms of claudication (i.e. Rutherford stage 1-3). Smoking status was classified as never, ever, former or current. Former smokers were individuals that had been smoking during some period of their lives. Current use of statins and antiplatelet agents were recorded according to the WHO Anatomic Therapeutic Chemical classification system (ATC-code) C10A A (HMG-CoA reductase inhibitors) and B01AC (platelet aggregation inhibitors).

Study II

Healthy 65-year-old men attending a population-based carotid screening program 2007-2009 (study I) and consecutive patients undergoing carotid DUS in 2012 for symptomatic cerebrovascular disease had both carotid arteries examined for presence of carotid stenosis. Symptomatic patients were included to increase the number of patients with carotid artery stenosis, since
a greater number of “events” facilitate comparison between the evaluated methods.

A carotid stenosis was defined as >20% (NASCET) and a significant stenosis as NASCET >50%. Greyscale and/or mosaic pattern findings were compared with presence of stenosis determined by PSV. The technician made further optimizations in cases of difficult morphology. Both the grayscale/mosaic method and PSV measurements were performed by the same technician without blinding. An interobserver variability analysis was performed on subjects from the same ongoing screening program in which 36 arteries were included with both normal findings and atherosclerosis.

Study III

A Markov cohort simulation was performed to investigate two hypothetical cohorts of 65 years old men assigned to either a strategy with one-time ultrasound screening of carotid arteries or a strategy of no screening (where management of ACAS was based on incidental detection). The study setting was the Swedish health care system with exception of annual stroke risk rates and mortality rates that were extrapolated from international cohorts. A carotid stenosis was defined as >50% stenosis, ECST-method (Jogestrand 2002, Nowak 2007). Individuals with screening detected carotid artery stenosis were simulated to receive best medical treatment (BMT). BMT included antihypertensive treatment, blood glucose control, lipid-lowering therapy and antiplatelet agents. The potential effect of preventive treatment in terms of reduction of risk of stroke among patients with screening detected ACAS was simulated in the model, in order to assess the minimum required effect to reach cost-effectiveness for screening.

A Markov state transition model was constructed to model disease progression and effect of preventive therapy for both screening and non-screening strategy of 65 years old men. Subjects were followed from the time of screening until death or 100 years of age. The model was made up of three exclusive health states: no-events, post stroke and death, represented by ovals in Figure 6. Each health state was associated with a cost and state outcome. The simulation progressed with cycles of one year. In each cycle individuals are subjected to risk of stroke as well as all-cause mortality. Markov model structure is described in Figure 6. The model was evaluated with Markov cohort simulation and Monte Carlo simulation.

At the end of the simulation accumulated costs and health outcome (QALYs) were summarized for each cohort. The screening cohort was subjected to screening costs and cost of BMT for all individuals, while the no-screening cohort was subjected to a lower cost of BMT, since only a fraction of the individuals with ACAS were receiving BMT. Cost of care for a stroke event was equal for both cohorts.
Key parameters with inherent uncertainty based on the available literature were range tested in a deterministic sensitivity analysis. Probabilities were tested with a Monte Carlo analysis that was set to 1,000,000 simulations. Cost-effectiveness acceptability was defined as an Incremental Cost-efficiency Ratio (ICER) below £20000-£30000 (€23000/€36000) per incremental QALY (NICE 2013) and a willingness to pay (WTP) thresholds of €100000/€50000 per incremental QALY as defined by the National Board of Health and Welfare in Sweden were evaluated (National Board of Health and Welfare 2011).

Parameters for the model were retrieved from the literature and contemporary population-based data (study I), Table 5. Annual risk of stroke in individuals with or without best medical treatment were estimated from a literature review. The stroke risks extrapolated from mixed cohorts was assumed to be the same for male population if specified data was not reported. General population age-dependent all-cause mortality was based on contemporary population statistics from Statistics Sweden. Utilities associated with each health state were age dependent, and retrieved from a gender and age-specific Swedish EQ-5D HRQoL population estimates for calculation of effect in quality adjusted life years, (QALYs), (Burström 2001).
### Table 5. Parameters in the model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Base case</th>
<th>Range tested in sensitivity analysis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence ACAS 65-year-old men</td>
<td>2%</td>
<td>0.5-6%</td>
<td>Högberg et al 12</td>
</tr>
<tr>
<td>Attendance rate</td>
<td>80%</td>
<td></td>
<td>Svensjö et al</td>
</tr>
<tr>
<td>Annual risk of stroke with BMT</td>
<td>1%</td>
<td>1-3%</td>
<td>Table 7</td>
</tr>
<tr>
<td>Stroke risk reduction with BMT</td>
<td>50%</td>
<td>9-67%</td>
<td>Table 16</td>
</tr>
<tr>
<td>Rate with BMT among individuals with ACAS without screening</td>
<td>40%</td>
<td>40-70%</td>
<td>Högberg et al 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Högberg et al 29</td>
</tr>
<tr>
<td>Population mortality</td>
<td>Life tables, ages 65-100</td>
<td></td>
<td>Statistics Sweden</td>
</tr>
<tr>
<td>Annual risk of death after stroke</td>
<td>4 x population mortality</td>
<td>x 3 – x7</td>
<td>Hankey 2017 30</td>
</tr>
<tr>
<td>Annual risk of death with carotid stenosis</td>
<td>2 x population mortality</td>
<td>x 1- x 5</td>
<td>Högberg et al 29</td>
</tr>
<tr>
<td>Utility general population</td>
<td>0.83(age 65-69) 0.81(age 70-79) 0.74(age 80-)</td>
<td></td>
<td>Burström 2001 27</td>
</tr>
<tr>
<td>Utility post stroke</td>
<td>0.51</td>
<td>0.25-0.76</td>
<td>Tengs et al 31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Haacke et al 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Luengo-Fernandez et al 33</td>
</tr>
</tbody>
</table>

Costs associated with screening were based on actual costs in the ongoing AAA screening program in Sweden, and cost of a bilateral carotid ultrasound was specifically calculated based on cost of ultrasound resources in study I. Costs for preventive medical treatment and stroke care were retrieved from costs analysis studies. Costs were based on 2016 prices and adjusted by the consumer price index and converted to euros (€) using the exchange rate 1€ = 9.48 Swedish kronor. Costs and effects were discounted annually by 3.5% (nice.org.uk). The costs are presented in Table 6.
Table 6. Costs in the model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>€</th>
<th>Range</th>
<th>Range tested</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitation</td>
<td>5.0</td>
<td></td>
<td></td>
<td>Actual cost from Swedish screening program</td>
</tr>
<tr>
<td>Ultrasound screening exam</td>
<td>16 (administrative costs) +16 (carotid)</td>
<td>30-200</td>
<td></td>
<td>Actual cost from Swedish screening program</td>
</tr>
<tr>
<td>Yearly cost of BMT</td>
<td>266</td>
<td>253-280</td>
<td>250-300</td>
<td>Ghatnecar et al 34 Lundström et al 35</td>
</tr>
<tr>
<td>Cost of stroke second and subsequent year</td>
<td>7100</td>
<td>2089-12936</td>
<td>2000-13000</td>
<td>Ghatnecar et al 34 Persson et al 36 Hallberg et al 37</td>
</tr>
</tbody>
</table>

The main outcome was the minimum required effect of a preventive intervention for a screening strategy to be cost effective. An ICER (€/QALY) was calculated based on the difference in effect and costs in the two strategies. In addition, absolute risk reduction from stroke (ARR), numbers needed to screen (NNS), relative risk reduction for stroke (RRR), and difference in stroke-free years was estimated for the strategy of screening for ACAS.

Study IV
Between 2007 and 2009 all 65-year-old men in the county of Uppsala in Sweden attending an abdominal aortic aneurysm (AAA) screening program were offered an additional duplex ultrasound examination of the carotid arteries (primary screening cohort, Study I). The cohort of men born 1942-1944 was re-invited 5 years later at the age of 70 years for a new duplex ultrasound of the aorta, and then also offered an examination of the carotid arteries (re-screening cohort). The study cohort is presented in Figure 7.

Information on smoking habits, medical history and current medication was registered at primary and secondary screening. Smoking status was classified as never, ever (former + current), former or current. Progression of atherosclerosis was documented with ultrasound and compared to findings at
Table 7. Annual risk of stroke

<table>
<thead>
<tr>
<th>Reference Year</th>
<th>Medical treatment (A/S)</th>
<th>Stenosis (E/N)</th>
<th>Patients</th>
<th>Age (y)</th>
<th>Male %</th>
<th>Follow up (m)</th>
<th>Risk annual stroke %</th>
<th>Risk annual death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers et al 39</td>
<td>-</td>
<td>0-100%</td>
<td>500</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>O’Holleran et al 40</td>
<td>-</td>
<td>&gt;75%</td>
<td>121</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Norris et al 41</td>
<td>A-55%</td>
<td>&gt;70%N</td>
<td>177</td>
<td>64</td>
<td>53</td>
<td>41</td>
<td>3.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Hobson et al (VA) 42</td>
<td>A-100%</td>
<td>&gt;50%N</td>
<td>263</td>
<td>65</td>
<td>100</td>
<td>48</td>
<td>2.4</td>
<td>8.4</td>
</tr>
<tr>
<td>ACAS 18</td>
<td>A-100%</td>
<td>&gt;60%N</td>
<td>834</td>
<td>67</td>
<td>66</td>
<td>31</td>
<td>2.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Irvine et al 43</td>
<td>-</td>
<td>&gt;40%</td>
<td>564</td>
<td>69</td>
<td>-</td>
<td>12</td>
<td>9.6</td>
<td>-</td>
</tr>
<tr>
<td>Longstreth et al (CHS) 44</td>
<td>-</td>
<td>&gt;70% N</td>
<td>5441</td>
<td>73</td>
<td>41</td>
<td>60</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Nadareishvili et al 45</td>
<td>-</td>
<td>50-99%N</td>
<td>106</td>
<td>64</td>
<td>58</td>
<td>120</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>AbuRahma et al 46</td>
<td>-</td>
<td>60-69%N</td>
<td>382</td>
<td>68</td>
<td>57</td>
<td>37</td>
<td>1.0-4.5</td>
<td>-</td>
</tr>
<tr>
<td>AbuRahma et al 47</td>
<td>A-100%</td>
<td>60-69%N</td>
<td>82</td>
<td>66</td>
<td>55</td>
<td>59</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td>Halliday et al (ACST-1) 19</td>
<td>A-80%</td>
<td>&gt;60%E</td>
<td>1560</td>
<td>68</td>
<td>66</td>
<td>40</td>
<td>1.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Nicolaides et al 48</td>
<td>-</td>
<td>&gt;70-99%E</td>
<td>1115</td>
<td>-</td>
<td>-</td>
<td>37</td>
<td>1.5-6.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Abbot et al 49</td>
<td>A-93%</td>
<td>60-99%E</td>
<td>202</td>
<td>74</td>
<td>68</td>
<td>34</td>
<td>1</td>
<td>6.1**</td>
</tr>
<tr>
<td>Sabeti et al 50</td>
<td>A-56-60%</td>
<td>&gt;50%</td>
<td>376</td>
<td>69</td>
<td>63</td>
<td>37</td>
<td>2.4</td>
<td>5***</td>
</tr>
<tr>
<td>Goessens et al 51</td>
<td>A-63%</td>
<td>&gt;50%E</td>
<td>221</td>
<td>65</td>
<td>73</td>
<td>42</td>
<td>1</td>
<td>7.6</td>
</tr>
<tr>
<td>Abbot 2</td>
<td>-</td>
<td>&gt;50%N, E</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.5-3.2</td>
<td>-</td>
</tr>
<tr>
<td>Aichner et al 52</td>
<td>A-68.7%</td>
<td>&gt;70%</td>
<td>3164</td>
<td>71</td>
<td>64</td>
<td>12</td>
<td>3.14</td>
<td>2.78</td>
</tr>
<tr>
<td>Spence et 3</td>
<td>A-68-69%</td>
<td>&gt;60%N</td>
<td>468</td>
<td>70</td>
<td>62</td>
<td>24</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Markus et al 53</td>
<td>-</td>
<td>&gt;70%N</td>
<td>467</td>
<td>71</td>
<td>74</td>
<td>24</td>
<td>1.1</td>
<td>2.0†</td>
</tr>
<tr>
<td>Hartog et al 54</td>
<td>A-64.5%</td>
<td>&gt;50%N</td>
<td>293</td>
<td>65</td>
<td>72</td>
<td>12</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>Conrad et al 55</td>
<td>A-86%</td>
<td>&gt;70%N</td>
<td>1791</td>
<td>72</td>
<td>50</td>
<td>43</td>
<td>-</td>
<td>5.4</td>
</tr>
<tr>
<td>Kakkos et al 56</td>
<td>A-84%</td>
<td>&gt;50%E</td>
<td>1121</td>
<td>70</td>
<td>-</td>
<td>48</td>
<td>1.1-2</td>
<td>-</td>
</tr>
<tr>
<td>Conrad et al 57</td>
<td>A-89%</td>
<td>&gt;70%N</td>
<td>115</td>
<td>73</td>
<td>51</td>
<td>63</td>
<td>2.4</td>
<td>6.0</td>
</tr>
</tbody>
</table>

A=antiplatelet agents, S=statins, E – ECST, N – NASCET, *bilateral disease with >90% contralateral stenosis, **non-stroke death, *** all subjects stenos 0-99%, †cardiovascular death,
the age of 65 years. Outcome of patients with normal arteries, plaques, moderate stenosis (50-79%) and severe stenosis (80-99%), (ECST method) found at the primary screening was analyzed.

Disease progression/regression was defined as transformation to another group, with more extensive or less extensive atherosclerotic disease at time of rescreening, and reported as percentage of those attending rescreening, or follow up because of ICA surgery. Those who have had ICA surgery of a screening detected carotid stenosis at age 65 were classified as having severe disease not prone to regression. Symptomatic carotid stenosis was defined as a carotid stenosis with ipsilateral neurological symptoms. Mortality data was retrieved from the National Population Registry for the full cohort invited to screening, including non-attenders at index examination. Five-year mortality rates were calculated for the different subgroups and compared to the overall mortality of the entire cohort.

Those who underwent CEA between age 65 and 70 (due to either symptomatic or asymptomatic disease) were identified in the Swedish Vascular registry. During the entire study period (2007-2014) there was a change in routine

Figure 7. Screening population flow diagram
of treatment for asymptomatic carotid stenosis towards best medical treatment and risk factor adjustment alone, and all CEA for asymptomatic disease were performed before the end of 2010. No other intervention (such as stenting) was performed in this cohort.

**Duplex ultrasonography**

The duplex ultrasound examination of both carotid arteries was carried out simultaneously with the AAA screening by experienced ultrasound technicians, with a Sequoia (Acuson, Mountain View, CA USA), equipped with a 6-8 MHz linear array transducer (94L) or Philips iU22 system (Philips Ultrasound, Bothell, WA USA) by using a L9-3 MHz linear transducer. A maximum insonation angle of 60º to the vessel was applied in all examinations. The carotid arteries on both sides were evaluated for the presence of plaque and stenosis.

A carotid plaque was defined as a focal intimal-media thickening (IMT) of ≥2 mm, over at least 6mm of length. The basis for this definition was a previous plaque-imaging study where 2x6mm was considered the threshold for a meaningful morphological-analysis by means of MRI (unpublished data). The degree of stenosis was determined by ICA PSV according to the NASCET or ECST method as developed by Jogestrand et al (Jogestrand 2002, Novak 2007), which are used for the accreditation of vascular laboratories in Sweden, Table 3 (Study I, II and IV).

The carotid arteries on both sides were evaluated for the presence of stenosis on B-mode grayscale and the presence of mosaic pattern on color Doppler. ICA PSV was then measured in the narrowest segment of the vessel as indicated by B-mode duplex ultrasound and/or color flow changes. To evaluate a simplified screening protocol stenoses on grayscale and/or mosaic pattern findings were compared with prevalence of stenosis defined by ICA PSV measurements (Study II).

**Statistics and Ethics**

Statistical evaluation of the data in all four studies was carried out with computer software package (SPSS PC version 21.0 and 23, SPSS, Chicago, IL, USA). Vassar Stats website for statistical computation (vassarstats.net) was used for some calculations in paper II.

**Paper I and IV**

Proportions were presented with 95% confidence intervals (95% CI). For comparison of two proportions, uncorrected Chi-square-test was used. To es-
timate the odds ratio for factors associated with ICA-atherosclerosis all variables with a p-value <0.1 in the univariate analyses (Pearson Chi Square-test) were explored in a multivariate logistic regression model. The different smoke-variables were entered separately into the multivariate analyses. Linear by linear association, a test for trends in a larger-than-2x2 table using the Chi-2 distribution, was used to test the association between risk factors and the severity of ICA-atherosclerosis in paper I. Due to an uncertain etiology subjects with an isolated occlusion were excluded from the risk factor analysis. A p-value <0.05 was considered significant.

**Paper II**
The $\kappa$ statistic was used to assess agreement between the two ultrasound methods and 95% confidence intervals (CI) were used. The levels of agreement were defined as follows: $\kappa<0.20$ poor, $0.21<\kappa<0.40$ fair, $0.41<\kappa<0.60$ moderate, $0.61<\kappa<0.80$ good and $\kappa>0.81$ very good agreement. $P<0.05$ was considered statistically significant. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with 95% CI.

**Paper III**
The data analyzed was retrieved from literature reporting data on a population level. The Markov model was developed and implemented with the TreeAge Pro 2016 Healthcare software package (TreAge Software Inc, Williamstown, MA, USA).

Study I, II and IV were approved by the Ethics Committee of the Uppsala Region. All subjects gave informed consent prior to the investigations. No ethics approval was necessary for study III.
Results

Study I

Attendance rate was high. Of 5936 65-year old men invited for AAA-screening, 4801 (81%) participated. Of those attending AAA-screening 97% accepted an additional duplex ultrasound examination of the ICAs. A total of 4657 subjects (9314 carotid arteries) were examined. There was a high prevalence of atherosclerosis (plaque) but only few had moderate to severe stenosis. 3488 (75%) subjects and 7730 (83%) carotid arteries were normal. An ICA-plaque was detected in 1169 (25%) subjects and in 1584 (17%) carotid arteries. An ICA-stenosis of 50-99% was observed in 94 (2.0%) subjects and in 107 (1.2%) carotid arteries. Sixteen subjects (0.3%) had an occluded artery.

Table 8. Factors associated with internal carotid atherosclerosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Atherosclerosis</th>
<th>Statistical analysis</th>
<th>univariate</th>
<th>multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No N=3488 %</td>
<td>Yes N=1169 %</td>
<td>p-value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td></td>
<td>(95 % CI)</td>
<td>(95 % CI)</td>
<td></td>
<td>(95 % CI)</td>
</tr>
<tr>
<td>Smoking:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40 (38-42)</td>
<td>27 (24-30)</td>
<td>&lt;0.001</td>
<td>0.6 (0.5-0.7)</td>
</tr>
<tr>
<td>Ever</td>
<td>60 (59-62)</td>
<td>73 (71-76)</td>
<td>&lt;0.001</td>
<td>1.7 (1.5-1.9)</td>
</tr>
<tr>
<td>Former</td>
<td>49 (48-51)</td>
<td>54 (51-57)</td>
<td>0.004</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td>Current</td>
<td>11 (10-12)</td>
<td>19 (17-21)</td>
<td>&lt;0.001</td>
<td>1.9 (1.6-2.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (39-42)</td>
<td>56 (53-59)</td>
<td>&lt;0.001</td>
<td>1.5 (1.3-1.7)</td>
</tr>
<tr>
<td>CAD</td>
<td>8 (8-9)</td>
<td>16 (14-18)</td>
<td>&lt;0.001</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27 (26-29)</td>
<td>37 (34-40)</td>
<td>&lt;0.001</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>Claudication</td>
<td>1 (0-2)</td>
<td>2 (1-2)</td>
<td>0.014</td>
<td>1.4 (0.8-2.6)</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (6-7)</td>
<td>9 (7-10)</td>
<td>0.037</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (9-11)</td>
<td>16 (14-18)</td>
<td>&lt;0.001</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>TIA/Stroke</td>
<td>4 (3-4)</td>
<td>5 (4-6)</td>
<td>0.04</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>19 (18-21)</td>
<td>21 (18-23)</td>
<td>0.40</td>
<td>-</td>
</tr>
</tbody>
</table>

CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, TIA; transitory ischaemic attack BMI; body mass index. The different smoke variables were entered separately into the model. The baseline analysis was based on “ever smokers”. 
Table 9. Factors associated with atherosclerosis extent

<table>
<thead>
<tr>
<th>Factor</th>
<th>Normal arteries % (95 % CI)</th>
<th>Unilateral disease</th>
<th>Bilateral disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40 (38-42)</td>
<td>30 (26-33)</td>
<td>22 (18-26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever</td>
<td>60 (59-62)</td>
<td>70 (67-74)</td>
<td>78 (74-82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former</td>
<td>48 (48-51)</td>
<td>54 (50-57)</td>
<td>55 (50-60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>11 (10-12)</td>
<td>17 (14-20)</td>
<td>23 (19-27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (39-42)</td>
<td>52 (49-56)</td>
<td>62 (58-67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypcholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>1 (0-2)</td>
<td>1 (0-1)</td>
<td>4 (2-6)</td>
<td>0.007</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (6-7)</td>
<td>9 (7-11)</td>
<td>9 (6-11)</td>
<td>0.019</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (9-11)</td>
<td>13 (11-15)</td>
<td>21 (17-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIA/Stroke</td>
<td>4 (3-4)</td>
<td>4 (3-6)</td>
<td>6 (4-8)</td>
<td>0.043</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>19 (18-21)</td>
<td>18 (16-21)</td>
<td>25 (20-29)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Percentages are given within each group of extension of atherosclerosis. The association of risk factors and the extension of atherosclerosis were tested by linear by linear association. CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, TIA; transitory Ischaemic attack BMI; body mass index.

Table 10. Factors associated with the severity of atherosclerosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Without plaque % (95 % CI)</th>
<th>With plaque</th>
<th>With stenosis</th>
<th>Univariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40 (38-42)</td>
<td>27 (24-30)</td>
<td>17 (9-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever</td>
<td>60 (59-62)</td>
<td>73 (71-76)</td>
<td>83 (75-91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former</td>
<td>49 (48-51)</td>
<td>54 (51-57)</td>
<td>53 (42-63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>11 (10-12)</td>
<td>19 (17-21)</td>
<td>30 (21-40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (39-42)</td>
<td>56 (53-59)</td>
<td>70 (60-79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>8 (8-9)</td>
<td>16 (14-18)</td>
<td>29 (20-39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypcholesterolemia</td>
<td></td>
<td>37 (34-39)</td>
<td>50 (40-60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Claudication</td>
<td>1 (0-2)</td>
<td>2 (1-2)</td>
<td>7 (1-12)</td>
<td>0.009</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (6-7)</td>
<td>9 (7-10)</td>
<td>7 (1-12)</td>
<td>0.025</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (9-11)</td>
<td>16 (14-18)</td>
<td>21 (12-29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIA/Stroke</td>
<td>4 (3-4)</td>
<td>4 (3-6)</td>
<td>12 (5-19)</td>
<td>0.037</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>19 (18-21)</td>
<td>21 (18-23)</td>
<td>27 (18-36)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

The association of risk factors and the extension of atherosclerosis were tested by linear by linear association. CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, TIA; transitory ischaemic attack BMI; body mass index,
Smoking, hypertension, diabetes mellitus and CAD were independently associated with prevalence of carotid atherosclerosis. Risk factors are displayed in Tables 8-10. Separate analysis regarding risk factor profiles showed higher prevalence of antiplatelet use and CVD in the CEA group compared to the non-operated group.

**Figure 8.** Prevalence (%) of atherosclerotic plaque/stenosis among never smokers, former smokers, and current smokers.

Figure 8 shows the prevalence of ICA-atherosclerosis according to severity of disease and smoking habits. Among individuals with a history of CVD 59 (31.6%) had uni- or bilateral ICA-plaque, 10 (5.3%) a stenosis and 5 (2.6%) an occlusion of the ICA. The prevalence of plaque and stenosis varied between 22-47% and 1.5-6.7% respectively among subgroups with one or multiple major risk factors, Figure 9.
Figure 9. Prevalence (%) of carotid plaques/stenosis among individuals with one or multiple of the four major risk factors (smoking, coronary artery disease, hypertension, and diabetes).

The use of medication was relatively high among 65-year old men. Four-hundred-forty-two (13%) of those without ICA atherosclerosis, and 257 (22%) with ICA atherosclerosis were medicated with antiplatelet agents, 95.5% ASA and 4.5% clopidogrel. The corresponding number of subjects treated with statins were 694 (20%) and 337 (29%), respectively.

The use of antiplatelet agents and statins was even higher in subjects with >50% stenosis, 40 (42%) and 39 (41%), respectively, Figure 10. When the thirteen patients with a history of CEA were excluded, a high usage of antiplatelet agents and statins remained among those with a screening detected carotid stenosis, 35% and 38% respectively.
Figure 10. Usage (%) of antiplatelet agents and statins among subjects with or without atherosclerosis.

Among 744 subjects with ICA atherosclerosis and 40 subjects with > 50% stenosis not on antiplatelet- or statin treatment 705 (95%) and 37 (93%) respectively, had no other clinically manifestation of atherosclerosis (i.e. history of coronary heart disease, cerebrovascular disease, or claudication) indicating that the need for secondary preventive treatment had not been identified.

Study II

A total of 4748 subjects (9493 carotid arteries) were examined, 99% were men and mean age was 65 years (± 12 standard deviation). An ICA stenosis was found in 121 (1.3%) arteries; 82 (0.9%) were graded 20-49%, 16 (0.2%) were 50-69%, and 23 (0.2%) were 70-99% (NASCET definition). Eighteen (0.2%) arteries were occluded. Ultrasound outcome is shown in table 11. An overall moderate agreement was observed between the two methods, with $\kappa = 0.455$ (95% CI: 0.399-0.511), $p<0.001$. 

\[ \kappa = 0.455 \]
Table 11. Contingency tables of ultrasound outcome

<table>
<thead>
<tr>
<th></th>
<th>Stenosis*</th>
<th>Normal</th>
<th>20-49%</th>
<th>50-69%</th>
<th>70-99%</th>
<th>occlusion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>238</td>
<td>71</td>
<td>16</td>
<td>23</td>
<td>4</td>
<td>352</td>
<td></td>
</tr>
<tr>
<td>Grayscale and/or mosaic**</td>
<td>No</td>
<td>9116</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>9141</td>
</tr>
<tr>
<td>Total</td>
<td>9354</td>
<td>82</td>
<td>16</td>
<td>23</td>
<td>18</td>
<td>9493</td>
<td></td>
</tr>
</tbody>
</table>

*Stenosis defined by ICA PSV (NASCET method). **Presence of stenosis on B-mode grayscale and/or presence of mosaic pattern on color Doppler.

For the detection of >20% ICA stenosis the grayscale/mosaic pattern method had a sensitivity 91% (95% CI: 0.84-0.95) and specificity of 97% (95% CI: 0.97-0.98). The PPV was 31% (95% CI: 0.26-0.36) and the NPV was 99.9% (95% CI: 0.998-0.999). For the detection of >50% ICA stenosis the sensitivity was 100% (95% CI: 0.89-1.0) the specificity was 97% (95% CI: 0.96-0.97), and the PPV was 11% (95% CI: 0.08-0.15) and the NPV was 100% (95% CI: 0.99-1.0). The G/M method detected all significant stenosis >50% but missed some <50% stenosis, of which most were borderline with an ICA PSV of <2.0 m/s, Table 11.

The total time taken to examine both carotid bifurcations using the grayscale/mosaic protocol ranged between two and three minutes. Interobserver agreement was very good with \( \kappa = 0.8 \) for both mosaic and grayscale evaluation and \( \kappa = 1.0 \) for PSV.

Study III

In base-case, in a life-time perspective there was an incremental gain in QALYs of 0.20 per individual invited in the screened cohort. This effect came at an additional incremental cost of €1144 per individual screened, resulting in an ICER of €5744/QALY for the strategy of screening for ACAS versus not screening. Base case effect and cost-effectiveness are presented in Table 12.

The ARR in prevented stroke was 135 per 100000 screened. A total of 741 men needs to be screened to prevent one stroke. In base-case, assuming that initiation of BMT for ACAS results in a 50% stroke risk reduction compared to no-BMT, a 65-year-old man would on average gain 0.44 stroke-free years by taking part in a screening program. Each prevented stroke resulted in a mean 6.5 additional stroke-free years for the individual who avoided a stroke.
<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>No screening strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICER, €/QALY gained</td>
<td>5744</td>
</tr>
<tr>
<td>Effect, QUALYs per person</td>
<td>7.67</td>
</tr>
<tr>
<td>Cost (€)</td>
<td>8707</td>
</tr>
<tr>
<td>Incremental effect</td>
<td>+0.20</td>
</tr>
<tr>
<td>Incremental cost (€)</td>
<td>1144</td>
</tr>
<tr>
<td>Stroke free years gained per individual</td>
<td>0.44</td>
</tr>
<tr>
<td>Stroke free years gained per prevented stroke</td>
<td>6.5</td>
</tr>
<tr>
<td>ARR, prevented stroke per 100000 screened</td>
<td>135</td>
</tr>
<tr>
<td>RRR from stroke by screening, %</td>
<td>33.5</td>
</tr>
<tr>
<td>QALYs gained per 40000* screened</td>
<td>160</td>
</tr>
<tr>
<td>QALYs gained per 100000 screened</td>
<td>400</td>
</tr>
<tr>
<td>NNS to prevent one stroke</td>
<td>741</td>
</tr>
</tbody>
</table>

ICER; Incremental cost-efficiency ratio, QALY; quality adjusted life-year, ARR; absolute risk reduction, RRR; Relative risk reduction, *Number of 65-year-old men screened in Sweden every year, NNS; numbers needed to screen.

The parameters with the most influence on cost-effectiveness were the assumed relative stroke risk reduction from BMT, cost of the ultrasound examination, and ACAS prevalence. The effect of variations in the different parameters on ICER is presented in a Tornado diagram, Figure 11.

The minimum stroke reduction effect required for BMT at the WTP threshold of €50000/QALY was 22%, increasing to 32% at a WTP threshold of €23000/QALY. At an assumed stroke-risk reduction from BMT of 62% or higher the strategy of screening dominated the strategy of not screening, Figure 12.
Cost-effectiveness of screening is depending on prevalence of ACAS. Figure 13, shows cost-effectiveness of screening depending on prevalence of ACAS and stroke risk reduction at different WTP thresholds. In Figure 14, the ARR is plotted against the estimated risk reduction of a preventive treatment.
Figure 12. One-way sensitivity analysis. Incremental cost-effectiveness ratio (ICER, (€/QALY), y-axis) plotted versus the tested range in assumed reduction in risk for stroke after initiation of BMT (% reduction in risk, x-axis) in those with screening-detected ACAS. Horizontal lines represent clinically relevant WTP thresholds.

Figure 13. Two-way sensitivity analysis of combined variations in assumed stroke-risk reduction from BMT (y-axis) and prevalence of ACAS in the screened population (x-axis). The upper borders of the colored areas represent the respective willingness-to-pay (WTP) threshold: Grey €10,000/QALY, Yellow €23,000/QALY, and Green €50,000/QALY.
Study IV

The study population consists of individuals screened at both index examination at age 65 and re-examined at age 70. Demographics of the study population are described in Table 13. Disease development is presented in Figure 15 and Table 14. Risk factors associated with atherosclerotic development are shown in Table 15.

The five-year cumulative neurological events rate was 0.2% in men with baseline normal carotid arteries, 0.6% in men with plaque, 6.5% in men with stenosis of 50-79%, and 42% in men with stenosis of 80-99% (average annual event rate of 0.04%, 0.12%, 1.3% and 8.4% respectively). A total of 571 men (19.0%, 95% CI 17-20) had disease progression, while 306 (41.4%, 95% CI 37.9-45.0) of those with atherosclerosis showed regression of their carotid lesion after 5-year follow-up, Table 14. Among the 60 men who progressed from normal or plaque-status at initial examination to carotid stenosis at five years, 8 (13.3%, 95% CI 6.9-24.2) developed neurological symptoms (annual rate 2.6%). Risk factors known to be associated with neurological symptoms did not differ between those with symptomatic disease and those without symptoms.

Eighteen subjects were operated on with CEA during five years after primary screening, of whom fourteen (78.0%, 95% CI 55.0-91.0) had developed a symptomatic carotid stenosis at the time of surgery.

Figure 14. Absolute risk reduction (ARR) for stroke (prevented strokes per 100000 screened) in relation to the assumed reduction in risk for stroke when best medical therapy (BMT) is initiated for screening-detected asymptomatic carotid artery stenosis versus a strategy of not screening. The calculations are done at an assumed ACAS prevalence of 2% in the population.
Figure 15. Natural history of study population

Table 13. Study population basic characteristics

<table>
<thead>
<tr>
<th></th>
<th>At age 65 N = 3057 (%)</th>
<th>At age 70 N = 3057</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque</td>
<td>696 (22.8)</td>
<td>888 (29.0)</td>
</tr>
<tr>
<td>Stenosis 50-79%</td>
<td>43 (1.4)</td>
<td>68 (2.2)</td>
</tr>
<tr>
<td>ICA surgery during 5 years follow up</td>
<td>18 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>1898 (62.1)</td>
<td>1866 (61.0)</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>338 (11.1)</td>
<td>255 (8.3)</td>
</tr>
<tr>
<td>CAD</td>
<td>283 (9.3)</td>
<td>371 (12.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1319 (43.1)</td>
<td>1689 (55.3)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>903 (29.5)</td>
<td>1062 (34.7)</td>
</tr>
<tr>
<td>Claudication</td>
<td>23 (0.75)</td>
<td>42 (1.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>190 (6.2)</td>
<td>231 (7.6)</td>
</tr>
<tr>
<td>DM</td>
<td>334 (10.9)</td>
<td>436 (14.3)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>428 (14.0)</td>
<td>653 (21.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>691 (22.6)</td>
<td>888 (29.0)</td>
</tr>
</tbody>
</table>

ICA; internal carotid artery, CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, DM; diabetes mellitus.
Table 14. Five-year carotid artery disease progression of the study population

<table>
<thead>
<tr>
<th>Age 65</th>
<th>Age 70</th>
<th>Stenosis &lt;50%</th>
<th>N (%)</th>
<th>Stenosis 50-79%</th>
<th>N (%)</th>
<th>Stenosis 80-99%</th>
<th>N (%)</th>
<th>Occlusion</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No plaque N=2318</td>
<td></td>
<td>2290 (98.8)</td>
<td>22 (1.0)</td>
<td>4 (0.17)</td>
<td>1 (0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque, no stenosis N=696</td>
<td></td>
<td>662 (95.2)</td>
<td>25 (3.6)</td>
<td>8 (1.1)</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis 50-79% N=31</td>
<td>14 (45.2)</td>
<td>13 (41.9)</td>
<td>4 (12.9)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis 80-99% N=12</td>
<td>2 (16.7)</td>
<td>0</td>
<td>9 (75.0)</td>
<td>1 (8.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 15. Risk factors for development of carotid atherosclerosis

<table>
<thead>
<tr>
<th>Risk factors at age 65</th>
<th>Normal at age 70 N=2460</th>
<th>Atherosclerosis at age 70 N=589</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (Ever)</td>
<td>60 (58-62)</td>
<td>69 (65-73)</td>
<td>&lt;0.001</td>
<td>1.4 (1.2-1.8)</td>
</tr>
<tr>
<td>- Never</td>
<td>40 (38-42)</td>
<td>31 (28-35)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>- Current</td>
<td>8 (7-9)</td>
<td>11 (9-14)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>- Former</td>
<td>52 (50-54)</td>
<td>57 (53-61)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>11 (10-12)</td>
<td>17 (14-21)</td>
<td>&lt;0.001</td>
<td>1.3 (1.0-1.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55 (53-57)</td>
<td>58 (54-63)</td>
<td>0.168</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>33 (31-35)</td>
<td>42 (38-46)</td>
<td>&lt;0.001</td>
<td>1.3 (1.1-1.6)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>6 (5-7)</td>
<td>7 (5-9)</td>
<td>0.818</td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>1 (1-2)</td>
<td>2 (1-3)</td>
<td>0.259</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>8 (7-9)</td>
<td>8 (6-10)</td>
<td>0.956</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>14 (12-15)</td>
<td>16 (13-19)</td>
<td>0.094</td>
<td>1.0 (0.8-1.3)</td>
</tr>
</tbody>
</table>

CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, DM; diabetes mellitus, TIA; transitory ischaemic attack,

All-cause mortality in the cohort attending 5-years follow-up scan was 3.4%. The 5-year mortality rate was 3.3% (95% CI 2.8-3.9) among men with normal carotid arteries at age 65, 3.5% (95% CI 2.5-4.7) among those with carotid
plaque, and 6.6% (95% CI 2.6-15.7) when a 50-79% carotid stenosis was present (p=0.428). None of those with severe stenosis died. Only two subjects had stroke listed as the primary cause of death. All-cause mortality among those who did not attend the 5-year follow-up scan was 13.0% (95% CI 11.3-14.9), significantly higher than for attendees (p<0.001).

General use of medical therapy was higher at rescreening (70 years of age) in comparison to primary screening (65 years). At age 65, 433 (14%) were treated with antiplatelet agents, 694 (22%) with statins and 1321 (43%) with antihypertensive medication while at age 70, 657 (22%) were treated with antiplatelet agents, 890 (29%) with statins and 1692 (55%) with antihypertensive medication (p<0.001). Among those with progressive disease 123 (23%) had antiplatelet agents, 175 (33%) had statins and 301 (57%) had antihypertensive medication. Use of statins, antiplatelet agents and antihypertensive medication in subgroups are presented in Table 16.

Table 16. Medication at age 70

<table>
<thead>
<tr>
<th>Carotid status at age 65 and development during 5-year follow-up</th>
<th>Antiplatelet agents</th>
<th>Statins</th>
<th>Antihypertensive medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal carotid arteries without progress</td>
<td>314 (18.0%)</td>
<td>439 (24.2%)</td>
<td>907 (51.4%)</td>
</tr>
<tr>
<td>Normal carotid arteries with progress</td>
<td>123 (23.1%)</td>
<td>175 (32.8%)</td>
<td>210 (39.4%)</td>
</tr>
<tr>
<td>Plaque without progress</td>
<td>117 (31.1%)</td>
<td>150 (40.0%)</td>
<td>256 (69.1%)</td>
</tr>
<tr>
<td>Plaque with progress</td>
<td>10 (33.3%)</td>
<td>14 (46.7%)</td>
<td>19 (63.3%)</td>
</tr>
<tr>
<td>Stenosis without symptoms</td>
<td>12 (22.6%)</td>
<td>19 (35.8%)</td>
<td>32 (60.4%)</td>
</tr>
<tr>
<td>Stenosis with progress to symptoms</td>
<td>5 (62.5%)</td>
<td>6 (75.0%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>All with regression</td>
<td>81 (26.5%)</td>
<td>95 (31.0%)</td>
<td>183 (59.8%)</td>
</tr>
</tbody>
</table>
General discussion

Early intervention to reduce risk factors can prevent, delay and in some circumstances, reverse the onset or progression of vascular disease. The main purpose of screening is to identify those who require treatment for previously undetected disease and at the same time avoiding harm in those not in need of treatment. In their World Health Organisation thesis on “principles and practice for screening of disease” Wilson and Jungner described ten criteria that are important in selecting diseases suitable for early screening:

1) The condition sought should be an important health problem
2) There should be an accepted treatment for patients with the recognized disease
3) Facilities for diagnosis and treatment should be available
4) There should be a recognizable latent or early symptomatic stage
5) There should be a suitable test or examination
6) The test should be acceptable to the population
7) The natural history of the condition, including development from latent to declared disease, should be adequately understood
8) There should be an agreed policy on whom to treat as patients
9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10) Case-finding should be a continuing process and not a “once and for all” project.

Carotid artery screening has been debated for several decades. In this thesis, we attempted to explore key aspects of carotid artery disease to gain more understanding in whether carotid artery screening could be beneficial in asymptomatic individuals. Using an established AAA-screening program we screened a cohort of 65-year-old men born 1942-1944 for presence of carotid disease (Paper I). The cohort of men was re-invited 5 years later at the age of 70 years for a new duplex ultrasound of the carotid arteries to evaluate natural history of men participating in a carotid screening program and disease progression (Paper IV). Results from these screening studies together with risk assessments from population-based studies were applied in a decision-analysis model to evaluate the minimum required effect of a preventive intervention to achieve cost-effectiveness (paper III). In an effort to find a simple way of
detecting significant carotid disease we studied a simplified ultrasound method used during the screening program (Paper II). The findings are interpreted and compared to previous epidemiological findings and contemporary guidelines in the following subsections of this discussion.

Prevalence and risk factors
Prevalence of a disease is one of the most important factors when considering a screening strategy. As described in the literature the prevalence of carotid atherosclerotic plaque in the population is common and some publications reported prevalence as high as 59-78% (Qureshi 2001, Hillen 2000, Sillesen 2012). Comparison across multiple studies are difficult as different definitions and methods are used and the populations examined varies. Investigators in the Tromso study found a 53% prevalence of plaque (defined as a focal IMT >50%), among 1726 men with mean age 59.6 years (Mathiesen 2011). Using the same definition, a plaque prevalence of 58% was found in the Northern Manhattan study, among 2189 asymptomatic subjects (40% men) with mean age 68 years (Rundek 2008). The MESA-study used a standardised self-made carotid plaque index and reported a prevalence of 45% in 3034 examined men with mean age of 63 years (Sharrett 2004). In study I, the observed prevalence of carotid plaques was relatively low (25%). This could be explained by the somewhat stricter definition of plaque (IMT>2x6mm) than definitions used in previous studies and a more homogenous population with no exclusion criteria used.

The reported prevalence of internal carotid stenosis in the literature vary between 0 and 22%, with a pooled prevalence estimate of 4.2% (de Weerd 2009). A large screening program in the US in which seniors >60 years of age were examined for carotid stenosis >50% found a prevalence of 7.5% (Lavenson 2004) while another screening study in Norway among seniors with mean age >65 years found a prevalence of 3.8% in men and 2.7% in women (Mathiesen 2001). Several factors contribute to this variation, such as non-population based cohorts, different exclusion criteria (i.e. CVD or diabetes), wide age intervals, low participation rates and different definition of stenosis, making relevant comparisons difficult. The prevalence of > 50% carotid artery stenosis in study I was 2.0%. Similar prevalence was reported in the Northern Manhattan study with a prevalence of 2.2% (Ratchford 2009) and in a recent meta-analysis pooled cohort data from four large population-based studies of clinical asymptomatic patients with carotid artery stenosis of >50%, demonstrated a prevalence of 2.3% for men aged 60-69 years (de Weerd 2010).

Smoking was reported the strongest independent risk factor for carotid artery atherosclerosis (O'Leary 1999, Sharrett 2006, Hunt 2002). In study I, 73% of individuals with atherosclerotic plaque, and 86% with moderate-severe stenosis, reported a history of smoking. The observed association between smoking and the degree and distribution of the disease in study I resembles a dose-respond relationship, implying a causative effect of smoking. Daily smoking among 65-year old Swedish men has decreased significantly
during the last three decades (Statistiska centralbyrån 2011) and the number of current smokers is lower in comparison to previous reports (Mathiesen 2001, Hunt 2002). Thus, even if current smoking is the single most important risk factor for carotid artery arteriosclerosis, the relatively low proportion of abuse could further explain the lower than expected plaque prevalence in the population studied in study I.

Hypertension, diabetes mellitus and CAD were also significantly and independently associated with prevalence of atherosclerosis in the carotid arteries, in agreement with previous reports (Mathiesen 2001, Sharrett 2006). Subgroup analysis in study I showed that individuals with multiple major risk factors have a further increased risk with a prevalence of carotid plaque up to 46.7% and carotid stenosis up to 6.7%. A predictive model that was developed based on patients participating in Lifeline Screening in USA, also identified smoking history, CAD, hypertension and diabetes as independent predictors of a > 50% asymptomatic carotid stenosis (Greco 2013).

Risk factor analysis in study I and IV was limited by a small number of individuals reporting some of the risk factors, making the analysis susceptible to type II statistical error. Another limitation is the questionnaire-based design, self-reporting data are prone to recall bias and those not reporting certain risk factor may still have them.

Recent discussion about total plaque area being a better predictor of stroke risk then the degree of stenosis could mean a higher prevalence of subjects with significant disease than previously discussed in the screening debate especially among individuals with cardiovascular risk factors.

Screening modality and method
Ultrasound is a non-invasive and readily available diagnostic tool with a sensitivity of 94% and specificity of 92% for 60-99% carotid stenoses (Jonas 2014), that already serves as an excellent screening method in other clinical contexts (e.g. screening for aortic aneurysms). Several definitions and grading-methods of an ICA-stenosis exist, all based on velocity measurements as ICA PSV (Sabeti 2004).

Carotid ultrasound is highly dependent on the expertise of the sonographer and there are considerable variations in the accuracy of the examination with a large number of false positives (Jonas 2014). Velocity measurements have certain technical aspects that are important for accurate assessment, such as correct positioning of the sample volume, complete sampling through an area of stenosis, and obtaining a correct Doppler angle of insonation (≤60º).

While the preoperative diagnostic analysis should be precise because of its utmost importance for the indication for surgery (ACAS, ECST, NASCET, ACST) a screening duplex scan does not have to be as precise. Instead, it should preferentially be a method that excludes healthy individuals as quickly
as possible and most importantly, identifies the few with a potentially significant stenosis, who can later be examined with higher precision to verify or rule out the diagnosis.

In a screening setting, a simplified carotid protocol as a primary evaluation may reduce the cost associated with the examination and therefore be preferred compared to a preoperative diagnostic tool. In this context, a simplified DUS protocol may allow the training of less specialized technicians who might concentrate on screening assessments, whilst more experienced technicians might continue to provide a thorough diagnostic assessment. This has been proven feasible in an AAA screening setting (Hartshorne 2012).

Study II showed that carotid artery stenosis could be excluded by means of a simplified DUS protocol, with a high negative predictive value (NPV) of almost 100%. The overall agreement with ICA PSV measurements was moderate and the grayscale/mosaic pattern method tended to overestimate the number of stenoses. The accuracy of detection of low-grade stenosis (20-49%) was very good, and the identification of moderate (50-69%) and high-grade (70-99%) stenoses was excellent. Findings in study II are consistent with the study of Hallam et al published in 1989, who showed in a double-blind comparison complete agreement between colour-flow assessment only and a full DUS assessment in 91% of cases (Hallam 1989). Another quick carotid scan method was also evaluated by Lavenson, among 500 consecutive carotid ultrasound patients in 2004, who found a sensitivity of 93-97% and a specificity of 87%, when comparing with a complete carotid ultrasound (Lavenson 1998). A quick ultrasound evaluation could be used in an outpatient clinic or a primary care setting and could be much better than primary physicians listening for a cervical bruit which has a sensitivity of only 50% with many patients consequently being falsely reassured.

An important limitation in study IV is that all technicians performing the assessments were experienced in carotid ultrasound and may have thus been more likely to recognize the hallmark signs of carotid stenosis during assessment with B-mode and colour Doppler. A natural next step in testing a simple protocol would be to assess how operators with limited previous experience in DUS of the carotid arteries perform compared to experienced ultrasound technicians. To minimize the risk of missing a significant carotid stenosis (in particular in individuals with difficult anatomy) subjects with uncertain findings should be referred for a complete carotid ultrasound. This approach would secure the reliability of the findings and enable screening in a wide setting.

There are new methods developing today with ultrasound measurements of carotid plaque burden, either by 2-dimentional assessment of total plaque area or 3-dimentional measurement of plaque volume that are more predictive of cardiovascular events than IMT (Mathiesen 2011, Inaba 2012). This approach could in the future be used for both detection of disease and for follow up.
Natural history
Among those attending rescreening at age 70 (study IV) the prevalence of carotid plaque increased from 23% to 29% and carotid stenosis from 1.4% to 2.2%. Almost one in five subjects of those without carotid artery disease at age 65 had developed atherosclerosis during five years follow-up scan but only 2.0% had developed a >50% stenosis, which indicates that development of severe atherosclerotic disease is low in this population. In the ACSRS study investigators observed progression of asymptomatic carotid atherosclerosis among 1121 patients with 50-99% stenosis and found a progression rate of 20%, similar to the findings in study IV (Kakkos 2014), while investigators in the CHS demonstrated that 63% had progression of atherosclerotic plaque (Spence 2002). Study IV shows that smoking, CAD and hypercholesterolemia were the only risk factors associated with progression of atherosclerosis while CHS study showed that increased age, hypercholesterolemia and male sex were predictors of plaque progression (Spence 2002).

An interesting finding was the relatively high regression rate of 41.4% (study IV) which was consistent with regression rate of 19.6-50.1% showed by Spence et al among 4378 referral patients (Spence 2010). A large percentage of subjects in this group was on antihypertensive treatment while the treatment with antiplatelet agents and statins was less frequent, 26.5% and 31.0% respectively. To fully understand this finding a more extensive evaluation is needed exploring risk factors and the point in time that the subjects received BMT.

Only a very small proportion progressed to clinically significant disease with neurological events among individuals with normal carotid arteries, plaque or moderate stenosis at age 65. Previous report by Conrad et al who studied natural history of 794 patients with moderate stenosis showed a five-year plaque progression rate of 39% and a 2.3% annual ipsilateral neurological event rate (Conrad 2013). Both progression and event rates were much higher in comparison to study IV that found a disease progression rate of 19%, and an annual neurological events rate of 1.3% among men with moderate stenosis. That can partly be explained by a different and wider definition of plaques in the present report. The low number of significant stenosis and neurological events could also influence the findings. The higher risk of neurological events found in study IV among individuals with progression is consistent with previous findings from the CHS that risk of cardiovascular events is twice that of patients with stable plaque or regression (Spence 2002).

Investigators in epidemiological studies such as Framingham Heart Study (D’Agostino 2008) and Prospective Cardiovascular Munster Study (PROCAM) developed a classification system to classify asymptomatic individuals in to low intermediate and high-risk groups for cardiovascular events (stroke, MI and cardiovascular deaths) (Wilson 1998, Assam 2002). These risk groups are defined according to whether the 10-year risk is <10% (<1.0% per year), 10-20% (1.0-2.0% per year), or >20% (>2% per year), respectively.
Using this classification an individual with >50% asymptomatic carotid stenosis would have an extremely high risk. All-cause mortality in individuals with carotid stenosis is very high in comparison to general population, with nearly two-third of the deaths being cardiac related (Giannopoulos 2015). Subgroup analysis in study IV showed that individuals with stenosis had twice as high all-cause mortality than subjects with normal arteries or plaque. In a recent systematic review, a 5-years all-cause mortality in patients with asymptomatic carotid stenosis as high as 24 % was found and three-time increase in annual mortality in comparison to general population was calculated (Giannopoulos 2015).

**Preventive treatment**

The primary goal of management of carotid stenosis is to decrease the risk for stroke and stroke related mortality, and a secondary goal is to reduce the overall risk of cardiovascular events and death. There are no present screening programs for carotid stenosis but when found, asymptomatic disease is not left untreated. The preferred treatment is widely debated with some physicians advocating surgical treatment as addition to modern medical treatment while others recommend medical treatment and risk factor adjustment alone. Treatment choice involves a trade-off between immediate treatment-related risk and future stroke risk. At present, there is a lack of well-designed contemporary studies that could answer which strategy is the most beneficial. Since there are no screening programs in Sweden individuals could only receive treatment when accidently discovered or treated for other manifestation of atherosclerosis.

*Figure 16. Annual trends in surgery for asymptomatic carotid stenosis. Proportion of patients in percent.*
Previous studies have shown that carotid endarterectomy (CEA) may be an effective treatment in ischemic stroke prevention in patients with asymptomatic carotid artery stenosis (ACAS 1995, ACST1 2004, Halliday 2010). After the results from the ACST1 trial were published, surgical treatment of asymptomatic carotid artery stenosis increased in Sweden, Figure 16 (Swedvasc annual report 2009).

Over the past decade, however, medical therapy has evolved and more recent studies show a much lower incidence of neurological and other cardiovascular events in patients receiving best medical treatment (BMT), consisting of anti-platelet agents, statins and anti-hypertensive medication (Spence 2010). There are indication that annual stroke rates have decreased from 2-4% to about 1% (Constantinou 2013). Today most patients with a diagnosed asymptomatic carotid stenosis are therefore treated with BMT and risk factor adjustment, while the practice of surgical intervention for asymptomatic stenosis has markedly declined in Sweden, Figure 17 (Swedvasc annual reports).

![Figure 17. Annual trends in carotid surgery.](image)

Internationally, practice varies significantly between countries (Venermo 2017). Surgery of asymptomatic individuals has decreased in Sweden during the last 10 years and most subjected to surgical intervention today are being included in RCT like ACST2. There were 18 individuals operated on in the 5 years between study I and Study IV, but only four had surgery because of asymptomatic disease and all of them had surgery before end of 2010.

Modern medical therapy may affect the progression of atherosclerosis in the population and adequate therapy leads to a decrease in stroke risk and other cardiovascular events with an effect on the general mortality. A recent review
by Rothwell et al confirms that medical treatment reduces the risk of stroke substantially, identifying antiplatelet agents as the key intervention (Rothwell 2016). The Asymptomatic Carotid Emboli Study (ACES) reported that antiplatelet therapy was an independent predictor of lower rates of stroke, TIA and cardiovascular death in patients with asymptomatic 70-99% stenosis (King 2013). In a Cochrane review of 14 RCTs of statin therapy in primary prevention, statins were associated with a 28% reduction in fatal and non-fatal CAD events, a 22% reduction in fatal and non-fatal stroke and a 17% reduction in overall mortality (Taylor 2013). In addition, the absolute benefit was found to be higher in those at higher baseline risk. A meta-analysis of RCT investigating the effect of antihypertensive treatment on carotid atherosclerosis showed a reduction in IMT progression (Wang 2006). Current standard therapy to reduce stroke risk includes use of statins, glycaemic control for persons with diabetes, anti-hypertensive treatment, antiplatelet therapy, and risk factor modification, with smoke cessation being the most important. Medical therapy in previous studies is often not clearly defined or standardized, is not kept constant during the study, and does not included treatments now considered to be best medical treatment.

Patients at greater risk for ipsilateral stroke may be more likely to benefit from surgery or endovascular intervention. However, there are no reliable risk-stratification tools available that can distinguish persons with asymptomatic carotid stenosis who are at increased risk for stroke despite current best medical therapy or those who are at increased risk for harms from CEA or CAS. The ongoing trial, CREST-2 may be able to answer some of these questions (Howard 2017). The trial will compare both CAS plus medical therapy versus medical therapy alone and CEA plus medical therapy versus medical therapy alone.

The observed relatively high usage of statins and anti-platelet agents in the population in Study I is in accordance with findings in the Northern Manhattan study (Rundek 2008), and may have contributed to the comparably low prevalence of carotid artery lesions. In many countries, the use of statins has increased substantially over the last decades, and lately about 9.5% of all Swedish men are treated (National Board of health and welfare 2009). Study I revealed that about 40% of those with a screening detected stenosis already were on statins and/or anti-platelet therapy. General use of medical therapy was higher at rescreening (study IV) in comparison to primary screening (study I). At age 65, 14% were treated with antiplatelet agents, 22% with statins and 43% with antihypertensive medication while at age 70, 22% were treated with antiplatelet agents, 29% with statins and 55% with antihypertensive medication. Although the health care system thus has identified a substantial proportion of those potentially benefitting from secondary preventive treatment, there is clearly more to be done. Since a majority of those at risk were not on preventive medical treatment the Swedish abdominal aortic
screening program of 65-year-old men could offer an opportunity to find individuals with carotid artery atherosclerosis, who may benefit from such intervention.

Strong conclusions about the effect of medical therapy on the natural history of plaque are difficult to make from study IV because small number of significant stenosis and the questionnaire-based study design with self-reported data that are prone to recall bias which may underestimate the effect of preventive medication.

**Cost-effectiveness**

Before considering a screening program it is important to evaluate the cost-effectiveness of such intervention. A recent review of cost-effectiveness studies of management of carotid artery stenosis found research gaps in economic evidence in the context of carotid artery stenosis diagnosis and treatment (Shenoy 2012).

In study III a screening strategy among 65-year-old men was evaluated. The target population consisting of 65-year-old men was chosen because this population is commonly targeted for AAA ultrasound screening, and the AAA screening examination could easily be complemented with a carotid ultrasound at the same screening instance. Although, the cost of invitation would already be incurred on the AAA screening program with such a strategy (as in study I and IV), we have included these costs in the analysis in order for ACAS screening to be judged on its own merits, as if ACAS had not been done concurrently with AAA screening.

In the Markov model analysis, comparing a strategy of offering carotid artery screening to 65-years old men with initiation of BMT in those with ACAS not already on BMT versus not screening, a screening strategy was cost-effective in base case. Previous much older studies evaluating cost-effectiveness of screening have been contradictory. One study compared multiple screening strategies including; power Doppler imaging, standard duplex Doppler, MRA and angiography and concluded that power Doppler imaging is cost-effective (Bluth 2000). Another study compared screening with ultrasound confirmed with angiography followed by CEA or screening with ultrasound followed by CEA versus no screening strategy and concluded that screening was not cost-effective (Lee 1997). Evaluations including other screening modalities then ultrasound and surgical treatment influences cost effectiveness results partly by additional cost and partly by stroke risk associated with the procedures.

Study III showed that the minimum required relative stroke risk reduction of BMT for the program to be cost-effective was 22%, at a WTP threshold of €50000/QALY. Available evidence indicates that the expected risk reduction from BMT can be plausibly estimated to 50%. In the base-case assumption, ACAS screening in this context remained cost-effective at a lower WTP
threshold of €23,000/QALY, as defined by the National Institute of Health and Care Excellence in the UK (NICE UK).

The factor that most influences the ICER is the reduction in stroke risk with a preventive treatment. As presented in Table 17, statins alone could potentially lower the risk of stroke in patients with ACAS in a range between 11% and 50% and antiplatelet agents in a range between 18% and 25%. One limitation of the analysis is that additive effect of smoke cessation, glucose control, and anti-hypertensive treatment is difficult to estimate. Another limitation is the assumption of 100% compliance with preventive treatment over-estimates the benefits since compliance to medication in an asymptomatic population would probably be lower. On the other hand, the effect of BMT on mortality is only included in study III as a decrease in stroke risk and deaths associated to stroke. Medical intervention in ACAS individuals can however also be expected to affect other cardiovascular morbidity and mortality, which thus would potentially increase the gain of a screening strategy. Even a small decrease in general cardiovascular mortality in the ACAS group would have a strong impact on cost-effectiveness of screening.

At the lower end of the range of risk reduction, 22%, ACAS screening would even be cost-effective at the maximum accepted WTP threshold. With an assumed risk reduction of 62% or more, ACAS screening would both be more effective in preventing strokes as well as less costly. Based on available evidence, an interval of 9%-67% was deemed a plausible variation in risk reduction from BMT. Even small variations within this interval had profound effects on cost-effectiveness as well as the clinical impact (ARR) of offering ACAS screening. Needless to say, additional contemporary data helping to pinpoint the stroke-risk reducing effect of BMT would greatly assist deciding on, and planning preventive health care programs associated with ACAS.

The number needed to screen in order to prevent one stroke was high (NNS 741) in comparison to screening for AAA (NNS 530) or breast cancer screening (NNS 233), (Svensjö 2014, Hendrick 2012). Although screening may be cost effective, the high NNS could raise questions of the clinical effectiveness of screening in unselected population. On the other hand, stroke is associated with a high level of morbidity with major effects on quality of life and costs. Thus, even a small reduction in stroke incidence would gain large value to the individual patient as well as to society.

Patients with ACAS have higher mortality than the general population (Giannopoulos 2014, Kragsterman 2006). The analysis in study III employed a two-fold increase in all-cause mortality for ACAS patients based on results from study IV.
<table>
<thead>
<tr>
<th>Reference Year</th>
<th>Study design</th>
<th>Treatment</th>
<th>Patients</th>
<th>Stroke risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diener HC, et al (European stroke prevention study 2) 1996</td>
<td>RCT</td>
<td>Aspirin vs dipyridamole vs placebo</td>
<td>6602</td>
<td>Aspirin 18.1% Dipyridamole 16.3 Combination 37.0%</td>
</tr>
<tr>
<td>The LIPID study group. (LIPID) 1998</td>
<td>RCT</td>
<td>Pravastatin</td>
<td>9014</td>
<td>16%</td>
</tr>
<tr>
<td>Schwartz GG, et al (MIRACL) 2001</td>
<td>RCT</td>
<td>Atorvastatin</td>
<td>3086</td>
<td>50%</td>
</tr>
<tr>
<td>Antithrombotic trialist collaboration 2002</td>
<td>Systematic review</td>
<td>Antiplatelet therapy</td>
<td>18270</td>
<td>25% reduction in stroke</td>
</tr>
<tr>
<td>Athyros VG, et al (GREACE) 2002</td>
<td>RCT</td>
<td>Atorvastatin</td>
<td>1600</td>
<td>47%</td>
</tr>
<tr>
<td>Colhoun HM, et al (CARDs) 2004</td>
<td>RCT</td>
<td>Atorvastatin</td>
<td>2838</td>
<td>47%</td>
</tr>
<tr>
<td>Collins R, et al (HPS) 2004</td>
<td>RCT</td>
<td>Simvastatin</td>
<td>20536</td>
<td>33%</td>
</tr>
<tr>
<td>Koren MJ, et al (ALLIANCE) 2004</td>
<td>RCT</td>
<td>Atorvastatin</td>
<td>2442</td>
<td>10%</td>
</tr>
<tr>
<td>Pedersen TR, et al (IDEAL) 2005</td>
<td>RCT</td>
<td>Atorvastatin or simvastatin</td>
<td>8888</td>
<td>17%</td>
</tr>
<tr>
<td>Amareneo et al (SPARCL) 2006</td>
<td>RCT, multicenter</td>
<td>Atorvastatin vs placebo</td>
<td>4731</td>
<td>16%</td>
</tr>
<tr>
<td>Knopp RH, et al (ASPEN) 2006</td>
<td>RCT</td>
<td>Atorvastatin</td>
<td>2410</td>
<td>11%</td>
</tr>
<tr>
<td>Paraskevas KI, et al 2007</td>
<td>Systematic review</td>
<td>Statin therapy (Simvastatin, atorvastatin, pravastatin)</td>
<td>-</td>
<td>Each 10% reduction in LDL cholesterol gave a stroke risk reduction of 15.6%. Decrease in LDL cholesterol level: atorvastatin 48.5%, pravastatin 27.2%</td>
</tr>
<tr>
<td>Sillesen H, et al (SPARCL) 2008</td>
<td>RCT, multicenter</td>
<td>Atorvastatin vs placebo</td>
<td>1007</td>
<td>16% (33% patients with carotid stenosis)</td>
</tr>
<tr>
<td>Ridker PM, et al (JUPITER) 2008</td>
<td>RCT</td>
<td>Rosuvastatin</td>
<td>17802</td>
<td>48% reduction in stroke risk</td>
</tr>
<tr>
<td>Collins R, et al (SEARCH) 2009</td>
<td>RCT</td>
<td>Simvastatin</td>
<td>12064</td>
<td>9% fatal and nonfatal stroke</td>
</tr>
</tbody>
</table>

RCT; randomized controlled trial
The higher mortality in this group has a significant influence on the individual’s gain from screening. Medical intervention in ACAS individuals can however also be expected to affect other cardiovascular morbidity and mortality, which thus would potentially increase the gain of a screening strategy. We suspect that the value of screening was slightly underestimated since the BMT effect on lowering mortality was not taken to account.

Cost of screening was also an important factor. Screening by means of a standard duplex examination has a relatively low cost especially if adjacent to an already established AAA screening. A reduction in administrative costs related to screening would not have as large influence on cost-effectiveness as use of a different screening modality. Other more expensive imaging techniques such as computed tomography or magnetic resonance angiography would strongly increase the cost per incremental QALY, and the risk reduction would have to be much higher for a screening strategy to maintain cost-effectiveness.

**Population screening**

Today there are no guidelines that recommend unselected population screening and the only country that have such screening is the USA where free or cash-on-the-barrel screenings are offered across the country (Hall 2008) despite the recommendations from the US Preventive Services Task Force, who recommends against screening for asymptomatic carotid stenosis (U.S. Preventive Services Task Force 2007 and 2014).

Guidelines issued by the American college of Cardiology Foundation, American Heart Association and American stroke Association suggest that carotid ultrasound may be considered for asymptomatic individuals if they have peripheral artery disease, coronary artery disease, aortic aneurysm or at least two risk factors for stroke including: hypertension, hypercholesterolemia, smoking, first degree relative with atherosclerosis that developed before age 60 and a family history of ischemic stroke (Goldstein 2006, Furic 2011, Brott 2011).

The “14” society guidelines advise against general population screening but recommend that screening might be considered in people who had at least two risk factors including hypertension, smoking, smoking, hypercholesterolemia or known cardiovascular disease (Brott 2011).

The Society for Vascular Surgery (SVS) recommend that screening for asymptomatic stenosis should be considered in selected patients with multiple risk factors, provided that “patients are fit for and willing to consider a carotid intervention if a significant stenosis is discovered” (Ricotta 2011).

ESVS guidelines recommend against routine population screening but advise that selective screening may be considered in patients with multiple vascular risk factors to optimise risk factor control and medical therapy to reduce cardiovascular morbidity and mortality (Naylor 2017).
Swedish guidelines do not recommend general population screening for carotid artery disease because of the small prevalence of carotid stenosis (Socialstyrelsen 2014).

The 2013 ACC/AHA guidelines (Stone 2013) recommend that non-diabetic individuals without clinical manifestation and a LDL-cholesterol of 1.8-4.9 mmol/L should be treated aggressively with statins in addition to other risk factor modifications when the 10-year risk of atherosclerotic cardiovascular events is >7.5% (average annual risk >0.75%). Individuals with carotid artery disease with much higher annual risk would belong to this group.

The profession is divided with some arguing for selective screening or general screening to detect individuals at high risk for all cardiovascular events, while others are against screening in any form. Some physicians are against screening for asymptomatic carotid stenosis because of the possibility of disease being found and then managed with CEA or CAS with a risk of procedural stroke (Jonas 2014). Most likely different treatment methods may be the best choice for some patients and not for others. Management of asymptomatic carotid stenosis with either CEA, CAS or BMT is far better than no treatment at all. Therefore focus should be on finding individuals in need of treatment and then choosing the best treatment for the patient.

Primary care physicians are using risk stratification dependent on presence of cardiovascular risk factors but studies have shown that most myocardial infarctions and strokes occur in people at average risk-factor level who are misclassified by risk factor scoring, as low or intermediate risk (Sillesen 2011). Both study I and IV show that a significant number of individuals is not being found and are being left untreated. Adding carotid imaging with measurements of atherosclerotic plaque burden to present strategy with risk factor scoring, could more accurately identify patients at high risk for cardiovascular events. Measurements of plaque with ultrasound could also be used to evaluate preventive treatment.

Many are mistaking the incidence of strokes due to carotid stenosis that occurs with medical management with the natural course of the disease and incidence of strokes that occurs without recognition or management of the asymptomatic stenosis. There are no recent studies were subject with clinically significant stenosis are just followed and not treated in order to see how many that will develop a stroke. That would be unethical. But we know that the annual stroke rates are at least as high as the 2% that occurred in subjects with >60% stenosis in ACAS and ACST who were treated with medical treatment of that time which differs from contemporary best medical treatment. A study measuring total plaque area identified patients at very high risk with total plaque area >119mm² that had a 10-year risk of stroke, death, or myocardial infarction approaching 40% (Spence 2002).
More recent studies suggest that annual stroke risk with best medical treatment is now <1% which indicates that finding individuals at risk and treating them could be beneficial. Early disease detection could also increase the compliance to preventive interventions such as taking statins, antiplatelet agents or anti-hypertensives, participating in exercise, managing weight, smoking cessation etc, thereby reducing the risk of vascular disease and early mortality. Since there is an already established screening program for AAA in Sweden and other countries it would be simple to complement it with evaluation of carotid arteries.
Conclusions

The prevalence of atherosclerotic plaques in the internal carotid arteries was common among 65-years-old men (25%), while the prevalence of >50% stenosis was low (2.0%).

Smoking, hypertension, diabetes mellitus and coronary artery disease were independent risk factors and individuals with several risk factors had a higher prevalence of both plaque and stenosis.

Smoking, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, COPD, claudication and TIA/stroke were associated with both the atherosclerosis extent and atherosclerosis severity.

The use of antiplatelet agents and statins was high in subjects with >50% stenosis, 40 (42%) and 39 (41%), respectively.

Most of those at risk had no other clinical manifestation of atherosclerosis, and therefore had no preventive treatment. As a consequence, carotid artery screening has a potential role in identifying individuals at risk and enabling the institution of best medical therapy and appropriate follow up for this cohort, including a small number even considered for operative intervention.

Ultrasound is a non-invasive diagnostic tool and is already being used as an excellent screening method (e.g. screening for aortic aneurysms). AAA screening programs use less experienced operators to examine the aorta and a simplified carotid screening protocol could be a beneficial addition to already existing screening programs.

The simplified grayscale/mosaic protocol had a high negative predictive value for detection of >50% carotid stenosis, suggesting that it may be suitable as a screening method to exclude significant disease. Although the protocol should be tested with less experienced operators in a screening setting.

The effect of BMT on stroke risk reduction is the key factor affecting cost-effectiveness of screening, and a minimum 22% reduction in the risk of stroke is required for screening to remain cost-effective at a WTP threshold of €50000/QALY.
A stroke risk reduction of 32% is required at a WTP threshold of 23000/QALY.

At an assumed stroke-risk reduction from BMT of 62% or higher the strategy of screening dominated the strategy of not screening meaning that a screening strategy would be less expensive then no screening.

The parameters with the most influence on cost-effectiveness were the assumed relative stroke risk reduction from BMT, cost of the ultrasound examination, and ACAS prevalence.

Assuming that initiation of BMT for ACAS results in a 50% stroke risk reduction compared to no-BMT, a 65-year-old man would on average gain 0.44 stroke-free years by taking part in a screening program. Each prevented stroke resulted in a mean 6.5 additional stroke-free years for the individual who avoided a stroke.

Among 65-year-old men 19% showed progressive disease after 5-year follow-up.

Neurological events rate among subjects with progressive disease was much higher in than among individuals without progression.

Smoking, coronary artery disease and hypercholesterolemia were risk factors associated with progression of carotid atherosclerosis.

Regression rate was high with 41.4% of individuals having less extensive atherosclerotic disease after 5-year follow-up.

Carotid atherosclerotic plaque and stenosis 50-79% has a relatively benign development during five years if treated with BMT and risk factor adjustment. Very few progressed to symptomatic disease and were in need of additional treatment.

More severe stenosis (80-99%) has higher rate of neurological events despite BMT, and may benefit from additional treatment.
Future perspectives

Before a successful screening program for carotid atherosclerotic disease could be implemented there are several areas that need further exploration:

- If detection of carotid atherosclerosis would have a negative effect on quality of life the benefits of screening would be outweighed by the costs. Therefore, there is a need for further assessment of long term quality of life among individuals participating in such screening programs.

- The exact effect of modern best medical treatment with risk factor adjustment in reduction of stroke risk is still not established. There is a need for further evaluation before the best intervention could be provided for individuals with disease when found.

- Medical intervention in ACAS individuals can also be expected to affect other cardiovascular morbidity and mortality, which thus would potentially increase the gain of a screening strategy. Even a small decrease in general cardiovascular mortality in the ACAS group would have a strong impact. This effect merits more studies.

- More research is needed to evaluate weather screening should be done as a one-time screening or as recurring evaluations. If once in a lifetime screening is found to be sufficient there is a need for evaluation of at what age the screening should be performed.

- Modern studies evaluating stroke risk indicate a strong connection between increased risk and high carotid plaque burden. There are new diagnostic methods available today such as 3-dimensional ultrasound that could measure plaque volume. Further studies of this method could improve present diagnostic strategy.
Asymptomatisk karotissjukdom definieras antingen som avsaknad av cæbral symptom eller som avsaknad av symptom de senaste sex månaderna. Sjukdom i karotis (halspulsåder) kärlen orsakar symptom genom ruptur av atherosklerotiska plack och embolisering av trombotisk material eller genom att förträngningen blir så tät att blodflödet till hjärnan minskar. Symptomen är amarousis fugax (övergående ensidig synnedsättning), transitorisk ischemisk attack (TIA), liten eller stor stroke (hjärninfarkt).

Kartotissjukdomen är orsaken till ca 20% av alla stroke och är den vanligaste orsaken hos medelålders patienter. Ischemisk stroke är den vanligaste orsaken till handikapp hos vuxna och tredje vanligaste dödsorsaken i sverige. Risken att avlida efter en stroke är stor (15-34%) och 15-30% av de drabbade har permanent handikapp. Förutom de katastrofala följderna för individen är stroke den mest vårdkrävande sjukdomen i samhället och strokevårdskostnaderna uppgår mot 18 bilioner per år.

En mindre förträngning i halskärlen kallas plack och en mer markant reduction av lumen benäms som stenos. Prevalensen av karotisstenos i populationen varierar mellan 0-22% med en snittprevalens på 4.2%. Kända riskfaktorer för hjärtkärlsjukdom som: ålder, manligt kön, rökning, hypertoni, diabetes och hyperlipidemi ökar risken för utveckling av atheroskleros karotiskärlen. Graden av förträngning och förträngningens progress är de två faktorerna som har starkast korrelation med risken för stroke. Individer med atheroskleros progress har en fördubblad strokerisk och risken ökar också markant med stenosgraden vilket har gjort att man definierat gränsen för operativ åtgärd av karotisstenos till >70% förträngning.

Duplex ultraljudsundersökning är en icke-invasiv undersökning med hög sensitivitet och speciflicitet och är idag standard metoden för diagnostik av förträngningar i karotiskärlen. Förträngningarna klassificeras som plack då man mäter intima-media tjockleken och stenos där man ser förträngningen på en gräskalebild och ett turbulent flöde på färgdoppler. Graden av stenos mäts genom att man tittar på flödeshastigheterna i käret.

Behandling av asymptomatisk karotis stenos har ändrats de senaste 20 åren från en operativ åtgärd (karotis endartärenotomi) till medicinsk behandling och riskfaktor sanering. Medicinsk behandling omfattar trombocythämmare, statiner, behandling av hypertoni och blodsockereglering. Införandet av ffa statiner har reducerat den årliga strokerisken till ca 1%.
Generell populationsscreening rekommenderas inte i dagsläget utan man rekommenderar endast screening av högriskindivider. Idag i Sverige förekommer screening av karotiskärlen endast inom ramen för forskning och efter att patienten har fått symptom. Screeningdebatten har till stor del handlat om att hitta högriskgrupper och vilken behandlingsstrategi som är bäst. I denna doktorsavhandling studeras olika epidemiologiska och hälsoekonomiska aspekter av screening för asymptomatisk åderförkalkning i karotiskärlen.

**Deltarbete I**

**Deltarbete II**
Preoperativ ultraljudsdiagnostik är en complex undersökning och kräver hög erfarenhet hos undersöken. I detta delarbete studierades en förenklad ultraljudsmetod för upptäckt av significant karotisstenos i rent screeningssyfte. Förekomst av karotisstenos på gråskalebilden ihop med förekomst av turbulent flöde synligt som “mosaic” på kolor Doppler jämfördes med mätning av flödehastigheter. Metoden visade sig ha ett högt negativt prediktivt värde vilket gör att den skulle kunna användas för att utesluta sjukdom.

**Deltarbete III**
Kostnadseffektivitet är en viktig factor när det gäller införandet av ett nytt screenings program. I en modell-baserad matematisk simulering evaluerades olika faktorer av screening av karotiskärlen för att se under vilka förhållanden skulle ett screeningsprogram vara kostnadseffektivt. Den absolut viktigaste faktorn för kostnadseffektivitet visade sig vara den strokerisk sänkande effekten av en primäpreventiv metod. Effekten behöver vara minst 22% för att man ska uppnå kostnadseffektivitet. Tidigare forskning visar att en risksänkande effekt på mellan 9% och 67% är möjlig med medicinsk behandling dock är den exakta effekten av komplett BMT och riskfaktorsanering dåligt studie-
rad. Med en 50% risksänkande effect hos 65 åriga deltagare i ett screeningprogram skulle varje förebygd stroke resultera i 6,5 extra strokefria år för individer som undvek en stroke.

**Delarbete IV**

Män som hade screenats vid 65 år inbjöds till en ny screening 5 år senare vid 70 års ålder. Progress av atheroskleros, utveckling av neurologiska symptom samt död inom 5 år studierades. Prevalensen av plack i karotiskärlen ökade från 23% till 29% och av stenos från 1.4% till 2.2%. Lindrig atheroskleros dvs plack och låggradig stenos hade ett beningt förlopp medan 42% av de med höggradig stenos utvecklade symptom trots insättning av medicinsk behandling. En hög andel av individer med progressive sjukdom saknade medicinsering vid rescreeningen. Majoriteten av individer avled av andra orsaker än stroke.

**Sammanfattning**

Prevalensen karotisstenos är låg i populationen av 65 åriga män och de flesta har en sjukdom med beningt förlopp på fem års sikt om de behandlas med medicinsk behandling och riksfaktorsanering. Det finns en förenklad ultraljudsmetod som skulle kunna användas som screeningsinstrument men behöver utvärderas i ett äkta screeningsscenario. I en population av 65 åriga män behöver en primärvirvabilitet metod sänka strokerisken med minst 22% för att screening skulle vara kostnadseffektivt, därför behövs en mer klar kartläggning av den effekt som uppnås av modern primärvirvabilitet behandling. En betydande andel individer med signifikanta atherosklerotiska förträngningar i halskällena har ingen preventiv behandling och skulle kunna ha nytta av ett screeningsprogram dock behövs en mer omfattande utvärdering av olika screeningsmodeller, bla selektiv screening av högriskgrupper innan man kan rekommendera populationsscreening.
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